Pressure ulcer or Decubitus
clinical and etiological aspects

Decubitus
klinische en etiologische aspecten

Ronald Han Houwing

Pressure ulcer or Decubitus
clinical and etiological aspects

omslag Roy Haaswinkel
lay-out Von Oerthel Bureau voor secretariële – en projectondersteuning
printed by Ovimex, Deventer

© 2007 R.H.Houwing
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without permission from the author or the corresponding journal

ISBN 978-90-393-4677-8

Pressure ulcer or Decubitus
clinical and etiological aspects

Decubitus
klinische en etiologische aspecten

Proefschrift
Ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus,
Prof. dr. J. C. Stoof

ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op

dinsdag 6 november 2007 des middags om 16.15

door

Ronald Han Houwing
geboren op 2 januari 1958
te Dordrecht

Promotoren	Prof. dr. J.R.E. Haalboom Prof. dr. C.A.F.M. Bruijnzeel-Koomen
Co-promotor	dr. J.W. Arends

"Age wrinkles the body. Quitting wrinkles the soul."

Douglas MacArthur

Voor mijn meisjes

Contents

Chapter 1

General introduction

Definition

A pressure ulcer (PU) is defined as a localized area of degenerative changes of the skin and underlying tissue caused by pressure, shear, friction and/or a combination of these factors. [1] [2] [3] Simply, it is any lesion caused by sustained mechanical loads such as the unrelieved pressure of lying on a hard bed, protracted sitting in a wheelchair or wearing a not-properly fitting lower limb-prosthetic.

Pressure ulcers are also known as decubitus, derived from the Latin word 'decumbere', meaning 'to lie down', 'to recline'. The clinical spectrum of decubitus ranges from simple redness with scaling (decubitus dermatitis) via non-blancheable redness with an intact skin and a superficial wound or blister on pressure points, to deep wounds with loss of the underlying fatty tissue, tendons, muscle and even joints.[4] [5] As the clinical presentation of PU may not reveal the full extent of damage, and the presence of an ulcer is not necessary, decubitus is perhaps a better term than pressure ulcer, since it describes the whole spectrum of degenerative changes. According to the definition, PU can be caused by pressure, shear, friction and/or a combination of these factors. In this definition pressure is not the only determinative factor and a wound in the sense of the breakdown of superficial tissue is not necessarily present. The name pressure ulcer in stead of bedsores or decubitus was accepted as the term that should be used during an international conference in 1975. At the same time, it was recognized that some of the lesions so classified were not necessarily caused by pressure insults.[6] [7] Since 'pressure ulcer' is the term most commonly used in the international-, predominantly Anglo-Saxon scientific literature, in this thesis the term 'pressure ulcer' (PU) will be used.

History

PU are concomitant with human (and animal-) life and have probably existed since the early recorded history of mankind. They have been observed in unearthed human mummies and addressed in scientific writings of the 19th century. Even evidence of surgical corrective procedures (the use of the skin of gazelles) is found in mummies as old as four thousand years.[8] [9] Until the early twentieth century PU were observed mostly in bedridden patients during the last period of their illness. They were associated with an unfortunate outcome of the disease and in fact regarded to be symptom of an imminent death. This meant that PU became the burden of nurses especially, since doctors tended to decrease their involvement in these cases. Advances in medical and nursing care improved the prognosis of patients for whom treatment or cure was previously unlikely. Since that time, PU were also noticed in younger persons suffering from a variety of wasting diseases, including tuberculosis, osteomyelitis, chronic renal disease and spinal cord injury.[10] Especially the second World War was a turning point. War victims were

treated better and better and they survived their injuries more often, even until recently life threatening events, but with the development of PU as a consequence. It entailed the start of preventive and treatment strategies as well as reconstructive surgical procedures. Only since the last two decades the prevention and treatment follow guidelines. Whereas in early ages death was commonly due to external causes, such as famine, cold, injury, violence or infectious diseases at a far younger age, people nowadays die predominantly from diseases associated with ageing. The combination of better medical and nursing care together with increasing age of the whole population caused an increase in the prevalence of PU.[11 12]

Currently PU are common in many healthcare settings, affect all age groups, and are costly both in terms of human suffering and use of resources. A high incidence of PU is seen in nursing homes and to a lesser extent in hospitals, especially – but not exclusively- in the elderly. Over 60 percent of PU are observed in patients with an age over 70 years, and with an ageing population, the extent of the problem will increase unless action is taken.[13] In younger patients it occurs especially in patients admitted to Intensive Care units and in patients after severe accidents, often with spinal cord lesions. Patients are particularly susceptible when they have neurological and cardiovascular diseases, dehydration, hypotension, and –more in general- when undergoing surgery.[8 11 14] Furthermore people with a limited ability or even inability to reposition themselves, not sensing the need to reposition, with faecal and/or urinary incontinence and the inability to feed themselves due to severe illness, are especially at risk. It is obvious that these risk factors often coincide in elderly patients admitted at nursing homes. It is important to emphasize that these kind of institutions are typical for the Dutch health care situation. The category of patients that is referred to nursing homes in the Netherlands, normally stays in regular hospitals in other countries. International comparisons with other countries should be interpreted cautiously, due to a different patient selection. Nursing homes in international literature mostly refer to institutions resembling what in the Netherlands would have been called an institution for the elderly (*rusthuis* or *verzorgingshuis*).

Impact of the problem

PU are associated with pain and discomfort, various other important morbidities, lost productivity, poor utilization outcomes of health care. PU seriously affect the quality of life (QoL) by social isolation, pain, malodour, drainage of deep defects, frustration, anger, helplessness, and hopelessness.[15 16] Patients with PU are prone to infections and sepsis, and deep defects often need additional surgical intervention. This leads to considerable prolonged hospital stay and a fivefold increase in mortality.[17 18 19] It has to be borne in

mind, however, that this increase in mortality is both due to the presence of PU, and to the usually more severe disease of the patient that has led to the condition as well.
From a socio-economic point of view PU is a costly problem: recent European cost-models to highlight the costs associated with PU have indicated that total costs may amount to about 1% - 4% (€268- to €2.100 million) of health care expenditure.[20] [21] Annual PU treatment costs in the US range from $9.1–11.6 billion with annual cost per PU case ranging from $21,000– 152,000.[2] [22] Although large sums of money are involved in prevention of PU, these costs are considerably lower than the costs involved in the treatment of an established PU. The costs-of-illness of PU are multifactorial: more time-consuming attendance of nurses since patients rise in category of care; longer stay in the hospital, also causing longer waiting lists for other patients; the use of medication and wound dressings; additional out-patient care; the use of expensive pressure relieving mattresses and/or bed systems.[23] [24] Furthermore, there is the increasing problem of litigation. In the past, relatives and patients appeared to accept that PUs were an inevitable result of chronic conditions and reduced mobility. Now they are considered to be the evidence of a failure to provide a reasonable standard of care and action for legal compensation can be brought against those responsible.[25] In the USA attorneys advertise on billboards placed directly outside the hospitals and even on television in search for PU cases, in which they directly sue the hospitals. Currently a median PU 'award' in the USA amounts to $250.000,-[26] Also in Europe costs of litigations tend to increase.

The Dutch Healthcare Inspectorate introduced PU as an indicator of the quality of healthcare, an instrument to compare the quality of care amongst institutions, to intend to encourage institutions to improve their PU care.[27] They considered the incidence of PU as a negative indicator of quality. To enhance the quality of care for PU prevention, it is mandatory to obtain clear evidenced-based guidelines in the hope that such guidelines can bring nurses and doctors, together and enlarge their awareness in PU care. However, in the currently used prevalence recordings the category of care of the patients is not taken into account. Since university-, and top-clinical hospitals obviously have more severely diseased patients with much larger chances to develop PU, a not-realistic picture could emerge. Although the Healthcare Inspection refrains from a judgement, the results of the yearly performance are public and published in the national papers without restrictions. Since the payment of hospitals in the near future will largely depend on the scoring of the quality indicators, a.o. PU, differentiation between the several types of institutions in health care and in categories of patients will be of eminent importance.

Pressure ulcer classification.

To guide the clinical discription of the depth of tissue destruction occurring with PU several classifications systems have been developed. The most commonly used classification system is developed by the European Pressure Ulcer Advisory Panel (EPUAP) and the National Pressure Ulcer Advisory Panel (NPUAP).[23]

Grade	Short Description	Definition
Grade 1	Non-blanchable erythema of intact skin	Non-blanchable erythema of intact skin. Discolouration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin.
Grade 2	Blister	Partial thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister.
Grade 3	Superficial ulcer	Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia.
Grade 4	Deep ulcer	Extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss.

EPUAP Classification [28]

A classification system is important in research and to obtain prevalence figures, since it provides a method for communication about the extent and volumes of anatomical tissue loss. It can be a predictor of the length of time of a healing process and it could suggest a therapeutic approach. Staging however is considered to be static while PU formation actually is a dynamic process that is constantly evolving. Recently, in Europe and the USA, attempts have been made to single out superficial skin loss in immobile patients with incontinence from early stages of PU lesions as a distinct entity. This kind of lesions named 'moisture-lesions', 'incontinence-associated dermatitis (IAD)' or 'moisture-associated skin damage (MASD)' are considered to have a different pathophysiological mechanism from superficial forms of PU, with moisture as the primary cause, and not tissue loading. As a consequence these lesions are excluded from the PU classification system [2 29 30 31] This behaviour could lead to the impression that prevalence changes in a positive way. Evolvement of a classification system should be the result of greater understanding of the pathogenesis of PU development.[32] However due to a limited fundamental knowledge related to the etiology of the clinical conditioning, classification systems are mainly based on so-called expert opinions. As some national guidelines restrict PU to cell death by a lack of oxygen, different from the broader definition of other countries, it is hard to obtain an uniform classification system, especially for the more superficial forms of PU. [1 2 3]

Pathogenesis

According to the definition PU represent areas of tissue breakdown due to sustained mechanical load. It looks straightforward: mechanical load causes lesions. However surprisingly there is no consensus about the pathofysiological response to mechanical loading that triggers soft tissue breakdown. Tissue loading will cause occlusion of blood vessels, leading to ischemia. The level of tissue loading, tolerated by tissues before damage occurs, differs in test specimens and experimental conditions.[33] [34]

When the loading stops and the circulation can restore, several processes may ensue: 1) Restoration of the blood flow without tissue damage. 2) Irreversible damage and tissue necrosis. 3) Failure to reperfuse the microcirculation (no-reflow phenomenon). 4) Reperfusion, leading to damage known as ischemia-reperfusion injury.

Most of experimental animal studies have been focussed on the occlusion of blood vessels due to sustained loading, leading to ischemia followed by tissue necrosis.[35] [36] [37] The length of time between the onset of ischemia and the occurrence of irreversible tissue damage widely varies between different tissues such as muscle; subcutaneous fat; and skin. Skin can withstand periods of ischemia for as long as 8 hours before irreversible damage takes place. The threshold tolerance for the length of ischemia is much lower for muscle and fat.[38] [39] [40] This phenomenon may explain why muscle damage underlying PU usually is more extensive than the damage of the overlying skin.[41]

When pressure of short duration is relieved, tissues demonstrate reactive hyperaemia, reflecting increased blood flow to the area. However, sustained high pressure leads to decreased capillary blood flow, and eventually occlusion of blood vessels. Doppler signal studies showed a critical moment when the length of pressure increases to such an extent that there is a failure to restore blood flow to an ischemic organ despite reperfusion, a phenomenon known as no-reflow. Swelling of capillary endothelial cells, plugging of capillaries by leucocytes, fibrin deposits and microthrombi, contributes to the failure of capillary perfusion after prolonged ischemia. [38] [41] [42] [43] [44] [45]

An ischemic phase can be followed by reperfusion when the tissue load stops, e.g. due to a change of position. Data from other organs such as brain, kidney, and heart, showed that not ischemia itself but reperfusion is responsible for most of the tissue damage.[46] [47]

A sudden decrease in oxygen tension in the cells results in the activation of control mechanisms to maintain steady state. With the restoration of the blood supply and re-introduction of oxygen, toxic oxygen derived free radicals may be formed. Under normal circumstances oxygen derived free radicals are buffered by free-radical scavenging mechanisms. However, when there is an overproduction of reactive oxygen species (ROS), or a decrease of scavengers as in oxidative stress, free radicals can initiate a sequence of biochemical and cellular events, causing extensive damage to the surrounding tissues.[48] The failure to reperfuse, the so-called no-reflow phenomenon, is

also a result of overproduction of free radicals.[49] [50] An important source of free radicals is derived from the neutrophilic leucocytes. After reperfusion the activated leukocytes adhere to the endothelial cell, and release protease and phospholipase enzymes, all of which are capable of causing inflammation with significant cellular and tissue injury.[51] Neutrophil-mediated endothelial injury has been demonstrated to result in loss of vascular integrity, oedema, haemorrhage, thrombosis, and tissue necrosis. At the cellular level the injury, resulting from the blood flow restoration to previous ischemic tissue, has been called Ischemia-reperfusion (I-R) injury. [33] [39] [47]

PU usually occur after- and not during- the period in which pressure is applied to the body. In the early phase of PU development a redness is seen before tissue necrosis. The skin lesions in PU (characteristically in a fixed order of appearance: reddening of the skin or non-blanching erythema, blister formation, superficial tissue breakdown and eventually ulceration and extension to deeper tissues) develop hours to days after cessation of the pressure application. Also in PU related animal experiments the reperfusion of tissues is followed by extensive inflammatory reactions.[52] Histopathological patterns in such animals models, in which ischemia and reperfusion play a role, show a strikingly similar picture to the histopathology of PU in man. 53 [53] [54]

In summary: during ischemia there is impaired tissue perfusion with inadequate delivery of oxygen and other substrates and an impaired removal of metabolic products. Restoration of the blood flow paradoxically results in injury, not apparent during the ischemic period. Reperfusion after a period of circulatory obstruction, can activate damaging processes by means of reactions of re-introduced oxygen, generating oxygen-derived-free-radicals. The cellular injury is known as ischemia-reperfusion (I-R) injury.

This thesis is focussed on the role of I-R injury and the possible therapeutic interventions based on this concept. Other hypotheses associated with the pathogenesis of PU are; occlusion of lymph vessels which leads to accumulation of anaerobic metabolic waste products resulting in cell damage[55] [56] and sustained compression which leads to cell deformation that can result in cellular breakdown, leading to tissue damage[57] [58] Each of these mechanisms can contribute to the causation of PU, depending on the nature of the tissue loading and patient characteristics, such as illness and age. For a breakthrough in prevention and treatment of PU a better understanding of the pathophysiological mechanisms of PU is necessary. A more complete understanding of the relationship between load and tissue damage has to be established.

Prevention

The development of a majority of PU is preventable. It requires the identification of patients at risk and the start of preventive measures as early as possible. The prevention of PU diminishes both pain and deterioration for the patient, and the costs of treatment

as well. It has been demonstrated that prevention is cheaper than whatever form of treatment of apparent PU. In effective PU management the first attention, therefore, must be focussed on PU prevention. However, under some circumstances the prevention of PU could play a secondary role. For instance, in patients with terminal illness and multi-organ failure, optimal preventive interventions are still indicated, but for palliative reasons the attention should be primarily focused on comfort and pain relief.[59]
Preventive strategies include:
1) decreasing of the effects of pressure, shear and friction
2) identification of patients at risk
3) optimal clinical observation of the skin and proper 'skin care'
4) improvement of the general condition of the patient, a.o. by adjusting nutrition

Ad 1) *Decreasing of the effects of pressure, shear and friction*
PU are primarily caused by sustained mechanical loading of the soft tissues. Prevention, therefore, should essentially be focussed on the relief of high degrees and extended duration of pressure. Patients who cannot change body position at a regular basis by themselves, should be helped by medical personnel (or other bystanders such as relatives) to change their body position. Proper positioning, regular weight shifts (the frequency of which should be listed in the medical record), other pressure relief interventions and the elimination of shear forces and friction should be incorporated into the nursing plan.[60] Depending on the main diagnosis (e.g. hemiparesis) the patient should be instructed and stimulated to help in these procedures as much as possible. In all care settings the individuals considered to be at risk to develop PU should have a personalised written prevention plan which may include a pressure redistributing device.
Based on the patient's risk and mobility status, these pressure redistributing devices may need to be employed. Individuals at risk for PUs who are likely to spend substantial periods of time in a chair or wheel chair should generally be provided with a pressure decreasing device also in these positions. [2]

Ad 2) *identification of patients at risk*
Although the main cause of the development of PU always depends on sustained mechanical loads, more factors play a role. One of these factors is the general condition of the patient. While some patients develop PU when subjected to a certain pressure, others do not. Basically, no one is resistant to the development of PU beyond some critical pressure or tissue load, but certain factors increase the risk of pressure damage.[61]
This is illustrated in e.g. a patient with multiple sclerosis, lying for years in the same position, without the possibility of alternating body position because of contractures, but who nevertheless did not develop PU. These only appeared when the patient contracted

pneumonia.[62] Especially in nursing literature it is stated that the factors determining the patients risk could be categorized as *external* and *internal* factors. External factors contribute to tissue load by means of increasing pressure, shear force and/or friction. Examples are immobility, loss of sensory perception, length of surgery, etc. Internal factors influence the individual susceptibility to extrinsic factors. Patient-bound factors are for example; fever, malnutrition, anaemia, and endothelial dysfunction. [4 8 62 63] Until now more than 100 factors have been reported which could attribute to the chance of getting PU. [1 64 65] Although it seems conceivable that these so-called intrinsic factors could add to PU risk, they have no defined place in pathofysiological mechanisms. These factors in part could be based on the increase of pressure (a patient with a complicating disease such as pneumonia in the example above perhaps moves even less than under 'normal' circumstances). In part they could also be based on more general deterioration, influencing the development of PU (in the same example of a patient with multiple sclerosis with a pneumonia the arterial oxygen concentration could be decreased because of the diffusion problems in the lungs, with less oxygen delivery to the threatened skin).

Basically, it is best to use the terms *risk factors* and *risk indicators*. In risk factors there is a causative relation based on pathophysiology between the factor and the development of PU. Risk indicators predict the development of PU without this direct causative relation, For example a patient with a denture or dental plate probably has an increased risk. Obvious there is no causative relation between dentures and PUs. Still elderly patients are more prone to develop PU and it is this patient category that uses dentures most. In elderly patients a deteriorated nutritional condition is often found and they suffer more frequently from other diseases. But age per se does not cause PU. Pressure-ulcer-risk-assessment scales (PURAS) were developed in an attempt to determine which patients need preventive measures and which patients do not. They are based on the enumeration and quantification of expected risk-indicators. Examples are the tools developed by Norton, Waterlow and Braden. In the Netherlands a comparable tool was introduced, the CBO in which more direct causative factors were introduced. [1] It is supposed that these tools predict the development of PUs. However the scientific basis of their use is almost lacking.[66 67] Still they are used with a kind of religious sentiment with abundant belief and lacking proof. It is striking that in most PURAS (developed by nurses) indicators such as age are frequently used in contrast with medical based risk tools, in which only direct causative factors are used. For example in the risk assessment tool used to predict the development of cardiovascular diseases factors like hypertension, increased cholesterol concentrations, smoking and diabetes are used, each and individually increasing the risk based on a well-known pathophysiological basis. In the

prevention of PU the development of PURAS based on pathophysiological factors should be strongly encouraged.

Ad 3) *optimal clinical observation of the skin and proper 'skin care'*
Skin care is defined as preserving the integrity of the skin. A healthy skin provides more resistance to mechanical disruption. The skin of buttocks and dorsal sites of the heels are not meant to undergo sustained loading. Moisture by sweat, wound drainage, urine, and faeces macerates and damages skin. The epidermis is more susceptible due to softening of the stratum corneum barrier with disruption of the intercellular lipid lamellae (which act as the biologically active glue), and tissue breakdown by faecal enzymes such as lipase and protease.[68] However, also an excessive dry skin (xerosis) is a risk factor for the development of PU[69]. Xerosis requires appropriate moistening for its prevention and treatment and to maintain skin health. Unfortunately no clear recommendations can be made which measures are best to obtain a healthy skin.[70] Skin should be assessed regular for skin problems, especially on the threatened areas. Although there is no evidence based practice determined for skin care, daily inspection, or if necessary more frequent, should be an integral part of every guideline focussed on PU prevention. Since the risk assessment tools now propagated only and invariably show a very limited value, without scientific proof, there definitely should be much more emphasis on observation and proper treatment of the skin. Skin is the most easy accessible parameter of PU care!

Ad 4) *improvement of the general condition of the patient, a.o. by adjusting nutrition*
The risk to develop PU is increased in patients with an illness as compared with healthy persons. Most risk indicators in PU are difficult or impossible to treat (age!). There is one important exception: malnutrition, strongly correlating with an increased incidence and severity of PU. This relation is found both in malnourished patients and with lower intakes of proteins and energy.[71] [72] [73] The observed correlation raises the question whether the nutritional status correlates with the development of PU, and if so, how malnutrition interferes in the prevention of PU.
There is until now no golden standard for the diagnosis of malnutrition. Malnutrition could mean *underfeeding*, that is the inadequate intake of sufficient amounts of calories, proteins and other nutrients. It could also mean *cachexia*. This wasting syndrome comprises a range of metabolic, hormonal, and cytokine-related abnormalities that occur in disease conditions varying from cancer and infections to cardiopulmonary, renal and rheumatologic diseases. In these cases the provision of adequate nutrition or even of extra feeding (drink feeding, tube feeding etc) will not correct the cachectic state.
Malnutrion can be the result of physiological and/or non-physiological causes.

- Physiological causes. With ageing, there is a decrease in appetite and food intake that may result in undesirable weight loss. This weight could be secondary to decreased physical activity and energy demands, but also there is a decline of smell and taste with increasing age.[74] Another physiological cause is called sarcopenia (Greek: poverty of flesh), referring to the decline in muscle mass and strength. It occurs in healthy ageing and is considered to represent both a process and an outcome indicator. People loose weight since they grow older, or they loose weight since their health declines with age.
- Non-physiological causes of weight loss are decreased intake of nutrients because of medical illnesses, social isolation and poor dentition. In medical illnesses the activation of anorectic and catabolic cytokines plays a role, e.g. in renal failure.[75] In cancer the production of TNF by the tumour strongly inhibits normal appetite. In earlier days this factor was even called 'cachexin'.

It is questionable whether malnutrition is to be considered a risk factor or an indicator, or whether malnutrition is causative in the development of PU. With more severe malnutrition somatic fat- and muscle mass decrease. Using a B-mode ultrasound in humans with PU it was shown that the depth of soft tissue covering the sacral region was decreased[76] More slim patients showed higher pressures over the trochanters than subjects with an average or even increased weight. Loss of muscle bulk and tone decreases the capacity to spread pressure both in malnourished patients and in patients with weight loss associated with the later stages of cancer. [35] Obese patients have a larger body area subjected to pressure, however, the maximum pressure forces are lower.[77] Fatty tissue is poorly perfused and probably more vulnerable to ischemia. Experimental studies in animal models suggest a biological relationship between malnutrition and the susceptibility for PU. Malnourished animals showed a more severe degree of ischemic skin destruction after pressure application than normally fed animals.[78] Decreased caloric intake, dehydration, and a drop in serum albumin may decrease the tolerance of skin and underlying tissue to pressure, friction and shearing forces, increasing the risk of skin breakdown and reducing wound healing.[79] Under normal circumstances the most important factor in the regulation of albumin synthesis is nutrition. Hypoalbuminemia, which can be a reflection of malnutrition, could contribute to skin breakdown by causing interstitial edema, which impedes the perfusion by increasing the distance between capillaries and cellular elements. [19] A poor nutritional status also predisposes patients to infection, which, once initiated, contributes to the general debilitation of the patient. [19] [80]

When nutritional interventions exert a demonstrable positive effect on the development of PUs this finding would strongly add to the idea that there is a causative relation between malnutrition and PU. Until now this relation is not established.

Why are prevalence or –better- incidence figures still unacceptably high?

The last decennia PU have attracted a growing attention and awareness. Not the burden of the disease for the individual patient and his/her direct relatives, but the considerable expenses for their prevention and treatment, have been responsible for especially political attention.

Prevalence of PU in the Netherlands ranges from 15% in acute care hospitals from 24% in nursing homes.[81] In 2000 the Dutch Health Council concluded that the scientific knowledge about PU was poor, guidelines for PU care were not well adhered to, and the knowledge about the results of preventive measurements was considered to be insufficient. [28]

At the moment (2007), attempts to prevent PU, so far have not led to a significant reduction of the problem. Recordings performed by the University of Maastricht tend to show some decrease in the occurrence of PU, but these are the result of prevalence recordings, which are basically not correct to use (continuous registrations leading to incidence recordings should be used). In the recordings used until now, the type of institution, the category of care of the patients, and the disease from which the patients suffer, are not taken into account. This information together with incidence recordings are needed to provide a correct impression of the magnitude of the PU problem and the developments within this field.

Although strict adherence to a 'best practice' guideline can result in a decrease in PU prevalence, it appears that even moderate adherence is hard to achieve in daily practice.[82] There is no doubt that regular repositioning of the patient appears to be a an effective nursing practice. However, the effectiveness of the optimal intervals between repositioning, and the most appropriate posture in which patients are to be positioned, are not exactly known. Despite the development of guidelines concerning the prevention of PU, the compliance with these is inadequate. Only about 50 percent of the patients, at risk for PU, or even with established lesions, are repositioned. [14] [83] The reasons for this lack of compliance appear to be a combination of shortage of knowledge, skills, underestimation of the problem by health care institutions and vagueness about responsibilities in PU management.[84] Many physicians and nurses report that they lack education on PU management, suggesting that guidelines do not reach their intended public. [13]

Since PU prevention is a multidisciplinary problem, involvement of doctors, nurses, other care providers, but also involvement of the management of an healthcare institution, insurance companies, patient organisations, as well as the government are needed. National and international centres of knowledge and professional organisations are necessary in particular for research and the education of the public. Unfortunately, few doctors are interested in the topic or feel responsible for it. It is seen as 'a part of the deal' and is regarded to be a decidedly unglamorous aspect of healthcare. Since PU is a multidisciplinary problem, education and study of prevention and pathophysiology are not straightforward but–spread over many different disciplines. Partly for this reason, the condition remains within the realm of the nursing staff. However, cooperation between the nurses and doctors is necessary for well organized PU prevention and educational strategies. These should be based on the best available evidence which may be enhanced by specific knowledge as well as input from both parties.

In summary, more effective measures in PU prevention and treatment are not to be expected, as long as our notions of the complex etiology of PU are fragmentary and insufficient. In order to be able to reduce the prevalence of PU it is essential to expand our knowledge of the pathogenesis, both in terms of basic science as well as clinical application. [85] [86] To predict who is at risk to develop PU, to obtain clear and instructive guidelines, rather than compare the effects of different interventions on PU prevention and treatment, fundamental research is required. However, this type of investigation has often been overlooked in the rush to compare the effects of different interventions on PU prevention and treatment.[87] A more solid scientific background could lead to a breakthrough in insight concerning which preventive measures are rational and in which category of patients these should be used. In addition, basic research should provide the opportunity to introduce new therapies based on evidence based medicine, aimed at decreasing the burden of PU.

Outline and aims of the thesis.

This thesis addresses some aspects of the etiology of superficial and deep PU. The possible benefits of nutrional supplementation, and the use of a risk assessment tool are evaluated. The role of reactive oxygen species (ROS) in the pathogenesis of PU coupled to possible therapeutical interventions with antioxidant drugs, being protective against ROS, is the main topic of this thesis.

The following questions are addressed:

1. Do moisture lesions exist as a separate entity ?
2. Do risk assessment tools really identify patients at risk?
3. Are nutritional supplements able to prevent the development of PU?
4. Is ischemia-reperfusion injury the main underlying cause of PU?
5. Is it possible to reduce the extent of the tissue damage in PU by means of antioxidants?

In order to answer these questions the following investigations were performed, and described in the following chapters:

Chapter 2 *Is the distinction between superficial pressure ulcers and moisture lesions justifiable? A clinical-pathological study*

Chapter 3 *Pressure ulcer risk in hip fracture patients*

Chapter 4 *A randomised, double-blind assessment of the effect of nutritional supplementation in the prevention of pressure ulcers in hip-fracture patients*

Chapter 5 *Pressure-induced skin lesions in pigs: reperfusion injury and the effects of vitamin E.*

Chapter 6A A *systematic review of the efficacy of topical skin application of dimethyl sulfoxide (DMSO) on wound healing and as an anti-inflammatory drug*

Chapter 6B *An unexpected detrimental effect on the incidence of heel pressure ulcers after local 5% DMSO cream application*

References

[1] *CBO Richtlijn Decubitus (tweede herziening 2002) Kwaliteitsinstituut voor de Gezondheidszorg CBO, [Dutch institute for Healthcare CBO] Utrecht 2002*

[2] *EPUAP European pressure ulcer advisory panel. Pressure ulcer treatment guidelines. http://www.epuap.org Accessed june 4 2007*

[3] *National Pressure Ulcer Advisory Panel. National pressure ulcer advisory panel. www.npuap.org Accessed june 4 2007*

[4] *Parish LC, Witkowski JA.Controversies about the decubitus ulcer. Dermatol Clin. 2004;22(1):87-91*

[5] *Parish C. Decubitus: The Word 9-11. From: The Decubital Ulcer in Clinical Practice. Ed. LC Parish, JA Wikowski, JT Crissey. Springer-Verlag*

[6] *Kenedi RM, Cowden JM, Scales JT, eds Bedsore Biomechanics. Baltimore: University Park Press, 1976.*

[7] *Lowthian P the distinction between superficial pressure ulcers and moisture lesions. Skin Med 2007:6(3);111-2*

[8] *Bansal C, Scott R, Stewart D, Cockerell CJ. Decubitus ulcers: A review of the literature. Int J Dermatol 2005;44:805-10*

[9] *Levine JM, Historical perspective on pressure ulcers: the decubitus ominous of Jean-Martin Charcot. J Am Geriatric Soc 2005;53(7):1248-51*

[10] *Reuler JB, Cooney TG. The pressure sore: pathophysiology and principles of management. Ann Intern Med. 1981;94(5):661-6*

[11] *Bliss M, Simini B. When are the seeds of postoperative pressure sores sown?. Often during surgery. BMJ 1999;319:863-4*

[12] *Reifsnyder J, Magee HS. Development of Pressure Ulcers in Patients Receiving Home Hospice Care. Wounds 2005;17(4):74-79*

[13] *Reddy M, Gill S, Rochon PA. Preventing pressure ulcers: a systematic review. JAMA 2006;296: 974-984.*

[14] *Clark M. Repositioning to prevent pressure sores: What is the evidence? Nurs Stand 1998;13:56-64.*

[15] *Langemo DK, Melland H, Hanson D, Olson B, Hunter S. The lived experience of having a pressure ulcer: A qualitative analysis. Adv Skin Woundcare 2000;13:225-35.*

[16] *Franks PJ, Winterburg H, Moffatt C. Quality of life in patients suffering from pressure ulceration: a case controlled study (abstract). Ostomy and Wound Management. 1999;45: 56*

[17] *Allman RM, Goode PS, Burst N, Bartolluci AA, Thomas DR. Pressure ulcers, hospital complications, and disease severity: impact on hospital costs and length of stay. Advances in Skin & Wound Care. 1999;12(1):22–30.*

[18] *Allman RM, Laprade CA, Noel LB, Walker JM, Moorer CA, Dear MR, Smith CR. Pressure sores among hospitalized patients. Ann Intern Med 1986;105:337-42*

[19] *Grey JE, Harding KG, Enoch S. Pressure ulcers. BMJ 2006;332:472-475*

[20] *Severens JL, Habraken JM, Duivenvoorden S, Frederiks CMS The cost of illness of pressure ulcers in the Netherlands. Advances in Skin & Wound Care. 2002;15(2):72–77*

[21] *Bennett G, Dealey C, Posnett J The cost of pressure ulcers in the UK. Age & Ageing. 2004;33:23–235.*

[22] *Zulkowski K, Langemo D, Posthauer ME, the NPUAP Coming to consensus on deep tissue injury. Advances in Skin & Wound Care 2005;18(1):28–29.*

[23] *Haalboom JRE. Some reamarks about overlays in the prevention and treatment of pressure ulcers. EPUAP Review 2000;2(2):67–70.*

[24] *Iglesias C, Nixon J, Cranny G, Nelson EA, Hawkins K, Phillips A, Torgerson D, Mason S, Cullum N; PRESSURE Trial Group. Pressure relieving support surfaces (PRESSURE) trial: cost effectiveness analysis. BMJ. 2006;332(7555):1416*

[25] *Dimont B. Pressure ulcers and litigation. Nurs Times. 2003;99(5):61-3*

[26] *Bennet RG, O'Sullivan J, De Vito EM, Remsberg R. The increasing malpractice risk related to pressure ulcers in the United States. J Am Geriatr Soc 2000;48(1):73-81*

[27] *Inspectie rapport. Decubitus doorgelicht: richtlijn onvoldoende in praktijk toegepast. Den Haag februari 2004 Gezondheidsraad Inspectie rapport Den Haag februari 2004.*

[28] *EPUAP European pressure ulcer advisory panel. Pressure ulcer treatment guidelines. EPUAP review 1999;1:31-33*

[29] *Gray M, Bliss DZ, Doughty DB, Ermer-Seltun J, Kennedy-Evans KL, Palmer MH. Incontinence-associated dermatitis: a consensus. J Wound Ostomy Continence Nurs. 2007;34(1):45-54*

[30] *Junkin J, Selekof JL.Prevalence of incontinence and associated skin injury in the acute care inpatient. J Wound Ostomy Continence Nurs. 2007;34(3):260-9.*

[31] *Defloor T, Schoonhoven L, Fletcher J, et al. Statement of the European Pressure Ulcer Advisory Panel-Pressure Ulcer Classification: Differentation between pressure ulcers and moisture lesions Journal of Wound, Ostomy and Continence Nursing, 2005;32:302-6*

[32] Npuap class: Black J, Baharestani M, Cuddigan J, Dorner B, Edsberg L, Langemo D, Posthauer ME, Ratliff C, Taler G. National Pressure Ulcer Advisory Panel's Updated Pressure Ulcer Staging System. Urol Nurs. 2007;27(2):144-150.

[33] Reswick JB, Rogers JE. Experience at Rancho Los Amigos Hospital with devices and techniques to prevent pressure sores. In: Kenedi RM,Cowden JM, Scales JT, editors. Bed sore biomechanics. Baltimore: University Park Pr; 1976. p 301-10.

[34] Swain I. Bader D. The Measurement of interface pressure and its role in soft tissue breakdown.In : M. Clark ed. Pressure Ulcers: Recent advances in tissue viability. 2004 pg 39-55

[35] Kosiak M. Etiology and pathology of ischemic ulcers. Arch Phys Med Rehabil 1959;40:62-9

[36] Dinsdale SM. Decubitus ulcers in swine: light and electron microscope study of pathogenesis. Arch Phys Med Rehabil 1973;54:51- 6.

[37] Daniel RK, Priest DL, Wheatley DC. Etiologic factors in pressure sores: an experimental model. Arch Phys Med Rehabil 1981;62:492- 8

[38] Husain T. An experimental study of some pressure effects on tissues, with references to the bedsore problem. J Pathol Bacteriol 1953;66: 347- 52.

[39] Nola GT, Vistnes LM. Differential response of skin and muscle in the experimental production of pressure sores. Plast Reconstr Surg

[40] Cherry GW, Ryan TJ. The Effect of Ischaemia and Reperfusion on Tissue Survival. Uit Microvasclar injury. pg 93-115

[41] Romanus M. Microcirculatory reactions to local pressure induced ischemia. Thesis University of Göteborg, Göteborg Sweden 1977

[42] Seiler WO, Stahelin HB, Zolliker R, et al. Impaired migration of epidermal cells from decubitus ulcers in cell culture: A cause of protracted wound healing? Am J Clin Pathol 1989;92:430-4

[43] Willms-Kretschmer K, Majno G. Ischemia of the skin. Am J Pathol. 1969:54; 327-53

[44] Barton AA. Prevention of pressure sores. Nurs Times 1977;73:1593- 5.

[45] Lowthian PT. Trauma and thrombosis in the pathogenesis of pressure ulcers Clin Dermatol 2005;23:116-23

[46] McCord JM. Oxygen derived free radicals in postischemic tissue injury. N Eng J Med 1985;312:159-63

[47] Bulkley GB Free radical-mediated reperfusion injury: A selective review. Br J Cancer 1987:55(suppl VIII);66-73

[48] Wang Y, Sanders J Skin model studies in Pressure Ulcer Research Current and Future Perspectives ed D. Bader. C.Bouten, D.colin, C. Oomens Springer Berlin Heidelberg New York 2005; pg 263-85

[49] Mustoe AT, O'Shaughnessy K, Kloeters O. Chronic Wound Pathogenesis and Current Treatment Strategies: A Unifying Hypothesis. Plast. Reconstr. Surg. 2006;117(Suppl.):35S

[50] Rezkalla SH, Kloner RA. No-reflow phenomenon. Circulation. 2002;105(5):656-62

[51] Weiss SJ.Tissue destruction by neutrophils. N Engl J Med 1989;320(6):365-76.

[52] Salcido R, Donofrio JC, Fisher SB, LeGrand EK, Dickey K, Carney JM, Schosser R, Liang R. Histopathology of pressure ulcers as a result of sequential computer-controlled pressure sessions in a fuzzy rat model. Adv Wound Care. 1994;7(5):23-40

[53] VandeBerg JS, Rudolph R. Pressure (decubitus) ulcer: variation in histopathology-a light and electron microscope study. Hum Pathol. 1995;26(2):195-200.

[54] Bohm E, Kuhlman I, Bótel U. Das druckgeschwür bei Querschnittgelähmten- eine vergleicehnde klinisch-histologische Untersuchung. Unfallchirurgie 1988;14(6):335-42

[55] Krouskop TA, Williams R, Krebs M, et al. Effectiveness of mattress overlays in reducing interface pressures during recumbency. J Rehabil Res Dev 1985;22:7-10.

[56] Reddy NP, Cochran GVB, Krouskop TA. Interstitial fluid flow as a factor in decubitus ulcer formation. J Biomech 1981;14:879-81

[57] Bouten CV, Oomens CW, Baaijens FP, Bader DL.The etiology of pressure ulcers: skin deep or muscle bound? Arch Phys Med Rehabil. 2003;84(4):616-9

[58] Stekelenburg A. mechanisms associated with deep tissue injury induced by sustained compressive loading. Thesis Technische Universiteit Eindhoven. Eindhoven The Netherlands 2005

[59] Calianno C. Assessing and preventing pressure ulcers. Adv Skin Wound Care 2000;13(5):244-6

[60] Staats WE, Cioschi HM, Jacobs B. Rehabilitation approach. 114-128. From: The Decubital Ulcer in Clinical Practice. Ed. LC Parish, JA Wikowski, JT Crissey. Springer-Verlag.

[61]Haalboom JRE. Decubitus, een overzicht Mod. Medicin 1996;129-35

[62] Marum RJ, Meijer JH, Ribbe MW. The relationship between pressure ulcers and skin blood flow response after a local cold provocation.Arch Phys Med Rehabil. 2002;83(1):40-3

[63] Meijer JH, Germs PH, Schneider H, Ribbe MW. Susceptibility to Decubitus Ulcer Formation. Arch Phys Med Rehabil. 1984;75:318-23

[64] Nixon, J. The pathophysiology and aetiology of pressure ulcers In Morison, M.J. (Ed.) The Prevention and

Treatment of Pressure Ulcers, Mosby, Edinburgh. 2001;17-36.

[65] *Schoonhoven L. Prediction of pressure ulcers: problems and prospects. Thesis,Utrecht University, Utrecht, The Netherlands, 2003*

[66] *Haalboom JR, den Boer J, Buskens E. Risk-assessment tools in the prevention of pressure ulcers. Ostomy Wound Manage. 1999;45(2):20-6*

[67] *VandenBosch T, Mosher C, Sevo D. pressure ulcer risk assessment- simple or complex? Decubitus 1992;5:47-52*

[68] *Atherton DJ. A review of the pathophysiology, prevention and treatment of irritant diaper dermatitis. Curr Med Res Opin. 2004;20(5):645-9*

[69] *Allman RM, Goode PS, Patrick MM, Burst N, Bartolucci AA: Pressure ulcer risk factors among hospitalized patients with activity limitation.JAMA 1995;273:865–870.*

[70] *Hogkinson B, Nay R, wilson J. A systemic review of topical skin care in aged care facilities. J Clin Nursing 2006;16:129-36*

[71] *Berlowitz DR, Wilking SV. Risk factors for pressure sores: A comparison of cross-sectional and cohort-derived data. J Am Geriatr Soc 1989;37: 1043-1050.*

[72] *Bergstrom N, Braden B. A prospective study of pressure sore risk among institutionalized elderly. J Am Geriatr Soc 1992;40:747-758*

[73] *Pinchcofsky-Devin G, Kaminski M. Correlation of pressure sores and nutritional status. J Am Geriatr Soc 1986;34:435-440*

[74] *Visvanathan R. Under-Nutrition in Older People: A Serious and Growing Global Problem! JPGM 2003;49(4):352-360*

[75] *Thomas DR. Prevention andTreatment of Pressure Ulcers J Am Med Dir Assoc 2006;7:46-59*

[76] *Clark M, Rowland LB, Wood HA, Crow RA. Measurement of soft tissue thickness over the sacrum of elderly hospital patients using B-mode ultrasound. J Biomed Eng 1989;11(3):200-2*

[77] *Lindan O. Etiology of decubitus ulcer: an experimental study. Arch Phys Med Rehabil 1961;42:774-83.*

[78] *Takeda T, Koyama T, Izawa Y, et al. Effects of malnutrition on development of experimental pressure sores. J Dermatol 1992;19:602-609.*

[79] *Thompson C, Furhman P. Nutrion and wound healing: Still searching for the magic bullet. Nutr Clin Pract 2005;20(3):331-47*

[80] *Arnold M, Barbul A. Nutrition and Wound Healing. Plastic & Reconstructive Surgery. 2006:117(7S) ;42S-58S*

[81] *Lpz Rapportage resultaten. 2006 Halfens, R.J.G., Janssen, M.A.P., & Meijers, J.M.M. (ed); Rapportage Landelijke Prevalentiemeting Zorgproblemen. Datawyse / Universitaire Pers Maastricht.*

[82] *Laat E. de Critical Pressure. pressure ulcer care in critically ill patients and hospitalised patient at large. Thesis Radboud University. Nijmegen The Netherlands 2006*

[83] *Bergstrom N Braden B, Kemp M, Champagne M, Ruby E. Multi-site study of pressure ulcers and the relationship between risk level, demographic characteristics, diagnoses and rescription of preventive interventions. J Am Geriatr Soc. 1996:44; 22-30.*

[84] *Westrate JTM. The value of pressure ulcer risk assessment and interface pressure measurements in patients. A nursing perspective. Thesis, Erasmus university rotterdam, rotterdam, the Netherlands, 2005.*

[85] *Bouten CV, Knight MM, Lee DA, Bader DL. Compressive deformation and damage of muscle cell subpopulations in a model system. Ann Biomed Eng 2001;29:153-63*

[86] *Bouten CV, Oomens CW, Baaijens FP, Bader DL.The etiology of pressure ulcers: skin deep or muscle bound?Arch Phys Med Rehabil. 2003;84(4):616-9*

[87] *Parish LC, Lowthian PT, Witkowski JA.Brouhaha across the atlantic: decubitus ulcers defy description. Skinmed. 2005;4(5):262-4.*

Chapter 2

Is the distinction between superficial pressure ulcers and moisture lesions justifiable? A clinical-pathological study.

Ronald H. Houwing, Jan Willem Arends, Marijke R. Canninga-van Dijk, Eddy Koopman, Jeen R.E. Haalboom

Skinmed 2007;6(3):113-7

In a prospective, observatory study, we performed a histopathological study of 14 admitted patients with superficial skin defects in combination with incontinence. These forms of early superficial pressure ulcers are singled out as a distinct entity by a statement of the European Pressure Ulcer Advisory Panel (EPUAP). In this study we investigate whether there is a justification for this statement. This study was performed in an acute care hospital, Deventer Ziekenhuis, Deventer the Netherlands.

Abstract

Pressure ulcers are classified into four distinct stages, allowing comparisons between institutions and even countries. Recently, attempts have been made to single out so-called 'moisture-lesions' from early stages of pressure ulcer lesions as a distinct entity. In order to investigate the justification for this development, 14 histopathological samples from patients with both incontinence and pressure ulcer lesions were studied, trying to delineate differences in the pathophysiology and histopathology.

Two distinct histopathological pictures emerged: an ischemic pattern and a pattern of irritation. The latter appeared to be associated with lesions that clinically fitted the description of moisture lesions, but this association was not absolute. It is concluded that there is no justification for singling out moisture lesions from pressure ulcer lesions. The distinction is even dangerous when proper preventive measures for the development of pressure ulcers are not taken because of the existence of a possible moisture lesion.

Introduction

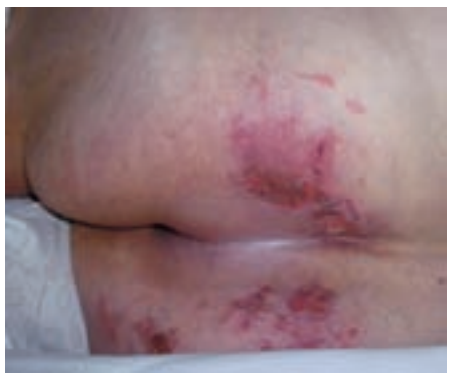
Pressure ulcers, varying from superficial lesions characterized as non-blanching erythema to deep ulcers, are areas of localised damage to the skin and underlying tissue caused by pressure, shear, or friction, or a combination of these. [1] [2] Apart from the personal suffering of the patients pressure ulcers form a major burden for current healthcare, especially when costs are concerned. The four-stage classification system, enabling bed-side clinical staging by all personnel involved with the treatment of patients, has become a subject of debate.[3] [4] [5] Although the European Pressure Ulcer Advisory Panel (EPUAP) in 2005 added a distinct other form of lesions, the so-called moisture lesion, to the 4 stages model, the moisture lesions is not based on pathological characteristics.[6] This new description of skin lesions due to pressure, shear and/or friction is subject of debate.

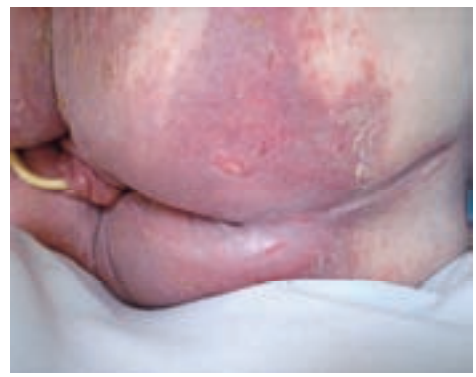
Observing skin lesions, especially when localized on typical pressure ulcer-locations such as the sacral area, it was conceived that they were not caused by classic factors such as pressure, friction and shear, but merely by the presence of moisture, caused by transpiration and/or incontinence of urine and/or faeces. Formerly these defects were often diagnosed as superficial, grade 2 pressure ulcers. Differentiation between these two types of lesions and etiology was thought to be of clinical importance since prevention and treatment strategies differ largely and have consequences for the outcome for the patient. [6] It also implies that recordings of prevalence and/or incidence in institutions of pressure ulcers depend on these distinctions. Since there is an increasing tendency to judge the quality of care in institutions based on these data, the identification of so-called moisture lesions implies less pressure ulcers and could provide a false picture. More moisture lesions result in less pressure ulcers. It is therefore important to investigate whether moisture lesions, until now not defined in the international classification of diseases (ICD), form a definite entity or are a representation of already known entities, and whether, if existent, they could be distinguished from pressure ulcers and other lesions.[7] Against this background we performed a clinical and histopathological study of superficial skin defects associated with moisture or pressure.

Methods

A prospective observatory study was designed to determine whether there is a difference between pressure ulcers and other lesions, characterized as moisture lesions.
Fourteen bedridden consecutive patients; mean age 74,1 years (11-94); 5 males, 9 females; admitted to Deventer Hospital all with a history of incontinence for urine and/or faeces, were seen by a nurse specialised in wound care and pressure ulcers (E. K.) and by a dermatologist (R.H.H.) because of skin defects on sacrum and/or buttocks. The clinical presentation differed from lesions with a non-blanching erythema or blanching

erythema. Following EPUAP descriptions a non-blanching erythema was diagnosed whenever an erythema did not blanch following the release of pressure that had been applied for longer than 10 minutes or turn white with the light pressure of a finger.
Of the 13 patients with blanchable erythema, 11 patients had superficial (partial thickness skin loss) ulcers, with diffuse or irregular edges, not located over a bony prominence.





Picture 1 Picture 2:

Picture 1:Partly non-blanchable erythema with superficial skin loss, in the combination with a grade 1 PU
Picture 2: Blanchable erythema with superficial skin loss 'moisture lesion'

Seven patients, in addition, showed ridging of the skin, perpendicular to the cleft, with a wrinkling appearance. According to the EPUAP classification the diagnosis differed from the combination of a pressure ulcer grade 1 with a moisture lesion 1 patient, that of a grade 4 in 1 patient with a blanchable erythema and a palpable deep induration, and that of moisture lesions in 12 patients with a blanchable erythema with or without superficial skin loss not located above a bony prominence.

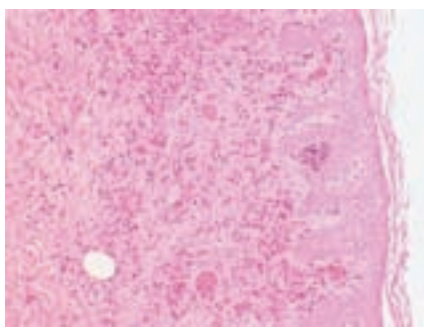
The goal of the study was explained, and informed consent was obtained. After administration of local anaesthesia (2% Lidocaïne with epinephrine) a 3 to 5 mm punch skin biopsy was taken 5 mm away from the superficial skin defect, if present. The patient with a grade 1 PU, the biopsy was taken from a non-blanchable erythema part of the skin. The biopsy wound was covered with a sterile bandage for at least 4 hours.

Beside proper skin care, consisting of frequent changes of the absorbent pads, the application of a barrier cream and, if possible, the treatment of the incontinence problem, the EPUAP guidelines for pressure ulcer treatment were strictly followed i.e., effective

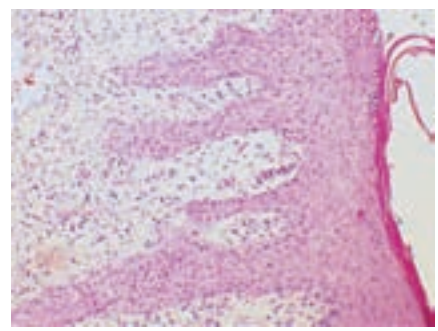
prevention of the development of pressure ulcers by change of body position every 2-3 hours and the use of a pressure-redistributing device. [1] Special attention was paid to the avoidance of shear and friction forces, by positioning patients in a semi-Fowler position. In all patients the biopsy wounds healed by second-intention, completely within 5-7 days. The skin biopsies were fixed in 4% buffered formalin and embedded in paraffin. Four micron thick sections were cut and stained with standard haematoxylin / eosin. The histopathological specimens were reviewed by three of the authors blinded to each others' evaluation and all unknown of the clinical descriptions (RHH; JWA; MC-vD).

Results

Clinical and histopathological appearances are listed in table I. Histopathologically two distinct patterns were found. **Pattern 1** showed the picture typical for ischemia. **Pattern 2** a picture with chronic irritation.



Pattern 1



Pattern 2

Pattern 1 H/E X 250, patient of picture 1. Ischemic pattern, with a partially avital epidermis, oedema in the more superficial layers of the dermis with vascular dilatation, engorgement of erythrocytes in the small vessels, extravasation of erythrocytes and a diffuse infiltration of polymorphonuclear cells.

Pattern 2 H/E X 250, patient of picture 2, irritative pattern showing a hyperplastic epidermis, with a partial loss, with elongated rete ridges, dilated vessels with some swelling of endothelium, oedema of the dermis and a perivascular histiocytic infiltration.

In two patients there was partial loss of the epidermis with some secondary infection and bacteria in the stratum corneum. From the data presented in the Table, it appears that pressure ulcers grade 1 and 4 are associated with the ischemic histopathological pattern, whereas in the case of blanchable erythema diagnosed as moisture-lesions, both the ischemic histopathological pattern and the chronic irritation pattern were observed.

No	Clinical diagnosis according to EPUAP Statement [1]	Clinical appearance	N0 Ischemic pathology.	N0 Chronic irritation.
12	Moisture lesion	Blanchable erythema with/or without superficial ulceration.	4	8
1	pressure ulcer grade 4	Blanchable erythema, superficial ulceration and a deep palpable induration.	1	-
1	Combination pressure ulcer grade 1 with a moisture lesions	Non-blanchable erythema without skin loss blanchable erythema with superficial ulceration	1	-

Table I Clinical picture and histological results.

The superficial ulcers and non-blanchable erythema in 12 patients vanished gradually within 21 days. One patient with originally a blanchable erythema and superficial skin loss developed a full thickness wound, grade 3 pressure ulcer, together with a clinically deteriorating condition. Another patient, presenting with a blanchable erythema and a deep palpable induration demonstrated the development of more extensive skin loss with a deep wound (grade 4 pressure ulcer). Due to renal insufficiency, the patient died after 4 weeks admission in hospital.

Discussion

In the present study an attempt was made to obtain more insight in the histopathological changes of superficial pressure ulcers, with the purpose to see whether it is possible to make a distinction between pressure ulcers and so-called moisture lesions. It is important to recognize the early presentations of pressure ulcers, as identification in an early stage allows the timely and effective start of preventive measures and stops the deterioration into more severe stages. Risk assessment scales have been shown to have a low capability to predict the occurrence of pressure ulcers.[8] Recognition of the clinical picture of early pressure ulcer injury, however hardly to recognize in dark skin, is essential. The distinction between pressure ulcers and other lesions, not caused by pressure, not only determines the correct use of costly preventive measures, but also is important in prevalence recordings, since the occurrence of pressure ulcers is more and more considered to be an indicator of the quality of (nursing-) care of institutions. Accurate diagnosis may have legal consequences because pressure ulcers may be considered to be caused by inefficient medical and/or nursing care. During the last decade, there has been a trend to warding determining budgets of institutions using epidemiological data. The more a complication occurs, the lower the budget: lack of quality is 'punished'. This may be counterproductive. Facilities practicing quality care but managing patients with higher risk of developing pressure ulcers are likely to suffer budget cuts in this scenario. This shifts funds away from those patients at greatest need

for resources to alleviate their risk factors. The incidence or prevalence of pressure ulcer in this way is used as an indicator of the quality of care. Stage 1and 2 pressure ulcers typically account for 60-75% of all pressure ulcers. The distinction of other lesions, non-pressure ulcers, caused by other mechanisms such as for instance moisture, directly influences these data. The number of pressure ulcers in prevalence recordings decreases and it looks like the institution concerned performs better. This phenomenon is more important than one assumes. Correct use of the pressure ulcer classification is needed when data are presented. Some years ago prevalence rates as low as 3% were found in Italy and Germany, while in Great Britain and the Netherlands a high figure of 20% was reported. This appeared not to be due to inferior care in the latter countries, but by the fact that in the former countries the first stage of pressure ulcers (non-blanchable erythema) in contradiction with the EPUAP definition was not considered to be a pressure lesion[9] Since preventive measures (such as the use of special mattresses and beds and the more intensive nursing care) are expensive, health care insurance companies and managers in institutions tend to misuse the current classification system in order to save money. [4] Furthermore, lawyers have started to use the pressure ulcer classification to determine the so-called 'neglect' on the part of health providers or to determine the amount of monetary compensation that should be awarded to families (the development of more serious wounds from less severe stages). [4] Differentiation in superficial forms of pressure ulcers, therefore, has financial and juridical consequences and above all, it is of eminent importance for the clinical outcome of patients, as therapeutic strategies should be customized to address each patient's salient risk factors. We have performed a clinical-pathological study of superficial forms of pressure ulcers. In our clinical-pathologic study of superficial forms of pressure ulcers, 14 lesions clinically fit in the diagnosis pressure ulcer and moisture lesion. In these cases, biopsies were performed and analyzed. The histopathological results could be divided into two distinct patterns. One pattern was characterized by signs of ischemia and necrosis probably caused by pressure, in line with the description of non-blanchable erythema by Witkowski.[10] The other pattern was characterized by signs of chronic irritation, probably caused by shear and/or friction, a picture consistent with senile gluteal dermatitis, as described by Bos and de Koning.[11] It proved to be impossible to predict the histopathological pattern on the basis of the clinical picture. An ischemic process may also occur in a patient with a blanchable erythema and superficial skin loss. In our opinion, it is therefore impossible to differentiate moisture lesions from superficial pressure ulcers. Also, it is questionable whether a distinction can be made based on the pathophysiology, since many of the pathophysiological components are shared in both conditions. The pattern with the hyperplastic changes of the epidermis with dilated capillaries is probably caused by shear and/or friction due to a half sitting position and therefore by chronic irritation. These

forces are increased in a moist skin.[12] Prolonged moistness leads to loss of water and maceration (softening) of the stratum corneum, together with an extensive disruption of intercellular lipid lamellae. This results in an impaired barrier function and the skin becomes more susceptible to external factors, like friction, shearing and pressure.[13] This process is augmented by the activity of destructive enzymes in the urine. Faecal proteases and lipase have been shown to play a major role in skin irritation and also in increasing the susceptibility of the skin to other irritants such as bile salts. This damage to the skin is known as irritative contact dermatitis. Dry or scaling skin has been found to be at least 2,5 times more likely to develop wounds from skin breakdown.[14] Incontinence alone should not lead to loss of the epidermis. Friction and shear are both needed to remove the necrobiotic or otherwise injured epidermis. Secondary infections of the skin due to loss of the barrier function, and decreased resistance may further augment the damage to the skin. Apart from pressure relief, preventive measures, such as proper skin care, the frequent changing of pads and drying of the skin to the air is essential in the prevention of deterioration of the condition of the skin. Incontinence is an indicator of a poor physical condition per se, and implies a significant risk factor for the development of pressure ulcers. Until now there is no proper classification system for pressure ulcers based on the pathogenesis.[5] The use of new diagnoses, such as moisture lesions and consequently subdividing superficial grade-1 and 2 pressure ulcer, will certainly not clarify the problem. It is more accurate and clinically useful to address excessive skin moisture as one of several validated risk factors for developing pressure ulcers, to be addressed as part of an evidence-based pressure ulcer prevention program.

In summary, in our opinion there is no justification for the introduction of a new entity such as moisture lesion. Introduction of this new diagnosis, not listed in the ICD-10 list, nor mentioned in medical textbooks, could, on the contrary, lead to diminished attention for the ever needed preventive measures.[7] It could even result in a higher incidence of pressure ulcers when correct preventive measures are not taken. Pressure, shear and friction avoidance is of eminent importance in the prevention of pressure ulcers. Especially in patients with validated pressure ulcer risk factors or experiencing pre-existing dermatoses that potentate these forces, meticulous skin care is essential. To enhance effectiveness of increasingly experienced nurses for both preventing and managing pressure ulcers, it is vital to add this knowledge to the multidisciplinary team. Consultation of dermatologists, the physicians with knowledge of skin diseases such as both dermatitis and pressure ulcers, is necessarily before introducing new diagnoses.

Acknowledgements: R.J. van Eck assisted with photography.

References

[1] *National Pressure Ulcer Advisory Panel. National pressure ulcer advisory panel. www.npuap.org*
[2] *Bansal C, Scott R, Stewart D, Cockerell CJ. Decubitus ulcers: A review of the literature. Int J Dermatol 2005;44:805-10*
[3] *Bethell E. Controversies in classifying and assessing grade I pressure ulcers. J Wound Care. 2003 Jan;12(1):33-6.*
[4] *Clark M. What drives pressure ulcer classification- scientific knowledge or fear of litigation? tissue viability society 2005 vol 15 no2 2005*
[5] *Parish LC, Lowthian PT, Witkowski JA.Brouhaha across the atlantic: decubitus ulcers defy description. Skinmed. 2005 Sep-Oct;4(5):262-4.*
[6] *Defloor T, Schoonhoven L, Fletcher J, et al. Statement of the European Pressure Ulcer Advisory Panel-Pressure Ulcer Classification: Differentation between pressure ulcers and moisture lesions Journal of Wound, Ostomy and Continence Nursing, 2005 - jwocnonline.com*
[7] *WHO ICD classifications. http://www.who.int/classifications/icd/en/*
[8] *Schoonhoven L, Haalboom JR, Bousema MT, et al. Prospective cohort study of routine use of risk assessment scales for prediction of pressure ulcers. BMJ. 2002 Oct 12;325(7368):797.*
[9] *O'Dea K.Prevalence of pressure damage in hospital patients in the UK. J Wound Care 1993; 2(4): 211-21*
[10] *Witkowski JA, Parish LC. Histopathology of the decubitus ulcer. J Am Acad Dermatol. 1982 Jun;6(6):1014-21*
[11] *Bos WH, Koning J de. A senile gluteal dermatosis caused by friction. European J Dermatol 1992;2:157-9*
[12] *Lowthian PT. Trauma and thrombosis in the pathogenesis of pressure ulcers. Clin Dermatol 2005;23:116-23*
[13] *Zhai, H. and HI Maibach, Moisturizers in preventing irritant contact dermatitis: an overview. Contact Dermatitis, 1998. 38: p. 241-244*
[14] *Ersser SJ, Getliffe K, Voegeli D, Regan S. A critical review of the inter-relationship between skin vulnerability and urinary incontinence and related nursing intervention.*
Int J Nurs Stud. 2005 Sep;42(7):823-35.

Chapter 3

Pressure ulcer risk in hip fracture patients

Ronald H. Houwing, Marja Rozendaal, Wendeline Wouters-Wesseling, Erik Buskens, Paul Keller, Jeen R.E. Haalboom

Acta Orthopaedica Scandinavica 2004;75(4):390–393

We evaluated a risk assessment tool for PU development in regard of sensitivity and specificity in hip fracture patients. This study was performed in three acute care hospitals in the Netherlands, St. Antonius Ziekenhuis, Nieuwegein; Rijnstate Ziekenhuis, Arnhem; Deventer Ziekenhuis, Deventer. This study was funded by Numico Research BV Wageningen, The Netherlands.

Abstract

Hip fracture patients have a high risk of pressure ulcers (PU). We followed 121 hip fracture patients for the development of pressure ulcers and evaluated a risk assessment tool for sensitivity and specificity. More than half of the patients presented with PU, mostly stage I. Risk factors for PU were high age and the length of time on the operating table. The risk assessment tool had a low predictive value, however. It is thus hard to predict which patients will develop PU and which will not. Accordingly, we propose maximum preventive measures against PU for all patients presenting with hip fractures.

Introduction

Pressure ulcers (PU) are frequently seen in hip fracture patients. Early studies noted a high prevalence, but these were difficult to compare due to differences in the definition of PU. [1] (Table 1) PU causes much suffering and high costs. [2 3] Pressure ulcers result from a combination of factors, including those affecting the susceptibility of the skin, such as low vascular supply and nutritional deficiencies. In addition, the presence of constant pressure, the imposition of shear force or friction to the skin and reduced mental awareness are recognized risk factors. [4] In this prospective study, we have investigated the incidence of PU in patients after a hip fracture. Our aim was to obtain more information on the incidence and moment of onset of PU in hip fracture patients. By using a risk assessment tool for PU, we hoped to predict what kind of patients are at higher risk of developing PU and to determine what kind of preventive measures could be taken to reduce the likelihood of PU occurring. [5]

Table 1. Incidence of PU in earlier studies

Reference	%Pu[a]	Notes
Ferris 1983	47	stage 1 not included
Versluysen 1986	43	23% PU stage 1
Jensen & Juncker 1987	30	stage 1 not included

[a]Stage 2 or more

Patients and methods

The study was performed in three general hospitals, i.e., Deventer Hospital (Deventer), Rijnstate Hospital (Arnhem) and St. Antonius Hospital (Nieuwegein), the Netherlands. Consecutive patients admitted with a hip fracture were invited to take part in the study. Exclusion criteria were terminal care and metastatic hip fracture. The study protocol was approved by the Ethics Committees of the three hospitals. Written informed consent was obtained from each patient. If the mental capability of the patient to decide on participation was uncertain, the legal representative of the patient was asked for consent. Measures for pressure ulcer prevention, such as pressure reducing mattresses and beds, regular reposition and mobilization, were provided in all hospitals according to the Dutch consensus protocol for the prevention of pressure ulcers. [6] All patients were investigated by medical staff for the presence of pressure ulcers on a daily basis, from

admission to discharge. The four-stage classification system of pressure ulcers according to the Treatment Guidelines of the European Pressure Ulcer Advisory Panel was used. [7] Specific instructions were given for recognition of stage 1 (non-blanching erythema of intact skin) pressure ulcers: only when the erythema did not disappear after diascopy with a plastic tongue depressor was it classified as stage 1. Time of onset, location and size of PU were recorded. Clinical data such as diagnosis, date of operation, date of the incident fracture, type of operation, time on the operating table, medication, medical history and pressure ulcer prevention procedures were collected. The likelihood of developing pressure ulcers was assessed using the risk assessment scale described by the Dutch Consensus Meeting. [8] (CBO) 10 items considered to have an influence on the development of PU were scored from 0 (low risk) to 2 points (high risk). The higher the sum, the higher the risk of developing PU. Statistical evaluation was performed using the Mann-Whitney or t-test. Statistical analysis was performed using SPSS for Windows, version 10. (SPSS Inc., IL, USA).

Results

179 patients were approached about participation. 58 patients were not included due to the various exclusion criteria. Informed consent was obtained from 121 patients (Table 2). 64 (53%) of the 121 patients developed PU, but only of stages 1 and 2. Patients with PU were significantly older, were at a significantly higher risk according to the risk assessment tool used, and the time spent on the operating table had been longer. There was no statistically significant difference between patients with and without pressure ulcers regarding the time elapsed between the accident and the admission or operation (Table 2). Only 1 patient developed PU before the day of operation. A prolonged length of time on the operating table was associated with higher incidence of PU, but statistically the kind of surgical technique, whether internal fixation (n = 70) or hemiarthroplasty (n = 51), had no influence on the likelihood of developing PU.

Most PU developed during the first 4 days after the operation. Most of the ulcers were smaller than 15 cm2 and their location was in accordance with known high risk areas such as sacral region (16%), trochanters (26%) and heels (43%). The risk assessment tool was unable to predict the likelihood of developing PU (Table 3).

Table 2. General characteristics and differences between patients who developed PU and those who did not

	Entire study group (n=121) Mean (SD)	PU (n=64) Mean (SD)	Non-PU (n=57) Mean (SD)	P-value
Sex Males	26	15	11	
Females	95	49	46	
Mean age	80 (8)	82 (8)	78 (9)	0,03[a]
Mean body mass index (kg/m²)	24,2 (3.2)	23,7 (3,1)	24,5 (3,3)	0,2[o]
Mean pressure ulcer risk score	10,4 (2,3)	11,0 (2.1)	9,7 (2,3)	0,001[a]
Mean duration of operation (h)	1,44 (0.44)	1,52 (0,41)	1,36 (0,38)	0,04[a]
Maximum stage PU				
0	57 (47%)			
1	40 (33%)			
2	24 (20%)			
Number of days between				
accident and admission	0,4 (1.7)	0,3 (1,3)	0,5 (2,2)	0,3[a]
accident and operation	1,0 (2.3)	1,1 (2,2)	1,0 (2,4)	0,2[a]
admission and operation	0,7 (1.5)	0,6 (0,8)	0,7 (1,9)	0,5[a]
operation and the first day of PU	4,4 (3.8)			

[a]Mann-Whitney U test
[o]bt-test

Table 3. Individual determinants of the pressure ulcer risk score

	Score 0 n % PU		Score 1 n % PU		Score 2 n % PU		Score 3 n % PU	
Medication	3	33	111	53	6	50	1	100
Mobility	2	50	14	43	24	38	81	59
Mental condition	62	35	42	67	16	69	0	0
Neurology	90	52	25	52	5	60	0	0
Circulation	49	43	59	59	5	80	0	0
Nutritional status	90	49	28	66	1	0	0	0
Incontinence	26	46	9	33	79	54	3	100
Diabetes	109	51	3	100	6	67	2	50
Temperature	40	58	73	52	4	25	1	0
Age	1	0	1	0	12	33	107	56

Discussion

Despite the use of preventive measures and early mobilization after surgery, there is still a high incidence of PU as found in earlier studies. [9] [10] [11] These studies are hard to compare due to a discrepancy in the definition of the stages of pressure ulcers used.
Definitions of PU as proposed by both the National and European Pressure Ulcer Advisory panels (Table 1) should be followed. [12] The risk assessment tool used has low discriminative capability, as seen also in a previous study. [13] We can only improve prediction by additional research focused on factors actually associated with formation of PU. A prolonged stay in an emergency and radiology department is a risk factor for the development of PU, as is a prolonged surgical procedure. [14] [15] We recommend that the use of pressure-reducing mattresses should start immediately at admission, and the use of pressure-reducing operating table overlays, special adjustments for heel protection (heels being responsible for more than 40% of the pressure ulcers in this study) and of pressure-reducing positions during operation. Since a risk assessment tool appears to be of limited value, and as the incidence of PU is high, our advice would be to give all hip fracture patients maximum preventive treatment against PU including beds and mattresses, regular reposition, mobiliza
tion and nutritional supplements.

The study was sponsored by Numico Research. We thank Dr. A.P.P.M. Driessen for his helpful comments. We also thank Johan Wilms of Deventer Ziekenhuis, Deventer, Dr. Van Ramshorst of St. Antonius Ziekenhuis, Nieuwegein, and Eliza Jolink, Bea Zomer Ziekenhuis Rijnstate, Arnhem for their assistance in performing the study.

References

[1] *Ferris B. Decubitus ulceration following prosthetic implantation for t traumatic subcapital fractured neck of femur. A preventable condition? Br J Clin Pract 1983; 37 (5): 175-7.*

[2] *Boereboom F.T., de Groot R.R., Raymakers J.A., Duursma S.A.. The incidence of hip fractures in The Netherlands. Neth J Med 1991; 38 (1-2): 51-8.*

[3] *Kannus P., Parkkari J., Sievanen H., Heinonen A., Vuori I., Jarvinen M. Epidemiology of hip fractures. Bone (1 Suppl) 1996: 1857S-63S.*

[4] *National Pressure Ulcer Advisory Panel (NPUAP). Etiology, assessment, and early intervention. Dermatol Nurse 1996; 8: 41-7.*

[5] *Haalboom J.R.E., den Boer J., Buskens E. Risk assessment tools in the prevention of pressure ulcers. Ostomy Wound Manage 1999; 45: 20-34.*

[6] *Haalboom J.R.E., Bakker H. Herziening consensus preventie en behandeling decubitus Ned tijdschr Geneesk 1992; 136: 1306-8.*

[7] *National Pressure Ulcer Advisory Panel (NPUAP). Etiology, assessment, and early intervention. Dermatol Nurse 1996; 8: 41-7.*

[8] *Haalboom J.R.E., Bakker H. Herziening consensus preventie en behandeling decubitus Ned tijdschr Geneesk 1992; 136: 1306-8.*

[9] *Ferris B. Decubitus ulceration following prosthetic implantation for t traumatic subcapital fractured neck of femur. A preventable condition? Br J Clin Pract 1983; 37 (5): 175-7.*

[10] *Versluysen M. How elderly patients with femoral fracture develop pressure sores in hospital. Br Med J (Clin Res Ed) 1986; 292 (6531): 1311-3.*

[11] *Jensen T.T., Juncker Y. Pressure sores common after hip operations. Acta Orthop Scand 1987; 58 (3): 209-11.*

[12] *National Pressure Ulcer Advisory Panel (NPUAP). Etiology, assessment, and early intervention. Dermatol Nurse 1996; 8: 41-7.*

[13] *Schoonhoven I., et al. Prospective cohort study of routine use of risk assessment scales for prediction of pressure ulcers. BMJ 2002; 325: 797. Url:http://bml.com/cgi/content/full/325/7368/797.*

[14] *Mullineaux J. Cutting the delay reduces the risk. Assessment of the risk of developing pressure sores among elderly patients in A&E. Prof Nurse 1993; 9 (1):22-30.*

[15] *Grous C.A., Reilly N.J., Gift A.G.. Skin integrity in patients undergoing prolonged operations. J Wound Ostomy Continence Nurs 1997; 24 (2): 86-91.*

Chapter 4

A randomised, double-blind assessment of the effect of nutritional supplementation on the prevention of pressure ulcers in hip-fracture patients

R.H. Houwing, M. Rozendaal, W. Wouters-Wesseling, J.W.J. Beulens, E. Buskens, J.R. Haalboom

Clinical Nutrition 2003; 22(4): 401–5

This study was performed in three acute care hospitals in the Netherlands, St. Antonius Ziekenhuis, Nieuwegein; Rijnstate Ziekenhuis, Arnhem; Deventer Ziekenhuis, Deventer. This study was funded by Numico Research BV Wageningen, The Netherlands.

Abstract

Background & aims

Malnutrition is a risk factor for development of pressure ulcers (PU). Nutritional supplementation may thus reduce the incidence of PU. We investigated the effect of nutritional supplementation on incidence of PU in hip-fracture patients at risk of developing PU.

Methods

Hip-fracture patients (n=103) were included in this double-blind, randomised, placebo-controlled trial. They received 400ml daily of a supplement enriched with protein, arginine, zinc and antioxidants (n=51) or a non-caloric, water-based placebo supplement (n=52). Presence and stage of PU were assessed daily for 28 days or until discharge (median:10 days during supplementation).

Results

Incidence of PU was not different between supplement (55%) and placebo (59%), but incidence of PU stage II showed a 9% difference (difference: 0.091; 95% CI: 0.07-0.25) between supplement (18%) and placebo (28%). Of patients developing PU 57% developed it by the second day. Time of onset (days) showed a trend (P=0.090) towards later onset of PU with supplement (3.670.9) than placebo (1.670.9).

Conclusions

Hip-fracture patients develop PU at an early stage. Nutritional supplementation may not prevent PU at this stage, but contributes possibly to a delayed onset and progression of PU. Nutritional supplementation may be more effective if initiated earlier.

Introduction

Pressure ulcers (PU) are a frequently encountered problem in health care centres, especially in nursing and rehabilitation homes.[1] The incidence of PU in different types of health care centres in the Netherlands varies from 18% to 44%.[1] Patients with hip fractures are especially at risk of developing PU. The incidence of PU in patients with a hip fracture ranges from 32% to 66%.[2 3] A recent study of Gunningberg et al. showed an incidence of 55% in these patients, which decreased to 29% by improving quality of PU care in this centre.[4] This shows that despite the important role of preventive measures, PU is still a common problem among hip-fracture patients. Unrelieved pressure, shearing forces and friction cannot account for the whole pathogenesis of PU. Endogenous conditions predisposing to PU such as old age, diabetes, terminal illness, sepsis, neurological and vascular disease are also involved.[5] Other risk factors include incontinence, immobility, altered mental status, lower blood pressure and higher body temperature.[6 7 8] Malnutrition is also thought to be an important risk factor for the development of PUs. It has been shown that several indices of malnutrition are associated with developing PU.[9] Prospective studies comparing the development of PU of non-malnourished with malnourished patients showed a higher incidence of PUs in the latter patients.[10] The elderly are often malnourished and patients with fractured proximal femur seem especially undernourished.[11 12 13] These patients may thus benefit from nutritional supplementation to influence the development of PU. Earlier prospective trials, however, showed inconsistent results on the preventive effect on PU of nutritional supplementation.[14 15 16] One study compared the effect of supplemental tube feeding with no supplemental feeding in patients with a hip fracture.[16] Because tube feeding was not well tolerated in this study, the results showed no effect of nutritional supplementation on the development of PU. Another study showed a decreased risk of developing PU when a nutritional supplement of 400 kcal was given daily compared to no nutritional supplementation.[14] Both studies, however, were not designed as double blind, placebo-controlled trials. Therefore this study 401 investigates the effect of a high-protein supplement enriched with arginine, zinc and antioxidants on the development of PU in patients with a hip fracture in a double-blind, placebo-controlled design.

Materials and methods

Design and patients

Between April 1998 and December 1999 a randomised, double-blind, placebo-controlled study was performed in three centres in the Netherlands. The Medical Ethical Committee of all participating centres approved of the study protocol. All patients with a hip fracture were eligible for enrolment. Risk of developing PU was assessed with the Dutch Consensus Meeting scoring system and patients with a PU risk score over 8 according to

the CBO-risk-assessment tool were included in the study.[17] This is a four-point scoring tool including the following 10 items: mental status, neurology, mobility, nutritional status, nutritional intake, incontinence, age, temperature, medication and diabetes. The following exclusion criteria were used: terminal care, metastatic hip fracture, insulin-dependent diabetes, renal disease (creatinine 4176 mmol/l), hepatic disease, morbid obesity [BMI 440], need for therapeutic diet incompatible with supplementation and pregnancy or lactation. Patients were included in the study immediately postoperatively. Written informed consent was obtained from all patients or their legal representatives. The sample size for this study was calculated based on an incidence of PU in hip-fracture patients with a risk score 48 of 40%, with 80% con.dence and accepting an a of 5%. In order to detect a 25% difference in PU incidence between treatments 350 patients per group would have to be included in the study.

Diets

Patients were randomised to receive the study or placebo supplement in addition to their regular diet. The study supplement was a high-protein nutritional supplement enriched with arginine, zinc and antioxidants (Cubitan s, N.V. Nutricia, the Netherlands) as these nutrients may be beneficial for prevention and treatment of Pus.[10] The placebo supplement was a non-caloric, waterbased drink containing only sweeteners, colorants and flavourings. Look and taste of both supplements were not exactly identical, but supplements were given in similar, blinded packages to mask the differences. The composition of both supplements is shown in Table 1. Patients received 400 ml daily between regular meals of either the study or placebo supplement starting immediately postoperatively for a period of 4 weeks or until discharge. Intake of the supplements was recorded daily by nursing staff.

Assessments

At study entry age, sex, weight, height, haemoglobin, type of surgery (internal exaction or hemiarthroplasty), duration of stay on operation table, medication and Decubitus risk score [17] were recorded. The presence of PU on tail-bone, heels, buttocks and other places was assessed daily by nursing staff according to the fourstage classification system of PU defined in the Treatment Guidelines of the European Pressure Ulcer Advisory Panel (Table 2).[18] The highest PU stage a patient reached was recorded. Specific instructions were given for Stage I; only when erythema did not disappear after diascopy with a plastic tongue depressor it was classified as stage I. Time of onset and size of PU at the different locations were recorded as well.

Statistical analysis

Data analysis was performed using SPSS 10.0 for Windows. The distribution of variables was evaluated visually and by a Kolmogorov–Smirnov test. Differences between both supplements of continuous variables were determined by a Students' t-test for independent samples or Mann–Whitney U-test (if variable was not distributed normally). Differences between both supplements of incidence rates of PU were determined by a Fisher's exact test. As the development of PU is related to age and length of stay on operation table (unpublished data), results were adjusted for age or length of surgery by analysis of variance. Differences were regarded significant when two-tailed P-values were below 0.05. Data are reported as means 7 SEM.

Table 1 Nutritional composition of 100 ml supplement and placebo

Nutrient	Supplement	Placebo
Energy (kcal)	125	0
Protein (g)	10.0	0
l-arginine (mg)	1.5	0
Zinc (mg)	5.0	0
Vitamin C (mg)	125.0	0
Vitamin E (mg a-TE)	50.0	0
Carotenoids (mg)	1.0	0

Table 2 Classification of pressure sores: definitions by the European Pressure Ulcer Advisory panel, 2nd general meeting, Oxford (UK), September 1998.[18]

Stage I	Non-blanch able erythema of intact skin. Discoloration of the skin, warmth, oedema, in duration or hardness may also be used as indicators particularly on individuals with darker skin.
Stage II	Partial thickness skin loss involving epidermis, dermis or both. The ulcer is superficial and presents clinically as an abrasion or blister.
Stage III	Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through underlying fascia.
Stage IV	Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full thickness skin loss.

Results

One hundred and three patients complied with selection criteria and were included in the study. Fifty-two patients were randomised to receive placebo and 51 were randomised to receive supplementation. Supplementation was started as soon as patients were on oral intake again (median: 2 days after surgery and admission to hospital) and median time between start of supplementation and surgery or admission to hospital was not significantly different between both groups. Both formulas were well tolerated (Table 3). Approximately 70% of patients consumed supplementation for a week or more. Furthermore, approximately 75% of the patients consumed 75% or more of their daily dose. Patient characteristics are shown in Table 3. No significant differences between groups were found for these characteristics. Fifty-seven per cent of the patients in the total study population developed PU and 23% of the patients developed a PU of stage II. None of the patients, however, developed a PU grade III or worse. Of the patients who developed PU, 57% developed it already in the first 2 days of the study and 76% by the fourth day. Results of the development of PU ulcers in both study groups are shown in Table 4. In the placebo group incidence of PU was 59%, which was slightly higher than in the supplement group (55%) but not statistically significant (difference: 0.037; 95% CI: -0.16 to 0.23). The incidence of PU of stage II was 9% (difference: 0.091; 95% CI: -0.073 to 0.25) lower in the supplemented (18%) than the placebo group (28%), but this did not reach statistical significance (P=0.345). Time of onset, however, showed a trend (P=0.090) towards a later onset of PU in the supplement (3.670.9days) than the placebo group (1.670.9days). Similarly, number of days with prevalent PU was lower in the supplement than the placebo group, but again not statistically significant (P=0.307).

Discussion

Malnutrition is a recognised risk factor for PU formation. Hip-fracture patients are at risk of developing PU, not only due to immobilisation and surgery but also because of their poor nutritional status. Our study showed that supplementation of a high-protein supplement enriched with arginine, zinc and antioxidants might delay the onset and progression of PU in hip fracture patients at risk of developing PU. However, in the current population of acute patients no significant differences in total incidence of PU between the supplemented and placebo group were found. This may be a problem of insufficient power to show a significant difference in the incidence of PUs, because unfortunately we did not succeed to include a sufficient number of patients due to practical problems in performing the study. The study was designed according to a randomised, double-blind, placebo-controlled trial. Patient characteristics or compliance were not significantly different between both groups and are therefore not expected to distort findings in this study. Non-blanch able erythema indicating a stage I PU is difficult

to determine objectively, which may have led to false-positive diagnoses. However, this will probably have occurred to the same extend in both groups and thus will not result in a systematic bias. Possibly, random misclassification of stage I may to some extend explain the fact that differences in PU incidence between groups were only observed for stage II. The incidence of PU was quite high in our study population (57%), but within the range (32–66%) of previous reports (1–4). The incidence of PU was not significantly different between both supplements, but incidence of PU of stage II appeared 9% lower in the supplemented than the placebo group. This suggests that nutritional supplementation might delay the progress of existing PU into a higher stage. This is consistent with a study of Delmi et al. (15) in patients with a hip fracture, which showed no effect of 1 month nutritional supplementation in the first weeks after surgery, but only in the recovery period and until 6 months. Fifty-seven per cent of the patients developed PU in the first 2 days of the study, which is consistent with another study (2). Therefore, the supplementation period might not have covered the period most vulnerable to the development of PUs. Possibly, only the onset and progression of PUs has been delayed. Supplementation was started after surgery when patients were already admitted to hospital for 2 or more days. The reason we were not able to lower the PU incidence may thus lie in the fact that supplementation was started after the critical moment of PU formation (directly after surgery). We have shown in an animal study with pigs, PU can be seen as an ischaemia-reperfusion injury followed by inflammation and pre-treatment with vitamin E prevented it.[19] Inflammation only starts after cessation of a period of unreleased pressure. So, in order to prevent PU, nutritional supplementation should be started in an earlier stage, probably well before the critical event.

Most parameters of PU severity were slightly better in the supplemented group, but did not reach statistical significance. This is similar to the findings of Hartgerink et al. who found no statistical significant difference of PU incidence and severity between supplemental tube feeding and no supplemental feeding (16). Tube feeding, however, was not well tolerated in this study and only 16 patients actually received supplemental tube feeding for 2 weeks. This led to insufficient power to detect differences, but in the actually tube-fed patients PU incidence and severity indeed decreased. Another study compared the incidence of PU after supplementation of 400 kcal daily with no supplementation in 672 critically ill elderly patients. Results showed a significantly higher risk of developing PU (OR=1.57) when no nutritional supplementation was given (14). This figure is very close to the increased incidence we observed in the placebo group (28/18=1.55). Although the number of patients of our study is insufficient to draw firm conclusions, the results suggest that prophylactic use of a nutritional supplement enriched with protein, arginine, zinc and antioxidants possibly contributes to a delayed

onset and progression of PU in patients with hip fractures at risk of developing PU. More profound effects on prevention of PU may possibly be found by earlier initiation of nutritional supplementation; before the critical event of PU formation. Future studies should address this issue and can build on our experience.

Table 3 Patient characteristics of both study groups*

	Supplement (n=51)	Placebo (n=52)	P-value
Age (y)	81.5±0.9	80.5±1.3	0.528
Sex (f/m)	40/11	44/8	0.456
Risk score CBO	11.1±0.3	11.2±0.2	0.629
BMI (kg/m2)	24.2±0.5	23.7±0.5	0.512
Haemoglobin	7.1±0.2	7.1±0.2	0.803
Duration of stay on operation table (min)	104±6	106±6	0.778
Type of surgery (Int/Hemi)y	22/23	26/21	0.677
# days supplementation	11.8±1.2	12.5±1.3	0.699
Mean intake (%/day)	77±3	77±4	0.899

*Mean±SEM

Table 4 Development of PU after supplementation or placebo*

	Supplement (n=51)	Placebo (n=52)	P-value
Incidence (n/%)	27/55.1	30/58.8	0.420
Incidence stage I (n/%)	18/36.7	16/31.4	0.674
Incidence stage II (n/%)	9/18.4	14/27.5	0.345
First day PU	3.6±0.9	1.6±0.9	0.090
# days PU	4.4±0.9	5.0±0.9	0.307
Total max wound size (cm2)	1.6±0.3	2.2±0.4	0.232

Acknowledgements

We would like to thank patients and staff of the participating centres for their co-operation in this study; Dr. P. Keller, Dr. van Ramshorst (St. Antonius Ziekenhuis, Nieuwegein); Eliza Jolink, Bea Zomer Ziekenhuis (Rijnstate, Arnhem); Johan Wilms, (Deventer Ziekenhuis, Deventer). This study was funded by Numico Research BV, Wageningen, the Netherlands.

References

[1] *Bours G J J W, Halfsen, R J G, Joosten, C M C. Landelijk Prevalentie Onderzoek Decubitus; resultaten vierde jaarlijkse meting 2001. Maastricht: Universiteit Maastricht; Sectie verplegingswetenschap, 2001.*

[2] *Versluysen M. Pressure sores in elderly patients. The epidemiology related to hip operations. J Bone Joint Surg Br 1985; 67: 10–13.*

[3] *Versluysen M. How elderly patients with femoral fracture develop pressure sores in hospital. Br Med J (Clin Res Ed) 1986; 292: 1311–1313.*

[4] *Gunningberg L, Lindholm C, Carlsson M, Sjoden P O. Reduced incidence of pressure ulcers in patients with hip fractures: a 2-year follow-up of quality indicators. Int J Qual Health Care 2001; 13: 399–407.*

[5] *Bliss M, Simini B. When are the seeds of postoperative pressure sores sown? Often during surgery. Br Med J 1999; 319: 863–864.*

[6] *Allman R M, Laprade C A, Noel L B et al. Pressure sores among hospitalized patients. Ann Intern Med 1986; 105: 337–342.*

[7] *Bergstrom N, Braden B. A prospective study of pressure sore risk among institutionalized elderly. J Am Geriatr Soc 1992; 40: 747–758.*

[8] *Maklebust J, Magnan MA. Risk factors associated with having a pressure ulcer: a secondary data analysis. Adv Wound Care 1994; 7: 25, 27–28, 31–34 passim.*

[9] *Finucane T E. Malnutrition, tube feeding and pressure sores: data are incomplete. J Am Geriatr Soc 1995; 43: 447–451.*

[10] *Thomas D R. Improving outcome of pressure ulcers with nutritional interventions: a review of the evidence. Nutrition 2001; 17: 121–125.*

[11] *Bonjour J P, Schurch M A, Rizzoli R. Nutritional aspects of hip fractures. Bone 1996; 18: 139S–144S.*

[12] *Foster M R, Heppenstall R B, Friedenberg Z B, Hozack W J. A prospective assessment of nutritional status and complications in patients with fractures of the hip. J Orthop Trauma 1990; 4: 49–57.*

[13] *Murphy M C, Brooks C N, New S A, Lumbers M L. The use of the Mini-Nutritional Assessment (MNA) tool in elderly orthopaedic patients. Eur J Clin Nutr 2000; 54: 555–562.*

[14] *Bourdel-Marchasson I, Barateau M, Rondeau V et al. A multicenter trial of the effects of oral nutritional supplementation in critically ill older inpatients. GAGE Group. Groupe Aquitain Geriatrique d'Evaluation. Nutrition 2000; 16: 1–5.*

[15] *Delmi M, Rapin C H, Bengoa J M, Delmas P D, Vasey H, Bonjour J P. Dietary supplementation in elderly patients with fractured neck of the femur. Lancet 1990; 335: 1013–1016.*

[16] *Hartgrink H H, Wille J, Konig P, Hermans J, Breslau P J. Pressure sores and tube feeding in patients with a fracture of the hip: a randomized clinical trial. Clin Nutr 1998; 17: 287–2192.*

[17] *Haalboom J R, den Boer J, Buskens E. Risk-assessment tools in the prevention of pressure ulcers. Ostomy Wound Manage 1999; 45: 20–26, 28, 30–34.*

[18] *(NPUAP) NPUAP. Etiology, assessment and early intervention. Dermatol Nurs 1996; 8: 41–47.*

[19] *Houwing R, Overgoor M, Kon M, Jansen G, van Asbeck B S, Haalboom J R. Pressure-induced skin lesions in pigs: reperfusion injury and the effects of vitamin E. J Wound Care 2000; 9: 36–40. Submission date: 22 August 2002 Accepted: 19February 2003*

Chapter 5

Pressure-induces skin lesions in pigs: reperfusion injury and the effects of vitamin E

R. Houwing,, M. Overgoor, M. Kon, MD, G. Jansen, B.S. van Asbeck, J.R.E. Haalboom

Journal of Wound Care January 2000; 9 (1): 36-40

An animal model was developed to investigate the role of oxygen-derived-free-radicals (ODFR) in the pathogeneses of PU, and the possibility to diminish the tissue damage with an antioxidant. This study was performed in the academic hospital UMCU and the animal laboratory in Utrecht the Netherlands. This study was undertaken with financial support from the Dutch government (Prevention Fund).

Abstract

The pathogenesis of the development of pressure ulcers is still unclear. The aim of the study was to investigate the role of ischaemia and reperfusion in pressure-induced tissue necrosis in the trochanteric region in pigs. Pressure application was achieved with a newly developed computer-controlled pressure device. Histological examination showed damage in the sub cutis and muscle tissue comparable with inflammation, extending in a vascular pattern beyond the area of pressure application. Electron-microscopic studies revealed neutrophil adherence to the capillary endothelium, which showed signs of injury. These observations were manifest two hours after the cessation of pressure. Pre-treatment with 500mg vitamin E per day resulted in significantly less tissue damage compared with untreated animals. Pressure alone caused a significant decrease in reduced glutathione and total glutathione, suggesting oxidative stress. After pressure release there was a significant increase in hydrogen peroxide concentration, suggesting a decrease antioxidant protection. After pre-treatment with vitamin E, however, there was no increase of hydrogen peroxide. It is concluded that the early signs of necrosis after pressure application are concordant with typical ischaemia-reperfusion damage and this can be prevented in part by treatment with vitamin E. Prophylactic administration of vitamin E may influence the occurrence of pressure ulcers in humans undergoing elective surgery.

Introduction

A pressure ulcer is an area of localised damage to skin and underlying tissue, caused by pressure shear, friction or a combination of these;[1] it is generally accepted that pressure and shear are the primary causative factors.[2] The condition is common in acute care, nursing home and home care populations; incidence ranges from 2.7-30%, prevalence from 3.5-30%.[3] [4] Pressure ulcers occur mainly in elderly hospital patients and in people who are critical ill, bed-bound or sitting for long periods. The population in the western world is ageing, and it is increasingly possible to treat diseases that were previously fatal; however, these developments mean that increasing numbers of people are at risk of developing pressure ulcers. Pressure ulcers have recently attracted attention from clinical scientists. The US-based National Pressure Ulcer Advisory Panel and the European Pressure Ulcer Advisory Panel help co-ordinate research in this area and its practical implementation in health care. Clinical observations of pressure ulcers led to the hypothesis that these skin lesions usually occur after, rather than during, a period in which pressure is applied to the body. Signs of inflammation occur characteristically in a fixed order:

- Reddening of the skin or non-blanching erythema
- Blister formation
- Superficial tissue breakdown
- Eventual ulceration and extension to deeper tissues.

These signs begin to develop hours or days after cessation of the develop hours or days after cessation of the application of pressure. This strongly resembles the phenomena observed during experiments in which the reperfusion of tissues is followed by extensive inflammatory reactions.[5] [6] [7] These phenomena usually follow a pattern involving not only the area under pressure itself, but also a more distal area related to the arterial supply of the affected area. The hypothesis of this paper, therefore, is that pressure ulcers are the result of inflammation caused by occlusion and reperfusion. A computer-controlled device was developed to deliver specific amounts of pressure to laboratory animals in order to investigate the influence of ischaemia and reperfusion after pressure application. The effect of the oxygen free-radical scavenger vitamin E was also investigated, since this antioxidant could play an important role in the prevention of pressure ulcers in humans.

Materials and method

Animals

The study was performed using eight-week-old Yorkshire pigs weighing 25-30kg, all fed with the same standard pig food. Two groups of eight pigs were used for the experiments: the control group received standard pig food, and the experimental group

received the same food with a vitamin E (500mg) supplement added for 14 days before the experiment. The animals were not fed for 24 hours before pressure application, but water was allowed as required. One hour before the experiment each animal was sedated with azaperon (4mg/kg) intramuscularly, and 15 minutes before intubation with metomidate (3mg/kg) and atropine (0.5mg/kg) intravenously. All animals were kept under general anaesthesia following standard procedures during the experiment. Each pig was placed on the operating table in the prone position (Fig 1), intubated, and ventilated with a mixture of nitrous oxide and oxygen (2:1) and halothane. Tidal volume was adjusted to the normal expiratory carbon dioxide concentrations (between +5% and – 5%, measured by means of a capnograph). Mean arterial blood gases ware monitored by means of foreleg artery catheterisation and electrocardiograph tracing. An intravenous cannula was inserted into an ear vein and flushed with saline. Body temperature was registered with a rectal probe and kept within normal limits by means of a heating pad under the animal.

Pressure application

The amount of pressure and duration of application were selected following procedures described in the literature,[8] and the model was standardised for amount and duration of pressure. Two Perspex pressure applications (diameter 5cm, thickness 1.5cm) were placed on the skin immediately above the greater femoral trochanters (Fig 1). Probes to measure skin temperature and tissue interface pressure were placed in the applicators. Tissue interface pressure was kept constant by means of a computer-controlled pneumatic applicator, able to deliver pressures of 0-400N. All registration devices were calibrated before and following each investigation by means of standard probes. A constant pressure of 100N was applied to a rectangular area for two hours. Samples of skin and muscle were taken at times varying from immediately after to two hours after withdrawal of pressure. Biopsies were taken with a diameter of 0.8mm. Only three biopsies per animal were taken in order to avoid effects of the procedure on the specimens. The samples were taken from areas of tissue directly under the applicator and several centimetres proximal and distal to this region. Control specimens, not exposed to pressure, were also taken from the animal's shoulder. The animals were sacrificed 2-330 hours after the experiment; samples of skin and muscle were taken immediately by surgical excision in order to investigate the extent of damage macro- and microscopically. The first days after pressure application the pigs evidently suffered pain in the hip region, recovering completely after two to three days. Paracetamol was used as analgesia, since it has no anti-inflammatory properties.

Pathological examination

Punch biopsies were used for both electron and light microscopy. Tissue for electron microscopy was fixed in Karnovsky medium, and small samples were selected from the biopsy. These samples were post-fixed in osmium tetroxide and EPON, embedded according to standard procedures to obtain ultra-thin sections. Sections were then placed in uranyl acetate an lead citrate contrast media. Material for light microscopy was fixed in 4% phosphate-buffered formaldehyde, dehydrated and embedded in paraffin. Serial 5 paraffin slides were stained with haematoxylin and eosin, and with Van Gieson's stain for connective tissue.

Biochemical analysis

Concentrations of hydrogen peroxide in whole blood were analysed following the method of Pick and Keisary, and expressed as mmol/L.[9] Total glutathione, defined as the sum of reduced glutathione and oxidised gluthaione, was determined enzymatically in deproteinised plasma following the method of Tietze,[10] and expressed as mmol/g protein, according to Bradford.[11] Reduced glutathione concentrations were measured according to Prins and Loos[12] and catalase activity, expressed as mg/g protein, following the method of Meerhof and Roos.[13]

Results

It is important to stress that the numbers of animals participating in this study were limited. Animal studies are extensively monitored by the ethical committees of the hospital and the veterinary faculty at Utrecht University. Only small biopsies and blood samples could be taken while the animals were under anaesthesia; large issue samples could be acquired only after the death of the animal. It was therefore not possible to obtain more than one tissue sample per animal after the cessation of pressure application. Results are described for five or six animals at each time point. The number of animals used for each parameter is shown in Table 1.

Macroscopic characteristics

No skin damage was visible, regardless of the magnitude and duration of applied pressure. The only external sign of pressure damage was non-blanching erythema, which lasted for several days.

Microscopic findings

Specimens taken immediately after cessation of pressure application showed no histopathological signs (Table 1, Fig 2). Early signs of damage in the muscles and subcutaneous tissue under the pressure device appeared only after a reperfusion time of

one to two hours. Histopathological specimens showed no damage to the epidermis. In the subcutis and muscles, however, increasing invasion of granulocytes was demonstrable, starting one to two hours after cessation of pressure, and increasing during the following days. Perivascular oedema was present, diminishing after one week. There was distinct evidence of destruction of muscle, sweat glands and fatty tissue after two days. Damage to all structures in animals in the experimental group, which received vitamin E, was significantly less compared with the control group. Electron microscopy revealed the adherence of granulocytes to the endothelium of small vessels, together with oedema, both typical characteristics of inflammation (Fig 3). After two weeks (330 hours after the cessation of pressure) some repair occurred, with formation of connective tissue. Histological damage was notable not only in tissues directly under the pressure applicator but also in more caudal tissue, following a pattern determined by the arterial supply; this was comparable with the tissue damage directly under the applicator. Proximal to the applicator, and in the control specimen from the shoulder, no damage was observed.

Biochemical findings

There was a significant increase in hydrogen peroxide in whole blood in the control animals after the cessation of pressure; in the experimental animals there was no increase. The two groups differed significantly at two hours: total glutathione decreased significantly in biopsies taken from areas under pressure compared with biopsies from non-exposed areas. The decrease was observed immediately after pressure release (t=0) and did not change significantly within the next two hours. There was no significant difference in reduced glutathione and total glutathione between areas under pressure in animals pre-treated with vitamin E and animals that were not.

Discussion

Although pressure is not the only contributing factor in the genesis of a pressure ulcer (friction and shearing forces almost certainly also playing a role), it is considered to be the primary cause. [1,2] In the present model, which resembles the clinical situation, pressure is transmitted to the underlying bony structures, compressing the muscles together with overlying skin. The results in this study show that pressure results in damage, but that this damage is not a direct result of the pressure itself. Histological specimens taken immediately after cessation of pressure showed no damage at all. The first signs of pathology appear after a minimum of two hours, the severity of damage being independent of the duration of pressure. Even after 10 hours of pressure application in some extra experiments (n=3), damage was notable only two hours after cessation of pressure application. The noted histopathology, together with time after

cessation of pressure, demonstrates that reperfusion is a contributing factor in this pathology. The noted damage distal to the pressure applicator, identical to the damage immediately below the applicator, shows that the process follows a vascular pattern and is a result of ischaemia, not of the pressure itself. Oxygen free radicals play an important role in the process of inflammation. When present in excess they damage the endothelium, attracting platelets and granulocytes, stimulating stasis of blood flow and thrombosis, further decreasing blood flow and thereby stimulating the development of tissue necrosis. Under normal circumstances they are buffered by free radical scavengers, such as reduced glutathione and glutathione. In tissues undergoing oxidative stress the amounts of these enzymes decrease. During reperfusion the oxygen free radicals are not buffered, or are buffered to a lesser degree; this is reflected by the increase in concentration of hydrogen peroxide. Application of pressure caused a significant decrease in reduced glutathione and total glutathione, which is suggestive of oxidative stress and consumption of antioxidants. This phenomenon was not dependent on pre-treatment with vitamin E. After the release of pressure, however, only the animals pre-treated with vitamin E showed no increase in hydrogen peroxide.

It can be concluded that an inflammatory process is the key mechanism in the development of necrosis in the deeper subcutis and in muscle. This is also illustrated by the biochemical results, showing increases in hydrogen peroxide and reduced glutathione in plasma and biopsies respectively, which is typical for inflammation. Pressures in solid tissue near to bony prominences are three to five times higher than those at the skin over the prominences. According to these observations, necrosis will start in deeper tissues. By the time it is evident in the skin, the necrosis, behaving in the same way as an abscess, has worked its way completely from bone to skin. This process of ulcer formation is seen clinically after a long period of immobility, for instance after extensive surgery. During the first two to three days the skin is red to purple, and after several days there is deep ulcer formation, extending to the fascias or skeleton. The sacral area and the hips are particularly prone to this type of damage. It has been suggested recently that the damage occurs as a post-ischemic reperfusion injury during the re-institution of flow in the ischemic tissue.[14] Whether an ulcer will depends on several factors. A decreased microvascular response, after a period of ischaemia, possibly depends to some extent on cardiac output.[15]

A histological study of all phases of pressure ulcer formation in humans showed the same histopathological changes in the epidermis, but particularly in the papillary and reticular dermis, comparable with the findings of this study.[16] A possible explanation for the absence of actual ulcer formation in the present study is that the duration of pressure application in the experiments (in most animals two hours although in some it was up to 10 hours) was too short. Epidermal necrosis occurs late in the course of the ulcer,

because epidermal cells are able to withstand prolonged absence of oxygen. Under normothermic conditions, skin can tolerate ischaemia for up to eight hours.[17] An earlier experiment showed ulceration after at least 16 hours of pressure duration.[3] The absence of friction or shearing forces may also be a reason for the absence of ulcers. Ulceration can be attributed to friction on the epidermis, which is susceptible to a loss in the attachment between basal cells and the dermis.[9] This kind of pressure ulcer is less deep than the type described above, and more often seen in bed-bound patients who are nursed in a semi-recumbent position.

Conclusion

The present study shows that the application of pressure causes damage to tissues; this damage starts at deeper levels, extending to the surface and, following a vascular pattern, to tissues distal to the exposed places. The changes observed are identical to those seen in occlusion-reperfusion experiments. The study also shows that pre-treatment with 500mg of vitamin E prevents damage caused by pressure to a large extent. Vitamin E does not prevent oxidative stress during pressure (reflected by the decrease in reduced glutathione and total glutathione), but it does prevent the excess production of oxygen free radicals and hydrogen peroxide during reperfusion. In the prevention and treatment of pressure ulcers these is emphasis on the role of nutrition, focused not only on sufficient amounts of calories, proteins, fat, and carbohydrates, but also on vitamins and trace elements. Vitamin E is considered to act as a scavenger of oxygen free radicals and has been demonstrated to do so in this experiment. The results merit investigation in people who are due to undergo extensive surgery associated with a high risk of developing pressure ulcers, such as the placement of artificial hips, or surgery on abdominal aneurysms of the aorta. A study investigating the effects of vitamin E in hip surgery has already commenced in the Netherlands. If vitamin E is found to have a positive effect in minimising the development of pressure ulcers, a rational prophylaxis for the prevention of pressure ulcers will have been established.

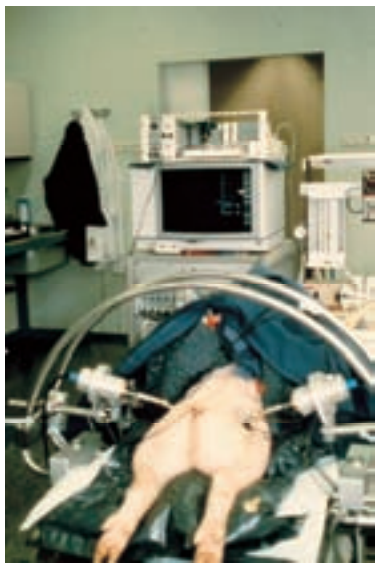
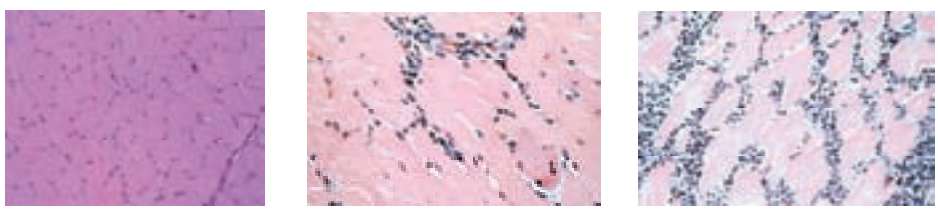
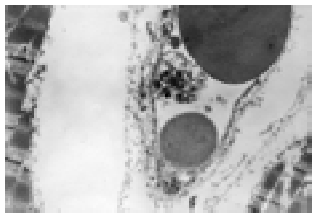


Fig 1. The pressure transducers are connected to the hemicircles over the pig. The anaesthesiological controls are built into the column at the rear.



[] Fig 2. Light-microscopic pictures (100x) of muscle in area under pressure transducer. (a) Biopsy taken immediately after cessation of pressure. No pressure damage is visible; (b) Biopsy taken one hour after release of pressure. Early signs of inflammation are visible, with swelling and influx of granulocytes; the fine anatomy of myocytes is disappearing and few myocyte nuclei are still visible; (c) Biopsy taken two hours after granulocytes and the structure of the myocytes has disappeared completely. The muscle is necrotic.



[] Fig 3. Electron-microscopic picture (6000x) of muscle biopsy taken immediately after cessation of application of pressure. The distance from the capillary to the striated muscle is too large, which is a symptom of oedema. In the preparation process, the extracellular fluid is washed away, creating an 'empty' space. Oedema is a symptom of increased vascular permeability, which is a symptom of inflammation. In the sectioned capillary, erythrocytes are visible (large circles) and a granulocyte, indicated with an asterix, has adhered to the capillary wall.

Table 1. Microscopic findings

	With vitamin E treatment					**No vitamin E treatment**					**Difference at 120 minutes**
Time after release of pressure (minutes)	**0**		**120**			**0**		**120**			
Neutrophil count **(leucocytes/mm²**	Mean	(s.d.)	Mean	(s.d.)	p-value	Mean	(s.d.)	Mean	(s.d.)	p-value	p-value
In epidermis (n=6)	0,56	(0,09)	7,89	(0,86)	<0,001	0,73	(0,23)	4,87	(1,06)	<0,05	<0,02
In muscle (n=6)	0,78	(0,32)	8	(1,5)	<0,01	1,11	(0.5)	3,44	(1,11)	<0,05	<0,1
In adnexae (n=8)	0	0	0,67	0,19	<0,01	0	0	0,2	0,1	<0,05	<0,1
Bichemical parameters											
Plasma	Mean	(s.d.)	Mean	(s.d.)	p-value	Mean	(s.d.)	Mean	(s.d.)	p-value	p-value
Catalase (mg/g protien) (n=6)	645	(1,6)	599	(132)	n.s.	702	(155)	739	(127)	n.s.	n.s.
H^2O^2 (mmol/L) (n=6)	355,5	(98.2)	509,8	(126,2)	<0,05	382,98	(100,1)	373,38	(81,97)	n.s.	<0,05
GSH (mg/g protein) (n=5)	16,76	(3,8)	16,88	(6,89)	n.s.	25,82	(17,8)	18,65	(3,56)	n.s.	n.s.
Biopsy (control group)	Mean	(s.d.)	Mean	(s.d.)	p-value	Mean	(s.d.)	Mean	(s.d.)	p-value	
GSH (mg/g Protein) (n=5)	21,98	(1,97)	22,26	(1,97)	n.s.	19,87	(0,9)	19,93	(1,65)	n.s.	n.s.
Glutathione (mmol/g protein) (n=5)	19,12	(0,69)	18,02	(1,49)	n.s.	16,07	(1,01)	12,77	(0,46)	<0,02	<0,02
Biopsy (study group)	Mean	(s.d.)	Mean	(s.d.)	p-value	Mean	(s.d.)	Mean	(s.d.)	p-value	
GSH (mg/g Protein) (n=5)	11,59	(0,08)	14,49	(1)	<0,05	10,49	(4,44)	12,94	(3,34)	n.s.	
Glutathione (mmol/g protein) (n=5)	10,78	(1,59)	8,4	(0,81)	n.s.	6,17	(0,18)	7,67	(0,42)	n.s.	n.s.
Differences (p-value) (control group vs study group)											
GSH (mg/g Protein) (n=5)	0,05		<0,05			<0,05		<0,05			
Glutathione (mmol/g protein)	<0,05		<0,05			<0,05		<0,05			

n.s. = Not significant
H^2O^2 =Hydrogen peroxide
GSH=Reduced glutathione

References

[1] *European Pressure Ulcer Advisory Panel. A policy statement on the prevention of pressure ulcers from the European Pressure Ulcer Advisory Panel, Br J Nurs 1998; 7: 888-890.*

[2] *Crenshaw, R.P., Lars B.S., Vistnes L.M. A decade of pressure sore research: 1977-1987. J. Rehab Res Dev 1989; 2: 6, 63-67.*

[3] *Haalboom, J.R.E., van Everdingen, J.J.E., Cullum, N. Incidence, prevalence and classification. In: Parish, L.C., Witkowsky, J.A., Crissey, J.T., The Decubitus Ulcer in Clinical Practice. New York, NY: Springer-Verlag, 1997.*

[4] *Agency for Health Care Policy and Research. Treatment of Pressure Ulcers. Clinical Practice Guideline Number 15. (AHCPR Publication Number 95-0652). Rockville, MD: AHCPR, 1994.*

[5] *Kosiak, M. Etiology and pathology of ischemic ulcers. Arch Phys Med Rehabil 1959; 40: 62-69.*

[6] *Daniel, R.K., Priest, D., Wheatley, D. Etiological factors in pressure sores: an experimental model. Arch Phys Med Rehab 1981; 62: 429-498.*

[7] *Shea, J.D., Pressure sores, classification and management. Clin Orthop 1975; 112: 89-100.*

[8] *Le, K.M., Madsen, B.L., Barth, P.W. et al. An in-depth look at pressure sores using monolithic, sillicon pressure sensors. Plast Reconstr Surg 1984; 7: 4, 745-754.*

[9] *Pick, E., Keisary, Y. A simple colorimetric method for the measurement of hydrogen peroxide produced by cells in nature. J Immunal Method 1980; 38: 161-170.*

[10] *Tietze, E. Enzymatic method for quantitative determination of nanogram amounts of Total and oxidized glutathione: applications to mammalian blood and other tissues. Anal Biochem 1969; 27: 502-522.*

[11] *Bradford, M.M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1976; 72: 248-254.*

[12] *Prins, H.K., Loos, J.A. Glutathione, In: Yunis, J.J. (ed) Biochemical Methods in Red Cell Genetics. New York, NY: Academic Press, 1969.*

[13] *Meerhof, L.J., Roos, D. An easy, specific and sensitive assay for the determination of catalase activity of human blood cells. J Reticuloendothel Soc 1980; 28: 419-425.*

[14] *McCord, J.M. Oxygen-derived free radicals in postischemic tissue injury. N Eng J Med 1985; 312: 159-163.*

[15] *Schubert, V. Hypotension as a risk factor for the development of pressure sores in elderly subjects. Age and Ageing 1991; 20: 255-261.*

[16] *Witkowski, J.A., Parish, L.C. Histopathology of the decubitus ulcer. J Am Acad Dermatol 1982; 6: 1014-1021.*

[17] *Willems-Kretschmer, K. Majno, G. Ischemia of the skin. Am J Pathol1969; 54: 327-353.*

Chapter 6a

A Systematic Review of the Efficacy of Topical Skin Application of Dimethyl Sulfoxide on Wound Healing and as an Anti-Inflammatory Drug

IGP Duimel-Peeters, RH Houwing, CP Teunissen, MPF Berger, LHEH Snoeckx, RJG Halfens

Wounds 2003;15(11): 361-370

In a systematic review we investigated the present state of knowledge regarding the use of DMSO in the prevention of pressure ulcer development. This chapter reports the results of our evaluation with respect to woundhealing and anti-inflammatory effects of different concentrations of DMSO, administrated by topical application to the skin. This chapter is also published in the thesis '*Massage to prevent pressure ulcers! Knowledge, beliefs, practice and effectiveness*' by I.G.P. Duimel-Peeters.

Abstract

Background

Preceding the authors' research about the evaluation of massage with a cream that contains dimethyl sulfoxide (DMSO) as a preventive method for pressure ulcers, a review study was completed. Articles on application of DMSO on the human skin in conditions where wound healing and/or inflammation characteristics are involved were included.

Objectives

The literature was evaluated with respect to the efficacy of DMSO in different concentrations on wound healing and as an anti-inflammatory drug, administered by topical application to the skin.

Methods

This systematic review was performed according to the rules of the meta-analyses. The authors searched for articles in MEDLINE, PUBMED, EMBASE-Excerpta Medica, the Cochrane Controlled Trial Register and Database for Clinical Reviews, and the Cochrane Skin and Wounds Group. Conclusions were made after blinded assessment of the methodological quality of the studies according to standardized methodological criteria. Disagreements between reviewers were identified and subsequently discussed. If disagreements were not resolved, a fourth, blinded, expert reviewer would be consulted.

Results and Conclusions

A review of the literature on experimental dermatological studies using DMSO revealed numerous studies using experimental animals. Dermatological studies with DMSO in humans have been scarce. Although the included studies were based on small samples and lacked reference groups, the authors concluded that DMSO seems safe to use in concentrations less than 50 percent, either by rubbing or by spraying; DMSO in concentrations higher than 50 percent gives an increasing risk of side effects; and at concentrations below 50 percent, DMSO has favourable effects on inflammation and wound healing, as well as an analgesic effect.

Introduction

Pressure ulcers, also commonly referred to as bedsores, pressure sores, decubitus ulcers, or simply decubitus, can develop when sustained load, friction, or shear is applied to localized areas of the body, leading to degeneration of the skin and underlying soft tissues. As in other countries, pressure ulcers form a major problem in Dutch institutions for healthcare services.[1] There are various theories that explain the etiology of pressure ulcers, with most experts adhering to the theory that pressure ulcers result from chronic occlusion of capillary blood flow, leading to alternating periods of ischemia and reperfusion. This process is associated with repetitive formation of reactive oxygen species (ROS) and concomitant tissue necrosis.[2] Recently, pilot studies have revealed that rubbing the intact skin with a dimethyl sulfoxide (DMSO)-containing cream during the first stage of pressure ulcers according to the four grade system of the European Pressure Ulcer Advisory Panel (EPUAP) leads to a decrease in pressure ulcer occurrence among high-risk patients.[3] [4]

DMSO [(CH3)2 S-O] is a water-white to straw-yellow-coloured organic liquid. It is an oily substance with a smell of sulphur and a slightly bitter taste. In topical application, this simple, highly polar chemical compound has been found to alleviate ischemic damage in several experimental animal models.[5] [6] In addition to an analgesic effect, the most important property of DMSO is the enhancement of percutaneous penetration.[7] When used in combination with other substances, DMSO facilitates diffusion through the stratum corneum of the skin, triggers the formation of deposits in the deeper layers of the subcutaneous tissue, and promotes transport into the local blood vessels.[8] Hence, dermatologists use it as a vehicle for other medications. In pressure ulcer tissue, like any tissue in which inflammation occurs, repetitive ischemia-reperfusion episodes lead to the local formation of ROS. The main representatives of these radicals are the superoxide anion (O?2-), hydrogen peroxide (H2O2), and the hydroxyl radical (OH-). Since DMSO is known to be a hydroxyl-inactivating compound, it can be assumed that its beneficial effects on pressure ulcers are based upon this activity. The purpose of this review was to evaluate the literature on the efficacy of DMSO in various concentrations on wound healing and as an anti-inflammatory drug administered by topical application to the skin.

Methods

A MEDLINE literature research was carried out covering the last 36 years (starting in 1966). At first, the search focused on studies involving DMSO by one specific disorder, e.g., pressure ulcers. However, this did not yield enough articles, so the domain was expanded. The following keywords were used: dimethyl sulfoxide, clinical dermatology, pharmacology and toxicology, bio-penetrator, the skin, hydroxyl radicals, ROS,

scavengers, treatment of ulcers, and inflammation. In addition, the references of all articles retrieved were further examined. The same search was done in PUBMED and EMBASE-Excerpta Medica. A last extensive search strategy was used in the Cochrane Library by means of the Cochrane Controlled Trial Register and the Cochrane Database of Clinical Reviews. Finally, the Cochrane Skin Group and the Cochrane Wounds Group were explored. Abstracts were not selected. One unpublished study was selected because of its relevance to the topic of the present review.[4] Studies were only included if DMSO was applied locally on the diseased skin in conditions involving wound healing and/or inflammation or on healthy skin in order to determine its sensitivity to various DMSO concentrations. Research using experimental animals was excluded.

Table 1 lists the criteria used, which were weighed by three independent reviewers with different backgrounds (dermatology, pharmacy, and physiotherapy and movement sciences). Detailed information about these criteria is presented in Appendix 1. The criteria are not listed according to the generally accepted principles of intervention research but based upon the more detailed four general dimensions proposed by Feinstein,[9] Bouter,[10] and Assendelft, et al.,[11] to describe the quality of scientific publications. These four dimensions are the external validity, the internal validity, the method of data presentation and data-analysis, and the good clinical practice dimension (GCP), which cover over 19 methodological criteria (A–S). Each criterion was given a weight, the sum of which determined the quality for each dimension. The score on each dimension revealed the value of each article on each of these dimensions. This system reveals both the strong and weak points of each of the presented studies.

Scoring methods

All publications were blinded for author(s), journal, and year of publication. The three reviewers independently scored all the criteria listed in Table 1 for each publication, using scores '+', '-', and '?', with the following meanings:

+: Informative description of each of the above mentioned criteria; adequate study design and implementation (preventing bias);

-: Informative description, but inadequate study design or implementation;

?: Absent or insufficient information or impossible to assign '+' or '-'.

The level of agreement between the reviewers was determined by calculating the inter-rater coefficient Cohen's Kappa (K). A K-value higher than 0.75 was considered to indicate good agreement, while a value between 0.40 and 0.75 was considered to indicate reasonable agreement. Below K = 0.40, reviewers were considered to disagree. Upon identification of disagreement, a consensus meeting was organized. If

disagreements could not be resolved, a fourth reviewer was to be consulted for a final independent judgment.

All methodological criteria rated '+' were scored using the weighting factors listed in Table 1. The assessments resulted in a hierarchical list for the four dimensions, determining the quality of a particular study/article. Higher scores indicated articles that provided more detailed descriptions of the elements referred to in each criterion for that specific dimension. Ranking the studies, according to their methodological quality, resulted in two scores: a total score without the GCP criteria ranging from 4 (poor) to 65 (good), and a second total score including the GCP criteria resulting in scores ranging from 7 (poor) to 71 (good). For the comparison of studies, the authors always applied the second score. An arbitrary cut-off point of 43 was chosen, which is 50 percent of the maximum total score when each criterion is totally fulfilled. Below this point, studies were defined as of poor methodological quality.

Table 1 Dimensions of quality table: A criteria list for the methodological assessment of articles about the efficacy of DMSO on wound healing and as an anti-inflammatory drug topically applied to the skin

Dimensions of Quality (Criteria*)	**Weight Factor**
External Validity	30
a. Homogeneity: selection and restriction	3
b. Interventions included in protocol and information described	10
c. Relevant outcome measures	10
d. Adequate follow-up period	5
e. Description of side effects	2
Internal Validity	35
f. Pragmatic study	5
g. Placebo-controlled study	5
h. Adequate randomization procedures/randomization concealment	5
i. Blinded assessment of outcome measures	7
j. Comparability of relevant baseline characteristics	5
k. Drop-outs described for each study group separately	3
l. Co-interventions avoided	5
Data (Presentation and Analysis)	20
m. Adequate presentation of data for each study group	5
n. <10 subjects in the smallest group	1
10-20 subjects in the smallest group	3
>20 subjects in the smallest group	5
o. Adjustment for confounding variables and/or differences at prognostic indicators at baseline	5
Good Clinical Practice (GCP)	7
p. Concentrations DMSO described	2
q. Application DMSO described	3
r. Informed consent of patients	1
s. Consent of medical ethical committee	1

* A more detailed description of the criteria is given in Appendix 1.

Adapted form Assendelft WJJ, Scholten RJPM, van Eijk JTM, Bouter LM. De praktijk van systematische reviews III. Methodologische beoordeling van onderzoeken (The practice of systematic reviews. A methodological assessment of research). Ned Tijdschr Geneesk 1999; 143(14); 714-8.

Appendix 1 Details of criteria listed in Table 1

External Validity

a. Description of inclusion and exclusion criteria (2 points). Restriction to a homogeneous study population (1 point).

b. Manipulative treatment explicitly described (5 points). All reference treatments explicitly described (5 points).

c. Relevant outcome measures, which include the following: 1) healing of erythema; 2) healing of ulcers/flattering of the scar; 3) softening of the skin and subcutaneous tissue; 4) analgesic effects/pain relief; 5) less fluid formation; 6) increased blood flow; 7) positive effects on one or more inflammation symptoms: rubor, dolor, tumor, calor; 8) histo-chemical changes (increased flow of ions); and 9) increased range of motion of the affected part of the body (Look for biological plausibility between the applied interventions and the outcome measures.)

d. Outcome of measures assessed during or just after the treatment (6 points). Outcome of measures assessed after 10 days or longer (4 points).

e. Description of side effects (skin irritation, a garlic breath odour, burning or prickling sensation of the skin, blister formation urticarial reaction) (2 points).

Internal Validity

f. Comparison with an established treatment (5 points).

g. Comparison with placebo (5 points).

h. Randomization procedure described (2 points). Randomization procedure that excludes bias; for example, sealed envelopes (=randomization concealment) (3 points).

i. Each blinded measurement of the first seven measurements mentioned under point C earns 1 point.

j. Comparability for duration of complaints, value of outcome measures (seriousness of complaints), age, recurrences, and sex (1 point each).

k. Information about which group patients withdrew (2 points) from and reason for withdrawal (1 point).

l. Other physical treatments or medical interventions are avoided in the design of the study (medication of no influence on the specific treatment or outcome measurements) (4 points). If there were other interventions these were identical for all the groups (1 point).

Data (Presentation and Analysis)

m. Frequencies or means and SD for each study group at intermediate (1 point) and final measurements (4 points).

n. Smallest group immediately after randomization (<10=1point; 10-20=3 points; >20=6 points).

o. Adjustment of results for confounding variables (differences of prognostic characteristics at baseline) by using multivariate analysis (5 points). This is especially important by non-experimental research. In case of experimental research, internal validity is guaranteed by the randomization procedure. Or, possible confounders were considered and were excluded (3 points).

Good Clinical Practice

p. Description of the used amount of concentration DMSO (2 points).

q. Description of how DMSO is applied to the patient (3 points).

r. All patients agreed with the informed consent (1 point).

s. There was a consent of the Medical Ethical Committee for the described study (1 point).

Table 2. Summary of studies (in order of ranking of Table 3) of the effects of DMSO on human skin and the efficacy of DMSO on wound healing and as an anti-inflammatory drug, topically applied to the skin

Authors	Purpose	Method	Sample	Results/ Conclusions
Salim [20]	To investigate the effects of DMSO and allopurinol as co-medications of cimetidine therapy in patients with refractory duodenal ulceration	A prospective, randomized, double-blind study whereby allopurinol and DMSO 50-percent were ad-ministered orally, four times a day for eight weeks	*N*=315; No placebo group; Ages ranged from 19 to 71 years	Positive effects of DMSO and allopurinol as co-medications of cimetidine especially on wound healing. Objective measurements are restricted through the type of research (scope)
Geertzen, et al [18]	To evaluate the use of DMSO as an early treatment in patients with reflex sympathetic dystrophy	One group (A) was treated with DMSO 50-percent four times a day for three weeks. The lotion with DMSO was applied with a brush on the affected hand. Group B received the regional intravenous ismelin block twice a week for three weeks	*N*=26; >21 years of age; No one had ulcers and wounds in the affected area or was pregnant. They had no other treatment before the start of the study. Results of treatment with regional intravenous ismelin was compared with the results of treatment with DMSO	Positive effects of DMSO on wound healing and as an analgesic; Statistics: Chi-square test
Lishner, et al [5]	To investigate the treatment of diabetic perforating ulcers with local DMSO	In a prospective clinical trial, DMSO 25-percent was applied every day for 20 min. If the progress of healing seemed unsatisfactory, the concentration of DMSO was raised to 50 percent for 20 weeks of therapy.	*N*=40l; Mean age= 65.5 years; Duration of diabetes mellitus ranged from 8 to 30 years; no placebo group; Too small of a population.	No conclusion with regard to wound healing effects of anti-inflammatory actions (patients with ulcers were excluded). Statistics: student t-test, but the meaning of it is doubtful.
Langendijk, et al [19]	To investigate the effects of a 50-percent DMSO cream as a treatment of acute reflex sympathetic dystrophy	A prospective study in which DMSO 50-percent cream was applied five times daily	*N*=37; selected by using a reflex sympathetic dystrophy diagnosis protocol; Ages ranged from 10 to 77 years; No placebo group	No description of wound healing effects. There were anti inflammatory effects when reflex sympathetic dystrophy considered an inflammatory process. Statistics: student t-test for some parts
Binnink, et al [22]	To investigate the effects of DMSO in the treatment of scleroderma	Concentration of 70 percent an 5 percent DMSO were compared. Painting and immersion techniques were used for evaluation	*N*=24; 19 with systemic scleroderma, 5 with localized scleroderma; Ages ranged from 30 to 65 years. Duration of disease form onset of symptoms to inception into study ranged from 2 to 18 years.	No effects on wound healing and inflammation. A positive analgesic effect was found
Van Rossum [4]	To investigate the treatment and prevention of pressure ulcers with DMSO	Patients were treated locally with DMSO cream (5%) twice daily during an experimental period of 36 months. The surrounding intact skin of patients with open ulcers was treated the same way.	*N*=39 with first stage pressure ulcers; Ages ranged between 80 to 83 years; All the patients were first observed during control period before rubbing with DMSO started	Very positive effects of DMSO on inflammation, if pressure ulcers are considered as such. Positive effects on wound healing. Statistics: student t-test

Table 2. Summary of studies (in order of ranking of Table 3) of the effects of DMSO on human skin and the efficacy of DMSO on wound healing and as an anti inflammatory drug topically applied to the skin, cont.

Authors	Purpose	Method	Sample	Results/ Conclusions
Goris, et al [17]	To investigate DMSO as a hydroxyl scavenger by reflex sympathetic dystrophy	During a crossover study, DMSO 50-percent and a placebo were each locally applied five times a day for one week. Before and after each treatment, the patients and examiners performed subjective evaluations as to clinical activity of reflex sympathetic dystrophy, and measurement of the range of motion of all joints in the affected extremities was performed	*N*=20 (with reflex sympathetic dystrophy); No age mentioned; Each patient was treated with placebo and with DMSO; The order was determined by randomization	The effects of DMSO are used to indicate that reflex sympathetic dystrophy is an inflammatory reaction
Agner and Serup [16]	A test for the assessment of sensitive skin. A quantification of DMSO response	DMSO 100-percent was applied to a test area on the flexor side of the upper arm. Each person had DMSO applied to two test areas. Clinical grading of the skin response to DMSO was preformed five minutes after removal of DMSO	*N*=12; Mean age-31.5 years; informed consent was obtained as well as local ethical committee approval; for comparison, measurements were performed simultaneously on adjacent normal, unexposed skin.	No effects on inflammation. Statistics: Wilcoxon matched-pairs test
Sulzberger, et al [7]	To investigate the effects of DMSO on human skin *in vivo*	Observation of the *in vivo* effects of topical application of DMSO (10-90%) on intact skin. Determination of the route and depth of penetration of visual tracers to the intact skin with DMSO	*N*=64; Healthy Caucasian men, physically normal with no medical history for allergy, organic disease, and skin disorders; Five subgroups with a strong variance in amount; No age mentioned	No specific conclusion on effects on human skin, wound healing, or as anti-inflammatory drug
Frosch, et al [21]	To quantify the healing response of human skin to DMSO	Concentrations of 90-, 95- and 100-percent DMSO were applied for five minutes to circular areas 8mm in diameter. Healing was scored on a five-point scale after 10 minutes.	*N*=200; students; Ages ranged from 18 to 30 years. No placebo group	No specific conclusion on effects on human skin, wound healing, or as anti-inflammatory drug
Alberts and Dorr [12]	To investigate the effects of DMSO for mytomycin-C-induced skin ulceration	DMSO, in 99-percent solution, was topically administered, twice daily	Case report of only two patients (47 and 56 years old)	Promising effects of DMSO on healing of skin ulcers after infiltration of mytomycin-C. Anti-inflammatory effects.
Engel [14]	To describe the indications and contra-indications of the use of DMSO in clinical dermatology	DMSO (40-80%) was applied with cotton-tipped applicators or by immersion 2 to 3 times daily. Where bilaterally similar lesions appeared, those lesions were treated only on one side in order to obtain some form of control	*N*=45; Divided in three groups of different dermatological disorders; No age mentioned	No specific conclusion and no statistics. Psoriatic patients suffered more from inflammation by using DMSO

Authors	Purpose	Method	Sample	Results/ Conclusions
Scherbel, et al [12]	The relation between DMSO and the improvement of generalized scleroderma	Each patient served as his own control inasmuch as previous treatment had been ineffective. DMSO (30-100%) was used for periods ranging from 3 to 23 months	*N*=42; Duration of the disease ranged from 1 to 25 years; All patients had varying degrees of systemic involvement; No placebo group; Ages ranged from 20 to 69 years.	No positive effects on wound healing. Anti-inflammatory effects were observed in the initial stage of treatment
Engel [15]	To investigate the application of DMSO in clinical dermatology	DMSO (40-80%) was applied with cotton-tipped applicators or by immersion 2 to 3 times daily. Where bilaterally similar lesions, the lesions of one side were used as control	*N*=36; All patients had completed blood counts and urinalyses; Biopsies were taken before initiation of DMSO treatment and at the termination of treatment	No specific conclusions were drawn

Results

The literature search resulted in the identification of 27 publications of which 14 met the inclusion criteria. An overview of the characteristics of these studies is given in Table 2. The overall quality of the majority of the studies was rather low (Table 3)[12 13 14 15 16 17]; only five studies received a total score exceeding 43 points (the authors' cut-off point).
The three reviewers initially agreed on 216 of the 266 items (81%). On the average the inter-rater agreement coefficient Cohen's K between observers 1 and 2 was 0.654 (reasonable), while that between observers 1 and 3 was 0.736 (reasonable) and that between observers 2 and 3 was 0.887 (good). Nearly all disagreements were due to reading errors or to different interpretations of the methodological criteria due to the different backgrounds of the reviewers. Since the three reviewers were able to resolve all disagreements, a fourth reviewer was not consulted.

Most effects of treatment with DMSO reported in these articles were beneficial, both for wound healing and for analgesia. Three of the five studies that scored higher than the cut-off point emphasized these effects.[18 19 20 21 22] The favourable results of DMSO related first of all to its positive anti-inflammatory effects (with a few exceptions), followed by wound healing effects and very often pain relief. In a few cases, DMSO application was associated with the occurrence of more inflammatory signs than with the fact that wounds grew worse. The concentrations of DMSO varied from 5 to 100 percent with only one study expressing a preference for five-percent DMSO.[4] A positive correlation was found between the DMSO concentrations and the appearance of side effects. It should be pointed out that at DMSO concentrations below 50 percent (e.g., 5 or 10%), side effects were almost absent, while the positive effects were still obvious.

The criteria upon which patients were selected varied across the studies and were often inadequately described. In a few cases, the sample size was too small to allow reliable conclusions. The design of the various studies was often inadequate (rated '-') in terms of loss to follow up, sample size, randomization procedure, or data presentation. In seven articles, some kind of information was given regarding dropout rates. The number of patients using DMSO in each of the studies ranged from 2 to 315.

Despite these large differences, some trends could be detected in the outcome measures, the most frequently mentioned being reduction of erythema and healing of ulcers, analgesic effects or pain relief, and positive effects on one or more inflammation symptoms, such as rubor, dolor, calor, and tumor. Negative effects of DMSO always involved deterioration of inflammation signs. The outcome measures are described in detail in Appendix 1. Of the five studies ranked highest, four studies (Lishner, et al.,[5] Geertzen, et al.,[18] Salim, et al.,[20] and Binnick, et al.,[22]) had high scores for relevant outcome measures. Other studies with only positive results also reached higher methodological scores. Only five articles mentioned the use of informed consent and approval by a medical ethics committee. The ranking of the 14 studies remained unchanged when scores were calculated without the GCP. Except for the study by Geertzen, et al.,[18] all studies scored relatively better on the external than on the internal validity criteria. The authors also computed the inter-item correlations and performed reliability analyses. Of all dimensions, the GCP showed a low item-rest correlation (rit = 0.59), which could be a reason to omit this item from further literature reviews. This conclusion was confirmed by the value of Cronbach's alpha for the total scale after deletion of this GCP item: the alpha value without GCP was 0.88, while the alpha value with GCP was considerably lower at 0.82. Omitting the GCP dimension would probably raise the reliability. This conclusion was confirmed by the correlation matrix (Table 4), which showed Pearson's correlation between GCP and the total score to be relatively low (r = 0.64) compared with the correlation between the other dimensions and the total score. The correlations between the external and internal validity values with the total score were highest.

Discussion

A review of the literature on experimental dermatological studies of the controlled trial type using DMSO revealed numerous studies using experimental animals. In contrast, dermatological studies with DMSO in humans have been scarce. The reason for this is not clear because the application of DMSO on the skin is not dangerous, causing only some occasional small side effects like itching and skin irritation, tingling or burning sensations, and bad breath (garlic odour). One possible explanation for the small number of studies in humans could be publication bias. The sample sizes of patients in these studies are very often too small, resulting in non-significant results, whether negative or positive. The present literature search was undertaken to find out whether or not DMSO application could be effective in the treatment of pressure ulcers. Although various shortcomings of the studies that were reviewed blurred a clear conclusion on the efficacy of DMSO, the authors identified sound results in seven studies. The most important effects appeared to be anti-inflammatory effects, wound healing effects, and pain relief. The seven remaining studies recommended the use of DMSO, but did not provide sufficient information to allow reliable conclusions. The most important conclusion of the present review is that DMSO is effective as an anti-inflammatory and analgesic agent with positive effects on wound healing at concentrations equal to or larger than five percent. Furthermore, the treatment has to be continued for a minimum period of one week, and DMSO has to be applied two to three times a day. The main advantage of such a low concentration is that side effects are almost absent. It is not clear if there are significant differences between various modes of application, e.g., spraying or rubbing, in the wound healing or anti-inflammatory effects. This was not investigated. Readers should bear in mind that rubbing introduces an additional variable, which could possibly affect inflammation, wound healing, and pain relief.

In most of the studies, the intervention program was implemented without the necessary relevant reference or placebo treatment. This prevented the authors from evaluating methodological quality of randomized, controlled trials, which the authors would have preferred to do in order to avoid conclusions based on trials of inferior methodological quality. The authors, therefore, decided to evaluate the studies that were included according to four dimensions instead of one methodological scale. Furthermore, a considerable amount of information that would have been relevant to the evaluation of the methodological quality seemed to be missing. An adequate description of the randomization procedure is very important, as randomization/matching is necessary to prevent selection bias. An adequate description of such randomization was provided in only 4 of the articles, while 3 others gave some information. It should be pointed out that even the use of an adequate randomization procedure does not guarantee equal

distribution of prognostic factors and confounding variables among the study groups, particularly if the groups are relatively small. Information about the participants and baseline values of outcome measures was indicative of the success of the randomization procedure. Seven articles reported at least some of the baseline characteristics. Six articles provided a description of co-interventions. Almost all the articles (13 of 14) presented relevant outcome measures of which pain relief and less dolor as an inflammation symptom differed from patient to patient because of its subjective character, but only two of the studies had applied a blinded assessment to them. Thirteen articles reported side effects. Although side effects were often considered to be moderate or mild in the studies evaluated here, a small number of participants discontinued application of DMSO because of adverse reactions. This review did not include an assessment of the quality of the outcome measures as the outcome measures included in the authors' criteria list for methodological assessment of these studies could not be ranked in a priority list. The authors' list included the most important ones based on literature findings; most of these measures probably have been designed on the basis of face validity. The studies reviewed were given one point for each outcome measure reported. Only five articles mentioned the presence of an informed consent procedure and approval by a medical ethics committee. One article mentioned the presence of an informed consent procedure only.

The interpretation of the efficacy of DMSO depends partly on information on the use of co-interventions and the participants' adherence to the treatment regimen. As mentioned above, six articles described the use or absence of co-interventions; the others presented little information about the use of co-interventions. Seven articles described dropout rates.

Although the studies were based on small samples and often lacked reference groups, the authors concluded that it seems safe to use DMSO on the human skin, either by rubbing or by spraying. The indication is to use DMSO in concentrations less than 50 percent because of the increasing risk of side effects at concentrations exceeding 50 percent. At concentrations below 50 percent, DMSO has favourable effects on inflammation and wound healing, as well as an analgesic effect, which is of course also an important aspect for the patient.

Table 3. Summary of the methodological assessment for each criterion of the four different dimensions of quality

Dimensions	External Validity					Internal Validity							DPA			GCP				Total Score 80 Without GCP* (p, q, r, s)	Total Score 87 With GCP* (p, q, r, s)
Criteria	a	b	c	d	e	f	g	h	i	j	k	l	m	n	o	p	q	r	s		
Max Weight	3	10	10	5	2	5	5	5	7	5	3	5	5	5	5	2	3	1	1		
Study																					
Salim [20]	3	10	7	5	2	5	2	5	5	4	3	3	3	5	3	2	2	1	1	65	71
Geertzen, et al [18]	2	6	7	3	1	4		3	5	3	3	5	5	3		2	2	1	1	50	56
Lishner, et al [5]	3	8	8	5	2	4	3	3	1	2	2		2	3	3	2	2			49	53
Langendijk, et al [19]	3	7	3	4	2	3				3	1	3	2	5	3	2	3	1		39	45
Binninck, et al [22]	1	6	6	5	3	3	1	2	1	4		1	1	1	3		2	3	1	38	44
Van Rossum [4]	3	6	4	4	1	4				4		4	4			2	3			34	39
Goris, et al [17]	1	5	4	1	2	2	2			2	1	2	2	3		2	2	1	1	27	33
Agner and Serup [16]	2	5	3	4	1	1							4	3	1	2	3	1	1	24	31
Sulzberger, et al [7]	2	3	8			3							1	2		2	3			19	24
Frosch, et al [21]	1	3	2		2											2	3			8	13
Alberts and Dorr [13]			5	3	1	1										2	2			10	14
Engel [14]		2	2	2	1						1					1	1			8	10
Scherbel, et al [12]	1	1			1						1			3		1	2			7	10
Engel [15]			2		1									1		1	2			4	7
Mean	14.36					8.21							4.71			4.86				27.28	32.14
Std. Deviation	7.75					8.86							3.79			1.46				19.18	20.08

*GCP = Good clinical practice; *DPA = Data presentation and analyses

Table 4. The correlation matrix

	External Validity	Internal Validity	Data Presentation and Analyses	Good Clinical Practice	Total Score
External Validity	1				
Internal validity	0.843	1			
Data Presentation and Analyses	0.818	0.760	1		
Good Clinical Practice	0.610	0.466	0.673	1	
Total Score	0.957	0.944	0.889	0.641	1

References

[1] *Bours GJJW, Halfens RJG, Huijer Abu-Saad H, Grol RTPM. Prevalence, prevention, and treatment of pressure ulcers: A descriptive study in 89 institutions in the Netherlands. Research in Nursing and Health 2002;25(2):99–110.*

[2] *Houwing R, Overgoor M, Kon M, et al. Pressure-induced skin lesions in pigs: Reperfusion injury and the effects of vitamin C. J Wound Care 2000;9(1):36–40.*

[3] *Four-Grade System. Presented at the European Pressure Ulcer Advisory Panel (EPUAP). Oxford, UK, September 20–22, 1998.*

[4] *Van Rossum JP. Behandeling en preventie van decubitus met dimethylsulfoxide—verslag van een pilot studie (Treatment and prevention of decubitus with dimethyl sulfoxide—a report of a pilot-study). Unpublished report, personal communication, 1997.*

[5] *Lishner M, Lang R, Kedar I, Ravid M. Treatment of diabetic perforating ulcers (mal perforant) with local dimethyl sulfoxide. J Am Geriatr Soc 1985;33:41–3.*

[6] *Kedar I, Jacob E, Ravid M. Dimethylsulfoxide in acute ischaemia of the kidney: Experimental models in the rat and in the dog. Ann NY Acad Sci 1983;411:131.*

[7] *Sulzberger MB, Cortese TA, Fishman L. Some effects of DMSO on human skin in vivo. Ann NY Acad Sci 1967;141(1):437–50.*

[8] *Kappert A. Experimental and clinical evaluation of topical dimethyl sulfoxide in venous disorders of the extremities. Ann NY Acad Sci 1975;243:403–7.*

[9] *Feinstein AR. Clinical Epidemiology: The Architecture of Clinical Research. Philadelphia, PA: WB Saunders, 1985.*

[10] *Bouter LM, van Dongen MCJM. Epidemiologisch onderzoek: Opzet en Interpretatie [Epidemiologic Research: Principles and Methods] [Dutch]. Houtem/Diegem: Bohn Stafleu Van Loghum, 1995:183–6.*

[11] *Assendelft WJJ, Scholten RJPM, van Eijk JTM, Bouter LM. De praktijk van systematische reviews III. Methodologische beoordeling van onderzoeken (The practice of systematic reviews. A methodological assessment of research). Ned Tijdschr Geneeskd 1999;143(14):714–8.*

[12] *Scherbel AL, McCormack LJ, Layle JK. Further observations on the effect of dimethyl sulfoxide in patients with generalized scleroderma (progressive systemic sclerosis). Ann NY Acad Sci 1967;141(1):613–29.*

[13] *Alberts DS, Dorr RT. Case report: Topical DMSO for mitomycin-c-induced skin ulceration. Oncol Nurs Forum 1991;18:693–5.*

[14] *Engel MF. Indications and contraindications for the use of DMSO in clinical dermatology. Ann NY Acad Sci 1967;141(1):638–45.*

[15] *Engel MF. Dimethyl sulfoxide (DMSO) in clinical dermatology. South Med J 1966;59(10):1318–20.*

[16] *Agner T, Serup J. Quantification of the DMSO-response, a test for assessment of sensitive skin. Clin Exp Dermatol 1989;14:214–7.*

[17] *Goris RJA, Dongen LMV, Winters HAH. Are toxic oxygen radicals involved in the pathogenesis of reflex sympathetic dystrophy? Free Radic Res 1986;3(1–5):13–8.*

[18] *Geertzen JHB, de Bruijn H, de Bruijn-Kofman AT, Arendzen JH. Reflex sympathetic dystrophy: Early treatment and psychological aspects. Arch Phys Med Rehabil 1994;75:442–5.*

[19] *Langendijk PNJ, Zuurmond WWA, Van Apeldoorn HAC, Van Loenen AC, De Lange JJ. Goede resultaten van behandeling van acute reflectoir-sympathische dystrofie met een 50%-dimethylsulfoxide-crème (Good results of the treatment of acute reflex sympathetic dystrophy by using a 50%-dimethyl sulfoxide cream). Ned Tijdschr Geneeskd 1993;137(10):500–3.*

[20] *20. Salim AS. Role of free radical scavengers in the management of refractory duodenal ulceration. J Surg Res 1994;56:45–52.*

[21] *Frosch PJ, Duncan S, Kligman AM. Cutaneous biometrics I. The response of human skin to dimethyl sulfoxide. Br J Dermatol 1980;102:263–73.*

[22] *Binnick SA, Shore SS, Corman A, Fleishmajer R. Failure of dimethyl sulfoxide in the treatment of scleroderma. Arch Dermatol Res 1977;113:1398–1402.*

Chapter 6B

An unexpected detrimental effect on the incidence of heel pressure ulcers after local 5% DMSO cream application.

R.H. Houwing, W.C. van der Zwet , B.S.E. van Asbeck, R.J.G. Halfens, J.W. Arends

A randomised double-blinded study with massaging DMSO in patients at risk for pressure ulcers.

Accepted for publication

In a controlled randomized clinical trial on patients prone to pressure ulcers, we evaluated the effects of massaging a DMSO-containing cream on the buttocks, heels and ankles. This chapter discusses the results of this study and the possibilities and limitations of a locally applied anti-oxidant.
This study was performed in nine Dutch nursing homes in the surroundings of Maastricht, the Netherlands. This study was undertaken with a financial support from the Dutch government (Zorg Onderzoek Nederland).

Abstract

Background

Ischemia-reperfusion injury and reactive oxygen species (ROS) are considered to play an important role in the pathogenesis of pressure ulcers (PU). Anti-oxidants may diminish the inflammation and damage of these ROS in pressure ulcer formation. Dimethyl sulfoxide (DMSO) is a hydroxyl antioxidant which inhibits leukocyte adherence. When used topically, DMSO is a safe and well-tolerated drug with excellent penetrating properties. In this prospective randomized study, the effect of topically applied DMSO on the prevention of PU formation is analyzed.

Methods

In a randomised double-blinded study, we intended to asses the effects of massage with or without DMSO creames against controls for two locations, ig. heel and buttocks, in 79 patients, prone for development of PU.

Results

For the buttocks, there was no difference in PU incidence between the three interventions. Surprisingly, the topical 5% DMSO cream group, however, showed an increase in superficial pressure ulcers for the heel location.

Discussion

This is a study on the possible role of DMSO in the prevention of PU. The results suggest an adverse effect on PU incidence in heel, whereas on the buttocks there seems to be no effect of DMSO cream. Possible explanations for this unexpected detrimental effect are discussed.

Introduction

Pressure ulcers(PU) continue to be an enormous healthcare problem that affects large segments of the patient population. A PU is an area of localised damage to the skin and underlying tissues caused by pressure, shear or friction.[1] Apart from relief of tissue loading there are no appropriate therapies for preventing PU. The complete etiology of PU is not yet fully understood. However, some components of the injury are caused by ischaemia followed by reperfusion.[2] Ischaemia-reperfusion (I-R) injury has been defined as the injury, at the cellular level, resulting from the restoration of blood flow to tissue with previous ischaemia. Reoxygenation promotes the generation of various reactive oxygen species (ROS) leading to the uncontrolled oxidation of vital cellular components. The hydroxyl radical ($HO^{\bullet}$), which is formed during the reaction between superoxide and hydrogen peroxide in the presence of iron, appears to be the critical oxidant and an important initiator of lipid-peroxidation during I-R injury.[3] [4] Several defence mechanisms are present within tissues and cells for the protection against ROS. In addition, a number of drugs, anti-oxidants, have been shown to prevent or scavenge damaging oxidants and free radicals. Studies in ischemia-reperfusion related PU animal studies showed a decrease of tissue necrosis after treatment with various systemically or locally applied anti-oxidants.[2] [5] [6] [7] Dimethylsulfoxide (DMSO [(CH3)2S-O] has a potentially complex mechanism of action as it has anti-ischemic, anti-inflammatory, and antioxidant properties. Due to its ability to scavenge the highly cytotoxic hydroxyl radical, and by inhibiting leukocyte adherence, DMSO is widespread used as antioxidant in both in vivo and in vitro models of I-R.[8] [9] Topical application of DMSO, an organic liquid with excellent penetrating properties, has been shown to increase the survival of primarily ischemic island skin flaps.[10] As I-R injury plays a role both in ischemic skin flaps and PU, topical DMSO could, likewise, be useful in the prevention of PU development.[11] Local therapy to improve the outcome of I-R damage in PU development other than pressure relief may open a new therapeutic window for PU prevention. Against this background therefore, we performed a double-blinded randomised study with a local antioxidant, DMSO. This study is a part of a cross-over study. [12] In this study we made a more in depth investigation of the effect of DMSO for the different locations as buttocks versus heel and ankle area.
The objective of this study was to determine whether topically applied DMSO in a 5% concentration prevents or attenuates PU formation in a population prone to this condition.

Methods

We performed a double-blinded randomised multicenter placebo-controlled study in a population prone for PU to investigate the effect of a 5% DMSO cream, for two separate locations:[1] the buttocks and[2] heel/ankle. Both buttocks and heel and ankle area are

vulnerable for PU development. Both the heel and ankle region are particularly prone because of their relatively lower resting blood perfusion, higher surface pressure under load, and due to the extent of subcutaneous tissue covering the heel bone, or malleoli of fibula and tibia. Due to similarities between heel and ankle they are taken together in the incidence rates. This study was approved by the Ethic Committee of the Academic Hospital Maastricht, The Netherlands.

Three intervention-groups were compared:

1) a control group without a topical application (Control),
2) a placebo cream group (Placebo) and
3) a group with 5% DMSO cream (DMSO).

The control group received the same preventive measures as the other groups, without a locally applied cream, and was introduced as a third arm in the study to exclude a possible effect of massaging. All groups received treatment for the period of 4 weeks.
The study was performed in eight nursing homes that were comparable in terms of guided PU policy. These kind of institutions are typical for the Dutch health care situation. The category of patients referred to nursing homes in the Netherlands, normally stay in regular hospitals in other countries. They have a high prevalence rate of PU and the population is rather stable over a long time.[11]

Patients

The following inclusion criteria were applied:

1) Written informed consent was obtained from each patient. If the mental capability of the patient to decide on participation was uncertain, the legal representative of the patient was asked for consent.
2) Patients had to be able to participate for an evaluation for 4 weeks,
3) Patients had to rest on an anti-pressure ulcer mattress
4) Patients had to be at high risk of developing PU according to the Braden scale using a cutt-off point of 20[12]

Exclusion criteria were:

1) patients who were treated with another, unrelated ointment or cream,
2) patients who were to undergo, or had undergone surgery less than 2 weeks ago,
3) patients with already manifest PU,
4) Patients with a dark skin, because of difficult skin assessment.

Interventions

For practical reasons the three intervention groups were randomly assigned at ward level, and not at patient-level. For ethical reasons we did not include a control group of patients not receiving any treatment. The three interventions were:

Control: 30° position change, repeated every 6 hours for 4 weeks

Placebo: Prevention as control group, with 3-minute massage of the buttock, heel and ankle regions, with an indifferent cream, combined with a 30° position change. This procedure was repeated every 6 hours for 4 weeks. Vaseline-cetomacrogol cream was used as the indifferent cream.

DMSO: Prevention as treatment placebo group, with massage with a "DMSO-cream". The DMSO-cream consisted of 5% dimethyl sulfoxide in vaseline-cetomacrogol cream.

Instruments

The presence of PU was evaluated with the help of the four-grade system of the European Pressure Ulcer Advisory Panel.[1] Special attention was given to grade I, non-blanchable redness. It is sometimes hard to differentiate between a blanchable redness and a grade 1 non-blanchable redness. If a local redness persisted after 10 minutes of pressure relief, a transparent convex lens (6.5 cm) was pushed against the skin. When the redness had not vanished, and was still present after 4 hours of pressure relief, confirmed by two external observers, these lesions were recorded as grade 1 PU. When PU did occur, the location, but not the patient was excluded from the study. The outcome measure of the study was the presence of PU.

Results

79 persons in total were included. 18 patients underwent only position changes (Control); 32 patients were massaged with the placebo cream (Placebo); 29 patients received the DMSO-cream (DMSO). There were no significant differences in patient characteristics. (Table1), and there was no fall-out. For all locations, an incidence rate of 44% was found. Especially the heel/ankle location was susceptible to PU (table 2). Only superficial forms of PU, grade 1 and 2 were seen. Massage with placebo cream neither showed a positive neither or negative effect on PU incidence in comparison with the control group, for all three locations. Massage with a 5% DMSO cream, however, demonstrated a higher incidence of PU development compared to the control and to the placebo group. (table 2) This was caused by a significantly higher incidence of PU for the location heel/ankle (OR 8.80, 95%CI 2.61-29.6). For the buttocks there was no difference. Since there is no difference between the control group and the placebo treatment group, a negative effect due to massage could be excluded. The statistically

significant increase of the PU incidence on heel/ankle location must therefore a result of the DMSO application.

Discussion

In the present study nearly half of the included patients suffered from PU formation, despite the extensive protocolized preventive measures. This confirms that PUs are still a major problem in daily patient care where preventive measures are often suboptimal This study was intended to investigate the preventive effect of a 5% DMSO cream on PU formation in a high risk patient population. To our surprise we found no effect for the buttocks and even a statistic significant worsening effect on PU risk for heel/ankle compared to the placebo cream. Reactive oxygen species (ROS), such as superoxide, hydrogen peroxide and the hydroxyl radical, play a major role in the inflammation seen in PU formation.[2 5 6 7] DMSO has a potentially complex mechanism of action as it has anti-ischemic, anti-inflammatory, and anti-oxidant properties. Widely used as home remedy, systemically and topically, it is a safe and well-tolerated anti-inflammatory drug.[9] As a potent scavenger of the hydroxyl radical, and by inhibiting leukocyte adherence, there is a rational basis for the use of DMSO to diminish the tissue necrosis in pressure ulcers.[11] However, we found more tissue damage with DMSO for the location heel and ankle. Since there is no difference between the control group and the placebo treatment group, a negative effect due to massage could be excluded. When used topically, 5% DMSO is a safe and well-tolerated drug. In high concentrations from 50-100%, it is known to cause irritation as a temporary erythema with scaling. Skin changes observed in this study, such as non-blancheable erythema and partial skin loss (grade I and II PU), are not known to be side effects of DMSO, not even in high concentrations.[9 11] The conclusion is therefore, topical 5% DMSO cream *in combination with* tissue loading by pressure, shearing, and/or friction must have been responsible for this unexpected effect.

Although, the detrimental effect on heel and ankle, opposite to a neutral effect on the area of the buttocks is hard to explain, we will speculate about possible explanations for this unexpected finding. It is unlikely that the penetration is different for the locations, as DMSO has excellent penetrating properties. The thickness of the epidermis of buttocks and heel are comparable, as a thick hyperkeratotic layer of heels is absent in long-lasting immobile patients. Firstly; an explanation could be a different pathophysiologic mechanism of PU formation for buttocks and heel. The response of mechanical loading in heel compared to the skin of the buttocks will vary greatly. Anatomical differences as thickness of the subcutaneous tissue layer and absence of muscle between skin and the bony prominence will cause high pressure points in heels and ankles in a lying position. Mayrowitz et al showed that the effects of occlusion of blood flow by direct tissue loading, or by an inflated vascular cuff placed above the ankle, are different.[15] As a consequence,

ischaemia followed by reperfusion, is probably not the only pathophysiological explanation for PU formation in heels; tissue loading appears to be a necessary contributing factor. The role of I-R injury is just one of the pathophysiological mechanisms in the pathophysiology of PU. Impaired interstitial fluid flow and deformation of cells can also contribute to the development of PU. [16] It is unknown what the influences of DMSO on pathophysiologic mechanisms other than I-R injury will be, as DMSO is a relatively non-specific compound that influences a variety of biological processes. [17] Secondly; the worsening of PU incidence on the heels can be the result of a paradoxical antioxidantal effect of DMSO. Scavengers have the ability to act as antioxidant, neutral, or pro-oxidant. An antioxidant could be harmful because of preventing the cell response to stress by up-regulating its antioxidants defence. A negative effect of an antioxidant, in contrast to what could be expected, is called a pro-oxidant effect. Other studies also have shown that antioxidantal therapy could have adverse effects. [18] Thirdly; the protective effect of antioxidants in oxygen stress related diseases is concentration-dependand. High concentrations have been proven to provide protection, low DMSO concentrations could affect intact cells by producing a submaximal but biologically effective stimulation of a tyrosine kinase.[8] [17] In our study we choose a low 5% DMSO cream for its low toxicity and the absence of garlic odour to allow for a double-blind study design. A high concentration DMSO cream would probably have been more appropriate.

Conclusion

Insight in the pathofysiological processes in PU formation provides the opportunity for therapeutical approaches other than pressure relief. Interventions concerning the process of oxidative stress open a therapeutic window to treatment and prevention. However, antioxidants can have an opposite effect, as shown in this study. Further studies will be required to fully understand and characterize the critical role of oxidants and the pharmacologic properties of the anti-oxidant in I-R injury. Double-blind randomised studies in humans are necessary, as discrepancies have been found in studies on the effect of anti-oxidants, orally or locally applied, in animals and humans.[19] Much still has to be learned about the uptake, biotransformation, and tissue distribution of molecules regularly thought of as antioxidants before we can reliably indicate that they have such functions in vivo [19] [20]

Table 1: patient characteristics

		control group (n=18)	placebo group (n=32)	DMSO group (n=29)
Gender	male	5 (27.7%)	8 (25%)	11 (37.9%)
	female	13 (82,3%)	24 (75%)	18 (72.1%)
Incontinence	no incontinence	3 (16.7%)	2 (6.3%)	0
	sometimes incontinent	6 (33.3%)	5 (15.6%)	12 (41.4%)
	always incontinent	9 (50%)	25 (78.1%)	17 (58.6%)
age	median (min-max)	81.5 (67-91)	85 (63-96)	80.5 (45-97)
Development of pressure sores	Heel/ ankle	3 (16.6%)	5 (15.6%)	16 (55.1%)
	buttocks	6 (33.3%)	7 (21.9%)	11 (37.9%)
	all locations	7 (38.9%)	10 (31.3%)	18 (62.1%)

Table 2: multivariate logistic regression analysis on risk factors for pressure ulcer formation

risk factor	location					
	buttocks		heel and ankle		all locations	
	OR	95%-CI	OR	95%-CI	OR	95%-CI
gender	0,61	0.21-1.77	1,58	0.44-5.58	1,26	0.44-3.62
age (years)	1,01	0.96-1.07	1,00	0.95-1.06	1,00	0.95-1.06
incontinence (ref)						
sometimes incontinent	0,45	0.05-4.05	0,22	0.02-2.38	0,29	0.03-2.48
always incontinent	0,50	0.07-3.78	0,15	0.02-1.39	0,37	0.05-2.65
no intervention (ref)						
placebo	0,57	0.15-2.20	2,18	0.31-15.4	0,74	0.21-2.66
DMSO	1,33	0.36-4.89	15,28	2.21-105	3,23	0.90-11.62
no intervention or placebo (ref)						
DMSO	1,87	0.66-5.30	8,80	2.61-29.6	3,89	1.41-10.7

OR; odds ratio, CI; confidence interval, ref; referencegroup
Statistically significant odds ratios are in bold

References

[1] *EPUAP. 1998a. September 20-22. four-grade system. Paper presented at the European pressure ulcer advisory panel, Oxford, UK.*

[2] *Houwing R., Overgoor M., Kon M., Jansen G., Asbeck van B.S., Haalboom J.R.E. Pressure-induced skin lesions in pigs: reperfusion injury and the effects of vitamin E. Journal of Wound Care, 9(1):36-40, 2000.*

[3] *McCord JM. Oxygen-derived free radicals in postischaemic tissue injury. N Engl J Med 1985;312:159-63*

[4] *Granger DN Role of xanthine oxidase and granulocytes in ischemia-reperfuison injury, Am J Physiol1988;255:H1296-75*

[5] *Sundin BM, Hussein MA, Glasofer S, El-Falaky MH, Abdel-Aleem SM, Sachse RE, Klitzman B. The role of allopurinol and deferoxamine in preventing pressure ulcer in pigs. Plast reconstr Surg 2000;105(4):1408-21*

[6] *Peirce SM, Skalak TC, Rieger JM, Macdonald TL, Linden J. Selective A(2A) adenosine receptor activation reduces skin pressure ulcer formation and inflammation Am J Physiol Heart Circ Physiol. 2001 Jul;281(1):H67-74)*

[7] *Sener G, Sert G, Sehiri AO, Arbak S, Gedik N, Ayanoglu-Dulger G. Melatonin protects against pressure ulcer-induced oxidative injury of the skin and remote organs in rats J Pineal Res 2006;40:280-7*

[8] *Sekizuka E, Benoit JN, Grisham MB, Granger DN. Dimethylsulfoxide prevents chemoattractant-induced leukocyte adherence. Am J Physiol 1989;256:H594-7*

[9] *Santos NC, Figueira-Coelho J, Martins-Silva J, Saldanha C. Multidisciplinary utilization of dimethyl sulfoxide: Pharmacological, cellular, and moleculars aspects. Biochem Pharmacol 2003;65:1035-41*

[10] *Carpenter JR, Angel MF, Morgan RF. Dimethyl su;foxide increase the survival of primarily ischemic island skin flaps. Otolaryngol Head Neck Surg, 1994,110:228-31*

[11] *Duimel-Peeters IGP, Houwing RH, Teunissen CP, Berger MPF, Snoeckx LHEH,Halfens RJG. A Systematic Review of the Efficacy of Topical Skin Application of Dimethyl Sulfoxide on Wound Healing and as an Anti-Inflammatory Drug. Wounds 2003 15(11):361-370*

12 Duimel-Peeters, IGP, Halfens RJG, Ambergen AW, Houwing RH, Berger MPF, Snoeckx LHEH. The effectiveness of massage with and without dimethyl sulfoxide in preventing pressure ulcers: A randomized, double-blind cross-over trial in patients prone to pressure ulcers. International Journal of Nursing Studies (2007), doi:10.1016/j.ijnurstu.2007.04.002

[13] *Rapportage resultaten. 2006 Halfens, R.J.G., Janssen, M.A.P., & Meijers, J.M.M. (ed); Rapportage Landelijke Prevalentiemeting Zorgproblemen. Datawyse / Universitaire Pers Maastricht*

[14] *Bergstrom N, Braden BJ, Laguzza A, Holman V. The Braden sclae for predicting pressure sore risk. Nurs. Res. 1987;36(4):205-10*

[15]*Mayrovitz HN, Sims N, Dribin L. Heels skin hyperaemia: direct compression versus vascular occlusion. Clin Physiol Funct Imaging 2003;23:354-9*

[16] *Bouten CV, Oomens CW, Baaijens FP, Bader DL.The etiology of pressure ulcers: skin deep or muscleboun?Arch Phys Med Rehabil. 2003 Apr;84(4):616-9*

[17] *Rubin RA, Shelton HE. Dimethyl Sulfoxide Stimulates Tyrosine Residue Phosphorylation of Rat Liver Epidermal Growth Factor Receptor. Science 1983;219(7):60-3*

[18] *Halliwell B Antioxidants in human health and disease. Annu Rev Nutr.1996;16:33-50*

[19]*Bast A, Haenen GR. The toxicity of antioxidants and their metabolites. Environ Toxicol Pharmacol. 2002;11:251-8*

[20]*Azzi A, Davis KJA, Kelly F. Free radical biology- terminology and criticical thinking. FEBS Letters 2004;558:3-6*

Chapter 7

General discussion

7.1 Introductory remarks

This thesis focussed on the pathophysiology and prevention of pressure ulcers (PU). The pathophysiology of PU in an animal model and superficial PU in man were studied. Since prevention is the key issue in PU care, the usefulness of a risk assessment tool was evaluated. The preventive effect of high protein food supplementation, enriched with arginine, zinc and antioxidants, and of the topical anti-oxidant, Dimethyl Sulfoxide (DMSO), was studied in patients prone to develop PU. In the general discussion the results as presented in the previous chapters will be discussed according to the questions formulated in the introduction of the thesis, being:

7.2 Do moisture lesions exist as a separate entity?

Skin problems are known to be particularly severe among nursing home residents with incontinence and immobility.[1] Recently, in Europe and the USA attempts have been made to single out superficial skin loss in incontinent and immobile patients from early stages of PU as a distinct entity. This kind of lesions named 'moisture lesions'[2] [3] or 'moisture-associated-skin-damage' (MASD) [4] [5] are considered by some nurses to have a patho-physiologic mechanism different from superficial PU lesions, with moisture as the primary cause, whereas pressure, shear and friction are supposed not to be involved. As a consequence, treatment and prevention are focussed on incontinence- and skin-care, and pressure relieving measures are thought not to be indicated.[4] [5] The prevalence of incontinence associated skin lesions in Dutch healthcare institutions is estimated to be 11%.[6] As described in chapter 2 we investigated whether these moisture lesions form a definite entity and can be distinguished from PU. The histopathology of skin biopsies from patients with moisture lesions, diagnosed according to the EPUAP statement, was investigated. Two distinct histopathological patterns were observed. 1) An ischemic pattern, with a partly avital epidermis, edema in the dermis with vascular dilatation, engorgement of erythrocytes, and a diffuse infiltration of polymorphonuclear cells. 2) The other pattern showed hyperplastic changes of the epidermis with elongated rete ridges and dilated blood vessels, sometimes with subepidermal blisters and a partial loss of the epidermis. These different patterns could not be related to differences in clinical aspect of the skin lesions where the biopsies were taken from. The skin biopsies, however, were only 5 mm in diameter, representing only a small part of the clinical lesion. For that reason it is possible that both histological patterns exist in the same clinical lesion. None of the skin biopsies showed a histopathological pattern compatible with that of irritant contact dermatitis.

Based on these results the pathogeneses, classification and prevention guidelines involving "moisture lesions" can be discussed along the following questions:

1) What is the pathophysiological mechanism for each of the two histopathological patterns found in moisture lesions?
2) Is moisture the only cause of moisture lesions?
3) How should the guidelines on prevention and treatment of skin lesions in incontinent patients be formulated?
4) Is it allowed to exclude this form of tissue damage in PU classification used for prevalence and incidence rates?

Ad 1) What is the pathophysiological mechanism for each of the two histopathological patterns found in moisture lesions?

Careful clinical observation of moisture lesions shows fine hyperkeratotic parallel ridges, often seen togheter with erosions or ulcers with a linear pattern, both directed perpendicularly to the anal cleft. This strongly suggests the influence of chronic shearing forces as earlier described by Bos.[7] PU are caused by sustained tissue loading. This loading can be applied *perpendicular* to the tissue surface (called pressure) or *plane* to the skin surface (called a tangential force).[8 9 10] Tangential forces are generated for instance when a patient is lying in a bed with the head end raised, causing the patients torso to slide down. Tangential forces can lead to *friction* when there is displacement between the skin and the supporting surface, or *shear* when there is no movement between skin and the bed sheets. Whether there will be friction or shear depends on the magnitude of the applied force and on the resistance between the two surfaces, known as the friction coefficient.[11 12 13] In patients with a moistened skin, as with incontinence, an angled force is unlikely to cause movement (due to a high friction coefficient) and will result in shearing. Shearing is an important etiologic factor in the development of PU, since it enhances the effects of pressure. The pressure, necessary to obstruct blood flow, is half the pressure that is required when shear is present. The combination shear *and* pressure is more damaging than pressure per se.[14 15 16 17] The ischemic pattern found in our study can be a result of occlusion of microvessels subjected to pressure and shear. This is consistent with the histopathology seen in early PU lesions, both in human[18] and in animal studies.[19 20 21] (chapter 2 & 5)

The pathologic consequences of a shearing force on the superficial skin layers depend on the following three factors: 1) the condition and thickness of the epidermis; 2) the interface between dermis and epidermis, the dermal-epidermal junction; 3) the architecture of the dermis[22 23 24 25] In the presence of moisture, which causes maceration of the epidermis and disruption of the skin barrier, shearing can easily lead to erosion. Eventually, this can result in ulceration, with subepidermal skin loss. Whether this will occur depends on the structure of the dermis and dermo-epidermal junction (DEJ). The DEJ is important for adherence of the epidermis to the underlying tissues. In the elderly, the DEJ, being important in resisting to external forces, tends to be more vulnerable. This is most probably due to flattening and loss of reteridges, but also to a detachment of the epidermal basal cells by ischemic injury, as well as enhanced by capillary fragility and decreased perfusion.[26 2728 29 30 31] Furthermore ageing results in alterations of the dermis, such as degradation of extracellulair matrix, collagen and elastin, including the basement membrane. These structural changes, enhanced by oxidative stress, will lead to reduced tensile strength and impairment of the strength of the DEJ.[32 33 3435 36]

Therefore the skin of elderly patients is susceptible for shearing forces. However, shear stress not only results in tissue breakdown but also in an adaptational response. Shear will enhance the tension in the skin, which appears to stimulate cellular proliferation. Proliferation of epidermal cells, in combination with alterations in the dermis, results in a hyperplastic pattern, with elongated reteridges.[23 24 37 38]

In conclusion

Tangential tissue loading, enhanced by a high friction coefficient due to moisture, can be responsible for the two histopathological patterns found in our study (chapter 2). Both a hyperplastic pattern with or without loss of the epidermis, and an ischemic pattern strongly suggest that shearing forces are an essential etiologic factor in moisture lesions.

Ad 2) Is moisture the only cause of moisture lesions?

In nursing literature it is stated that moisture has to be considered as the main cause of the superficial skin loss in moisture lesions. [2 3 4 5] Prolonged skin contact with moisture due to incontinence of urine and/or faeces can result in well-demarcated areas of erythema, edema, and scaling particularly in the perineal area. In infants this is known as *diaper rash*, a so-called *irritant contact dermatitis*. Persistent occlusion, maceration, friction, the presence of irritating agents such as stool and urine, cleaning agents, and bacterial colonization may all be contributing factors.[39 40 41 42] Due to maceration (Latin: *macerare*, "to soften") there is loss of the stratum corneum barrier, enhanced by digestive enzymes in faeces.[43] Severe irritant contact dermatitis is characterized by erythema, edema, blistering, weeping and pain, or even erosions (suprabasal skin loss). However, subepidermal skin loss and ulceration, as seen in patients with moisture lesions are not observed. The histopathological picture of an irritant dermatitis shows spongiosis and mild inflammatory changes in the dermis, a pattern different from patients with moisture lesions. (chapter 2)

Moisture-lesions or MASD are not based on etiology or histopathological proof, but exclusively on so-called expert opinion. Since moist or humidity *per se* does not cause skin lesions, the term "moisture lesions" is not well chosen. Moreover the introduction of new nosologic diagnoses only based on expert opinion is fundamentally wrong. New diagnoses are only to be introduced when based on proper medical principles and investigations and according the rules of the WHO Update Reference Committee.

In conclusion

The sole influence of urine and/or faeces is not sufficient to cause epidermal skin loss. In immobile and incontinent elderly the skin has a diminished tolerance for tissue loading, which can result in subepidermal skin loss. More research is needed to study the influences of shear and friction in the etiology of superficial PU, especially in damaged and vulnerable skin by maceration or other pre-existent perineal skin diseases.

Ad 3) How should the guidelines on prevention and treatment of skin lesions in incontinent patients be formulated?

From the above it may be clear that diminishing tissue loading is important in both prevention and treatment. However, treatment only consisting of the use of pressure redistributing devices, will be of limited value. A more useful strategy will be the reducing of shearing and friction by means of the elevation of the head-of-bed together with leg elevation at 10º- 30º in order to reduce body displacement at the sacral area.[44] Also of importance is the change of body position with a certain frequency (turning scheme) since it diminishes both tissue loading and the deleterious influence of urine, faeces and pain as well. Maceration of the skin has to be treated by maintaining a dry and clean skin, and prevention of occlusive effects of moist sheets or soiled under pads. Mattresses soiled by urine or stools contribute to additional tissue-interface pressure and therefore increase the risk of skin ulceration.[4] Inadequate skin care increases the risk of breakdown and the development of chronic wounds.[40] [45] [46] [47] Incontinence for urine and/or faeces is a major healthcare problem. Worldwide more than 200 million people suffer from incontinence, especially in people with a low ADL score (activities of daily living) in institutional settings.[48] Since the quality of care of incontinence problems was estimated to be not optimal in the Netherlands, starting 2006 the Dutch Health Council considers the incidence of incontinence as an indicator of the quality of care. With personal and tailored care elderly people are longer capable to help themselves to the toilet.[48] Improvement of the quality of care will diminish the incontinence problems as well as the incidence of PU. The deleterious effects of faecal incontinence could be diminished by means of dietary interventions and if necessary with an anal device.

In conclusion

The guidelines on prevention and treatment of skin lesions in incontinent patients should be based on three main interventions: 1) managing the incontinence problem 2) adequate skin care and 3) diminishing tissue loading. Methods and effectiveness of proper skin care on treatment and prevention of skin damage in individuals prone to develop PU deserves more research, attention and education.

Ad 4) Is it allowed to exclude this form of tissue damage in PU classification used for prevalence and incidence rates?

The purpose of a staging system is to provide a method of communication to assess the extent of anatomical tissue loss.[49] [50] The two classification systems most widely used are those of the European Pressure Ulcer Advisory Panel (EPUAP) and of the National Pressure Ulcer Advisory Panel (NPUAP).[51] [52] These classification systems provide a description of the depth of tissue destruction, and are designed for a quick and easy assessment for every healthcare professional.

There has been much debate about the superficial forms of PU, grade 1 and 2 that is, without skin loss or with partial skin loss.[53] [54] [55] [56] [57] [58] A few years ago, all skin tears, fissures or excoriations were considered to be decubitus lesions, even if they were not likely to be caused by prolonged pressure insults. However, a possible negative side-effect of the strict adherence to a staging system could be its use for other than pure medical or nursing purposes. In The Netherlands and the United Kingdom PU prevalence is used as an indicator for the quality of care. One step further is its use to judge a so-called " neglect" on the part of the heath providers, by public prevalence rates and by lawyers.[59] [60] Hence, classifying moisture skin lesions as PU can negatively affect regulatory and legal liability associated with the F314 Pressure Ulcer Tag in the USA.

Controversies in grading are inevitable, since the classification system is based on consensus and not on pathofysiology. Our study shows that based on clinical and histopathological aspects moisture lesions cannot be differentiated from PU grades 2 or 3. (chapter 2) This could be the explanation of the fenomenon that training of medical and nursing personnel, in an attempt to enhance the intra- and interrater reliability of the EPUAP classification, seems to have little results.[61] With the introduction of the diagnosis moisture lesions (until very recently classified as grade 2 and 3 PU) the reliability and conformity of the system, necessary for prevalence and incidence surveys, decreased. Objective evaluation of possibly effective measures in superficial skin loss is made much more difficult in stead of easier and in fact not possible anymore.

In conclusion

There is no justification to consider moisture lesions as a clinical entity different from superficial PU. According to our data moisture lesions should be classified as grade 2 or 3 PU. A sore and odorous skin loss in the incontinent elderly is not a sign of a good quality of care. By eliminating this almost always preventable skin condition from prevalence and incidence surveys, there is a lack of recordings needed to increase the quality of patient care.

The Dutch Inspectorate of Health should, when PU classification is concerned, adhere to the classification as used in the latest CBO guideline, which is supported by the Dutch medical scientific organisations.

7.3 Do risk assessment tools really identify patients at risk?

In the prevention of PU it is essential to identify patients who are at risk to develop PU as early as possible. A so-called pressure ulcer risk-assessment scale (PURAS) is based on identification, enumeration and quantification of expected risk-factors and is meant as a tool that supports clinical judgment in order to identify patients at risk. A PURAS should always be coupled to the use of preventive measures.[62] The identification of patients with an increased risk, however, is only of value when this knowledge is immediately followed by measures such as the start of a frequent turning scheme or the installation of a special bed or device. A PURAS with high-sensitivity and specificity enables the determination which patients *do* require these preventive measures, and –equally important- which patients *do not*.

We investigated the predictive value of a PURAS in 121 patients admitted to the hospital with a traumatic hip fracture. Patients with this type of trauma are considered to be a rather homogenous patient population, prone to develop PU.[63] Incidence, moment of onset of PU, and the efficacy of the PURAS used were studied. The tool consisted of ten items considered to have influence on the development of PU. The results showed that the tool had a low discriminative capability. Only a prolonged time on the operation table proved to be an independent predictor associated with a higher incidence of PU. (chapter 3)

The present study confirms the findings of other studies reporting that there is insufficient evidence for the effectiveness of a PURAS in reducing the development of PU in patients admitted to hospital.[64] [65] [66] Although the studied scales (Norton, Waterlow, Braden, CBO) predict the development of PU to some extent, strict application of the scales leads to both ineffective and inefficient use of preventive measures.[67] It means that some patients who *do not* need specific preventive measures will receive them, while others who *do* need them, will be deprived with all deleterious consequences. In constructing a risk assessment tool only factors should be included that are coupled to the pathophysiology of the disease concerned and that attribute to the disease by themselves. Pressure for instance, in one way or another eventually causes PU, but age (most PU patients are elderly) per se does not. Inclusion of age in a PURAS indeed renders higher scores, but these do not reflect increased specificity and sensitivity. When only factors proven to be associated with the susceptibility for the development of PU

with an evident or plausible pathofysiological background should be incorporated in a PURAS, the predictive value would enhance.[68] [69] Assessing PU risk is a complex process implying both a thorough overall assessment and the use of skills resulting from experience. [66] [70]

In recent guidelines and publications there is far less emphasis on skin assessment in PU care than on the use of PURAS and classification systems. However, by frequent and thorough examination of the possibly threatened skin, it is often possible to foresee whether the skin is at risk to develop PU.

A *blancheable erythema* is reversible in most cases, only in a small percentage a PU will develop. It is not efficient to start with a prevention protocol whenever in a patient a blancheable erythema develops, since it will prove to be unnecessary in the majority of patients.[71] In contrast a *non-blancheable erythema* represents a more profound alteration in the underlying subcutaneous vessels and can progress to full-thickness breakdown despite appropriate intervention. Contrary to a recent study, in our opinion, preventive measures should not be delayed until a non-blancheable erythema appears,since this approach will lead to an inacceptably high PU incidence.[67] Although blancheable erythema subsides in most cases, clinical observations indicate that some specific forms of these alterations could develop into a PU. These lesions are to be suspected when there is a clinical picture of a blancheable erythema with a sharp demarcation, when the redness does not disappear after 2 hours of pressure relief, when an induration is palpable and when the patient indicates discomfort at the sustained area. All these signs and symptoms are indicators of a deteriorating situation and should lead to the immediate start of preventive measures. Blisters, bruises and excoriations (whether as a result of extensive maceration and shearing or friction forces against bed sheets or skin-to-skin contact) are signs of early breakdown. As a consequence frequent changes of body position are of eminent importance in these situations (chapter 2). Even when the risk based on a PURAS is low, these clinical signs and symptoms are indicators of an increased risk for the development of PU. Inspection and palpation of the skin at a regular basis is critical for all patients and necessary to decrease the incidence of PU. The comprehensive assessment should be documented in the medical and/or nursing record and be re-evaluated periodically.

In conclusion

Only based on the use of a PURAS it is not possible to identify patients at risk for PU. However, they should not be abandoned. In clinical practice PURAS should not be used as a diagnostic instrument, but merely as tools to observe a patient according to a specific protocol. An obviously increased PU risk should alert a clinical team.

The identification of a patient at risk, should be based on the combination of the following items: 1) a PURAS, 2) the clinical judgement of the medical and nursing personnel, 3) the prognosis of the underlying disease and mobility, 4) the discomfort of the patient and 5) a skin assessment.
Until now there are insufficient medical technology assessment studies to allow more rational decision making about the use of preventive measures in patients with an increased risk to develop PU. Skin assessment seems to be an useful tool and deserves more research, attention and education.

7.4 Are nutritional supplements able to prevent the development of PU?

Treatment of risk factors, i.e. factors known or expected to be of influence on the individual susceptibility to extrinsic factors, is often not feasible. Since malnutrition is a potentially reversible intrinsic factor it can foster the use of prevention strategies. Malnutrition is correlated with the incidence and severity of PU.[72 73 74 75 76] Observational studies, comparing the development of PU of non-malnourished with malnourished patients, showed a higher incidence in the latter patients. The risk of PU development is three times increased in undernourished patients as compared with well-fed people.[77] Although malnutrition is usually associated with developing countries and lower social standards, it also occurs in the more developed western countries.[78] Undernutrition is seen according to the definitions used in 5-12% of community-dwelling older persons, in 30-61% of hospitalized older persons, and in 40-85% of persons in long term-term care institutions.[77 79] The finding that nutritional intervention decreases the incidence of PU would strongly support the existence of a causal relationship between malnutrition and the development of PU. Therefore we studied the effect of nutritional supplementation, enriched with antioxidants, on the prevention of PU in hip fracture patients (chapter 4). These patients are often undernourished.[80] The results suggest that prophylactic use of a nutritional supplement as compared with placebo possibly contributes to a delayed onset and progression of PU. However, no statistically significant effect was observed. Three other prospective intervention studies on the effect of mixed nutritional supplements on the prevention on PU have been performed, as listed in table I. The effectiveness of these studies has been evaluated in two Cochrane reviews.[74 81] Two other studies included patients admitted for a hip-fracture, comparable with our study.[82 83] One trial included seriously ill older patients admitted to an acute care hospital.[84] Three studies compared the preventive effect of a standard diet vs. standard diet plus nutritional supplements. One study compared a standard diet vs. standard diet and overnight nasogastric tube feeding.

Several methodological limitations were identified for the four studies. The study of Delmi was of limited value due to a poor methodology, no description of randomisation, allocation and blinding. The study of Hartgerink using tube feeding showed a high drop-out. Only 40% accepted the tube for 1 week, and 29% for two weeks. Blinding was not possible.[83] In the large study of Bourdell-Marchasson the groups were not comparable at baseline. Randomisation was done by ward rather than by individual patient. There was no clear differentiation between erythema and non-blanchable erythema. Our study is the only one providing adequate blinding of participants and comparable patients at baseline.

Table I
Nutritional intervention studies in the prevention of PU

First author	No completed	category	Length follow-up d.	Intervention	Risk reduction	95% CI	Incidence reduced?
Delmi 1990	52	H-F	180	Standard diet vs standard diet plus nutritional supplement	0.79	0.14-4.39	No
Hartgerink 1998	101	H-F	14	Standard diet vs standard diet and overnight nasogastric tube feeding.	0.92	0.64-1.32	No
Bourdel-Marchasson 2000	672	YR > 65 jr	15	Standard diet vs standard diet plus nutritional supplement	0.83	0.70-0.99	Yes
Houwing 2003	103	H-F	28	Standard diet plus water placebo vs standard diet plus nutritional supplement	0.92	0.65-1.3	No

Abbrevations :
H-F Hip-fracture patients
C-I : Critical illness

Results

All three studies in H-F patients groups, detect a lower incidence in the supplementation group, but the trials were far too small to determine whether these differences were due to chance or to a true effect. The study in patients with a critical illness, showed a statistically significant effect, however the value of this trial is limited. [84]

What can be the reason for the lack of a positive result in the prevention of PU by nutritional supplementation, as described in chapter 4?
In the first place the start of the supplementation was given *after* surgery, the critical moment of PU formation. Probably, and in accordance to the results shown in chapter 3,

the first stages of PU development started earlier, beginning directly after the accident. A prolonged stay on ambulance stretchers, in emergency and radiology departments as well as a prolonged surgical procedure are accepted and recognised risk factors for the development for PU.[85] [86] Based on this concept, but obviously not possible in an acute event, intervention with extra nutrition *well before* the critical event would be more appropriate. It has been shown that extra nutrition, started two month prior to an elective surgical intervention, improved woundhealing.[87]

In the second place it is possible that the follow-up time in this study was not long enough. One study with a longer duration showed only a positive effect on PU incidence in the recovery period and until 6 month.[82] The duration, needed to reverse an undernutrition, can be longer than the period of follow-up we used.

In the third place the negative results might suggest that the presence of clinical undernutrition is not due to inadequate ingestion of calories, but rather to the influence of the underlying disease.

Undernutrition in the presence of adequate food sources may be due to hypercatabolic states (cachexia), failure to ingest calories (anorexia), or inability to process nutrients (malabsorption).[88] The possible positive effect of supplementation is dependent on the nutritional state of the patient. An underfed state can be reversed by adequate intakes. In cachexia, however, adequate nutrition will not correct this.[89] [90] In the available intervention studies no distinction was made between these different forms of malnutrition. The failure to distinguish an underfed patient from a cachectic one might explain why outcome studies in nutritional support only show little benefit.[91]

In the fourth place, PU may occur independent from nutritional status. The relationship between (mal-) nutrition and the development of PU is often assumed but is based on limited evidence. The fact that both undernutrition and PU frequently coexist in the same persons, not necessarily implies a causal relation.[77] [88] The odd ratios for well-known riskfactors such as cerebrovascular accidents, immobility and the need for assistance with activities of daily living (ADL) are higher than for nutritional status.[89] Patients with malnutrition are less mobile and have an impaired physical and mental health. This could imply a decreased possibility for self-care or to change body position with a certain frequency. Elderly patients have a decreased sense to the urge for pressure relief, or (for instance after a stroke with aphasia) do not have the capability left to indicate such or to draw the attention of nurses. In most studies the epidemiological association of markers for undernutrition and PU is not adjusted for comorbidity or other risk factors and may merely indicate that ill patients are more likely to develop PU, for instance simply because they are bedridden.

So the question arises whether the possible existing relation between malnutrition and PU susceptibility is the result of a diminished resistance to tissue loading, or a result of

an increased tissue loading? Correction of malnutrition will not have a positive result in the latter option.

Screening for malnutrition, preferably with a simple questionnaire, must be part of the risk assessment for developing PU.[92] Malnutrition is associated with decreased function of muscle and the immune system, impaired wound healing, quality of life, increased length of hospital stay, and mortality.[93] However, less than half of patients with undernutrition receive nutritional support due to low adherence of the guidelines, patient inability, or even refusal.[94 95] Tube feeding could be promoted since it requires less staff time as an alternative method of feeding as compared with for instance careful spoon-by-spoon feeding. However, tube feeding is associated with an increase in morbidity (with debilitating conditions such as diarrhoea, and immobility due to the tube itself, factors that contribute to an increased risk for PU) and mortality because of aspiration.[77 90 96] In the terminal patient, care should be focussed on comfort rather than on measures in order to prevent or even treat PU. Time for good patient care, also implying careful assistance in the ingestion of healthy and tasty food of good quality, should be the first gain. [97 98]

In conclusion

We found no statistically significant positive effect of extra nutritional supplementations by drink foods in the prevention of PU. (chapter 3) Before advocating the use of extra nutritional supplements in PU prevention, further research of high methodological quality is required to produce evidence. Preferably, this research should be done without financial support of the food industry to prevent biased reporting of data.

This will not imply that until these evidences are provided no attention has to be given to the nutritional state of the patient. However, interventions with especially drink foods can interfere with the normal daily intake, they are expensive and do not integrate physical care with measures to improve quality of life. Food adjustments by offering healthy and tasty food of good quality in a social ambiance should be the first gain.

7.5 Is ischemia-reperfusion injury the main underlying cause of PU?

In attempts to explain the etiology of pressure ulcers several theories have been launched. According to the definition of PU mostly used, they represent areas of tissue breakdown due to sustained mechanical load. It looks straightforward: mechanical load causes lesions. However surprisingly there is little consensus about the pathophysiologic response to mechanical loading that triggers soft tissue breakdown. When a patient is submitted to a prolonged period of sustained loading, for example during surgery, the first clinical sign is redness of the skin, especially above bony prominences, before actual tissue necrosis occurs. This clinical observation led to the hypothesis that the inflammation of the skin, seen *after*-, rather than *during* a period of pressure application to the body, resembles the phenomena known as ischemia-reperfusion (I-R) injury.[99] In the past it was assumed that the tissue injury associated with the ischemia was caused by a lack of oxygen and nutrients. Although a persistent vascular occlusion will ultimately lead to tissue necrosis, a substantial component of the damage paradoxically occurs during reperfusion and re-oxygenation of the ischemic tissue. The re-introduced oxygen is able to activate damaging processes by generating reactive oxygen species, initiating a cascade of biochemical events, eventually leading to tissue necrosis. [99] [100]
By means of a newly developed and constructed pressure delivery system we investigated in an animal study with pigs the role of reperfusion after a period of ischemia, in the pathophysiology of PU formation (chapter 4). By applying a pressure device we produced damage in muscle and skin. Since damage extended according to a vascular pattern to a larger area than where the pressure applicator was located, we concluded that it was merely the ischemia and not the pressure itself, that was the causative factor. Histopathological and electron-microscopic examinations of tissue that sustained a period of pressure supported the hypothesis of I-R injury. Only minimal damage was demonstrable in tissue biopsies taken immediately after a phase of ischemia, whereas damage increased in extent and severity when biopsies were taken longer after the release of pressure. This observation suggests a deleterious effect of reperfusion and the role of highly reactive oxygen species (ROS) in the inflammatory processes that occur in PU development.

In earlier studies only constantly applied pressure over a bony prominence was investigated.[101] [102] [103] [104] PU created by such one-time constant pressure application does not reflect accurately the types of ulcers mostly seen in the clinical setting. These models neglect the contribution of ischemia followed by reperfusion to ulcer formation. In our study (chapter 4) a pig animal model was chosen. The anatomic and physiologic characteristics of a fixed skin and soft tissue coverage of bony protrusions, show a great

similarity to humans. However, the use of a large animal model precludes the possibility of conducting a large number of individual experiments. The pigs were very susceptible for –often lethal- stress reactions initiated by the anaesthesia. This was one reason why it was not possible to apply intermittent pressure cycles, or pressure cycles on consecutive days. A constant pressure was applied for two hours. We only noticed muscle and skin damage without ulcer formation. Probably the two hour of pressure application was not sufficient to produce a grade 3 or 4 PU. We have shown in chapter 3 that a prolonged time on the operation table proved to be an independent predictor associated with a higher incidence of PU. PU formation is not only dependent of tissue loading, other factors play a role. Since in the experiments we used eight-week old, healthy, well fed pigs, which lack these contributing factors, the absence of severe skin ulceration or massive muscle necrosis, can be attribute to this circumstance.

Rats, contrary to human and pigs, have a so-called *loose skin*; the results of pressure application in rats are therefore not comparable with human studies. However, studies with intermittent pressure cycles, in which occlusion is alternated with reperfusion, seem to be possible in this model. It offers the advantages of low initial costs and maintenance.[105] [106] A computer-controlled pressure device in a rat model, with five consecutive days of pressure applied during sessions of 6 hours, showed muscular necrosis with infarction of the skin, identified as a precursor of PU formation.[107]

Another PU model in rats compared ischemia-induced injury with ischemia-reperfusion-induced injury.[108] The tissue damage accelerated with the increase of the total number of ischemia-reperfusion (I-R) cycles, the duration of ischemia and the frequency of the I-R cycles. Even when the total period of the ischemia was constant, a greater number of reperfusion events during that period resulted in increased tissue damage. First damage consisted of early necrosis in the epidermis and follicular units, leukocyte extravasation and decreased skin thickness. Repeated I-R injuries seem to be more damaging to tissue than prolonged ischemia alone.[108] These studies supports our investigations on the role of I-R in the injury of muscle and skin due to tissue loading.

The histopathological patterns found in our study (chapter 4), were strikingly similar to the damage seen in the few studies on the histopathology of PU in humans. Histological studies of animals and humans of the early phase of PU showed a pattern with dilated capillaries with swollen endothelial cells, perivascular cell infiltrates, red blood cell engorgements in the capillaries, intra- and perivascular fibrin deposits. [101] [102] [109] [110] [111] [112] [113] Accumulation of neutrophils in and around the capillaries is consistently found both in human and animal studies.[110] [111] [114] A similar picture of the ischemic pattern is found in moisture lesions. (chapter 2) Electron microscopic analysis showed an adherence of leukocytes to the endothelial cell after reperfusion. (chapter 4). Leukocytes are an important source of free radicals and release protease and phospholipase enzymes,

capable to initiate inflammation with significant cellular and tissue injury. Neutrophil-mediated activation and infiltration is followed by the generation of Reactive Oxygen Species (ROS) and has been demonstrated to result in loss of vascular integrity, edema, haemorrhage, thrombosis and subsequent tissue necrosis.[115 116]

In conclusion

Although other mechanisms such as occlusion of lymph vessels and sustained deformation of cells can contribute to the development of PU, our study showed that reperfusion injury plays an important role in the pathophysiology of PU.

7.6 Is it possible to reduce the extent of the tissue damage in Pressure Ulcers by means of antioxidants?

Tissue injury in PU is at least in part caused by ROS, released during perfusion after a period of ischemia. Normally the production of ROS is kept in balance by means of the activity of antioxidants. Antioxidants eliminate the ROS and so protect tissue before they are able to exert their damaging effects. Tissue damage occurs when the balance between ROS and antioxidants is disturbed. This could be caused by an abundance of ROS, shortage of antioxidants or both. Antioxidants can be administered orally, either as a drug, as a food supplement, or can be locally applied.[99 110] Both glutathione and hydrogen peroxide (H_2O_2) can be considered to be reflectants of the presence of more ROS. In our animal study we demonstrated after pressure release a significant decrease in blood total- and reduced glutathione together with a significant increase of the blood H_2O_2. Both suggest a decreased antioxidant reserve. After prophylactic administration of the anti-oxidant vitamin-E pressure tissue damage in histological specimens was less severe and H_2O_2 increased significantly less. These observations suggest that I-R injury is implicated in PU tissue injury and that anti-oxidant therapy may be beneficial. (chapter 4) Vitamin-E is the major lipid antioxidant in cellular membranes. It is believed to exert its action by means of trapping of lipid peroxyl radicals and lipid radical species, thus breaking the lipid peroxidation chain. Vitamin-E acts as a direct antioxidant, but also limits tissue infiltration by neutrophils during ischemia-reperfusion.[117 118]

Other animal studies also investigated the protective effect of antioxidants in PU formation, and are listed in the table II.

Table II

Animal studies performed on tissue damage to loading, and an antioxidantal effect.

First author publ. Year	Animal. Applied pressure	Used antioxidant	Results
Salcido 1995	Rat 5 days, 6 hr/day	Ibuprofen ip. + im.	More tissue damage after im. Ibuprofen. No effect after ip. Ibuprofen.
Houwing 2000	Pig 2 hr pressure	Vitamin-E Orally	Less tissue damage after or. it.-E
Sundin 2000	Pig Cycle pressure	Allopurinol deferoxamine i.v.	Less tissue damage with deferoxamine. No effect allopurinol
Peirce 2004	Rat I/R	ATL-146e subc	Less tissue damage skin
Şener 2006	Rat I/R	Melatonin Loc. + ip.	Less skin damage after loc. Melatonin Less remote damage after ip. Melatonin

ip.: intraperiteneal Im.: intramuscular or.: orally
Loc.: local applied i.v.: Intravenous
m. : muscle sk.: skin
subc.: subcutaneous I/R. : ischemia reperfusion cycles

Deferoxamine, inhibiting the formation of the hydroxyl radical by a high binding affinity for iron, showed a protective effect in a PU pig experiment.[119] Other anti-inflammatory drugs, as ATL-146e (an adenosine A (2A) agonist which reduces the release of ROS and leukocyte adhesion); and melatonin (an hydroxyl radical scavenger) decreased injury of dermis and epidermis in PU rat models.[120] [121] However, the protective effect of antioxidants is not consistently present, as ibuprofen (an anti-inflammatory drug with antioxidant characteristics) showed a harmful effect in the severity of PU in a rat model.[107]

Nutrition and antioxidants

Since under normal circumstances large quantities of antioxidants are provided to the organism by means of the diet, a poor nutritional condition could be associated with a deficit of antioxidants.[122] [123] Surveys indicate that the elderly are particularly at risk for marginal deficiencies of vitamins and tracer elements.[124] In ageing, and during oxidative stress-related diseases or states, antioxidant micronutrients are consumed in a higher rate than they are generated and their concentrations may decrease below normal ranges.[125] Vitamin C is required for an effective immune response. Vitamin B1 deficiency can cause an accumulation of deleterious metabolites such as free radicals and advanced glycation end products (AGEs). Deficiency of vitamins reduces the production of matrix substances, such as fibronectin, laminin, collagen, proteoglycans, and proteases.[125] [126] A retarded collagen synthesis decreases wound tensile strength, and reduces the number of fibroblasts by inhibition of the inflammatory response.[127] Therefore, deficiencies of these vitamins can contribute to the susceptibility for PU. When treating malnutrition in patients it can be of value not only to correct the protein and caloric deficits, but also to

supply antioxidants, which can contribute to the prevention and treatment of PU. Our intervention study (chapter 4) and others as listed in table I all used mixed nutritional supplements that include high-protein supplements, vitamins and tracer elements. However, none of them showed a convincing effect.[82] [83] [84] Results of clinical trials in treatment of PU, by using only antioxidant supplements (vitamin C; zinc) without energy supplementation, neither showed significant results in improvement.[128] [129] [130] Amino acids such as arginine and glutamine exert beneficial effects in wound healing in animal studies. However, in human studies with regard to PU a positive effect on prevention or healing has not been shown.[127] [131]

Locally applied antioxidants

In the past decade the strikingly increasing number of publications on oxidative stress in skin indicates the importance of this field in experimental dermatology.[132] Studies have demonstrated a beneficial health effect of antioxidant application on intact skin to prevent UV-induced carcinogenesis and photo-ageing.[133] As a consequence of the role of oxidative stress in PU, topical application of antioxidants could be useful in the prevention of PU. As dimethyl sulfoxide (DMSO) is a powerful hydroxyl scavenger with excellent penetration properties, we evaluated the literature with respect to the efficacy of DMSO application on the skin on woundhealing and as an anti-inflammatory drug. (chapter 5a) Human dermatological studies have been scarce, in spite of the fact that the compound is frequently used as a topical inflammatory ointment for home remedies. Based on the literature, we concluded that the use of topically applied DMSO in low concentrations seems to be safe and can have a beneficial effect on PU prevention. Since there was no conclusive clinical evidence for positive effects of DMSO we performed a randomised double-blinded study in a patient population prone to develop PU, using a 5% topically applied DMSO cream on heels and buttocks. (chapter 5b). We found – in contrast to our expectation- a significant detrimental effect of PU incidence on the heels.

Other double-blinded randomized controlled trials to impair skin health for reduction of PU incidence are scarce. Five RCT's, all with a local therapeutical with possible anti-inflammatory or some anti-oxidant properties, are listed in table III.[134135] [136] [137]

Table III

RCT addressing to impaired skin health for PU reduction

First author year	No pat. completed	Length of follow-up d.	Setting	Intervention vs. control	Incidence
Green 1974	167	21	ac.	allantoin lotion vs. placebo	Reduced n.s.
Camme van der 1987	104	21	ac.	Top. Nicotinate vs. allantoine lotion	No
Torra I Bou 2005	331	30	ac. and ltc.	Hyperox. Fatty acids comp. vs. placebo	Reduced n.s.
Meaume 2005	1121	56	ltc.	Hyperox. Fatty acids comp+ Vit.E. vs. placebo	Reduced n.s.
Houwing	79	28	ltc	DMSO vs. placebo	Increased on heels s.s.

ac.: acute care ltc. ; long term care
n.s.: not statistical significant s.s.: statistical significant

Fatty acids have been thought to protect against friction and pressure and also reduce hyperproliferative skin growth. Topical nicotinic acid could enhance subcutaneous vascular supply. Allantoin might stimulate cell proliferation and tissue growth. The four poorly developed RCT's were of limited methodological quality.[138] It was unknown whether the patients were randomly allocated. Apart from our study (chapter 5b) no statistical significant results were obtained.

Interest in the use of antioxidants in the treatment of human diseases, associated with oxidative stress, has been sustained for two decades. Development in both therapeutic and nutritional fields has been punctuated by some successes, but also by some spectacular failures.[139] Supplementation with antioxidants must be used with caution, since oversupplementation could prevent the activation of normal defence mechanisms.[140] The total elimination of free radicals from humans possibly interferes with some essential defensive mechanisms like apoptosis, phagocytosis and detoxification.[141] The negative result demonstrated with a locally applied antioxidant, in contrast to what could be expected, is called a *pro-oxidant effect*. (chapter 5b)[139 141 142] This effect is also shown in other studies, which have indicated that antioxidant therapy could have adverse effects on adults, both healthy and with specific diseases. [79 143 144 145] Although the results may not be universally applicable, this analysis serves as a reminder that disease-nutrient relationships are complex and that isolated nutrients may exert effects that dramatically differ from the same nutrients when consumed in a food source. More insight on the molecular aspects of the action and toxicity of the active ingredient(s) in food supplements is mandatory. Therefore it is unclear whether nutritional supplementation with antioxidants or trace elements is safe for patients to prevent PU. In addition, evidence for supplementation of specific micronutrients, however plausible in the process of woundhealing and PU formation, lacks all together.[79 89] Since there is a potential harm of these agents, it is important to supply micronutrients with caution, and

replenish a deficiency by means of normal food, containing fruits and vegetables, rather than with special drink food by increased concentration of these micronutrients, much advocated by the food industries. For the universal use of antioxidants for PU prevention or treatment, further research is needed both to identify which patients could profit and which products exert such possible positive effects.[79 146]

In conclusion

We showed that it is possible to reduce the extent of the tissue damage in PU by means of antioxidants in an animal model. However, we were not able to demonstrate a significant effect of adding nutritional supplements, enriched with antioxidants in humans. Moreover, we demonstrated an even detrimental effect on the incidence of PU on the heels in humans with a locally applied antioxidant.

The preventive effect of vitamin E in the prevention of PU, as shown in our pig study is promising. Maybe, a potential therapeutic benefit in preventive treatment of a patient 'at risk' for PU with antioxidants can be of value, in bedridden patients in general or in patients prior to surgery. However, an oxidant found to be effective in an animal study, still has to be evaluated in humans, since discrepancies have been found in *in vivo* studies of antioxidants in animals and humans. Antioxidants can decrease various chronic and/or acute oxidative stress related diseases. In human studies however, with respect to the prevention or treatment of PU, no studies with a positive result are known.

More animal and human studies are required to establish the efficacy and safety of antioxidant therapy.

References

1 Schnelle JF, Adamson GM, Cruise PA, al-Samarrai N, Sarbaugh FC, Uman G, Ouslander JG.Skin disorders and moisture in incontinent nursing home residents: intervention implications.J Am Geriatr Soc. 1997;45(10):1182-8.

[2] Schoonhoven L, Defloor T. Vochtletsels zijn geen decubitusletsels. Tijdschr Verpleegk 2007:4;42-5

[3] Defloor T, Schoonhoven L, Fletcher J, et al. Statement of the European Pressure Ulcer Advisory Panel Pressure Ulcer Classification: Differentation between pressure ulcers and moisture lesions Journal of Wound, Ostomy and Continence Nursing, 2005;32:302-6

[4] Gray M, Bliss DZ, Doughty DB, Ermer-Seltun J, Kennedy-Evans KL, Palmer MH. Incontinence-associated dermatitis: a consensus. J Wound Ostomy Continence Nurs. 2007 Jan-Feb;34(1):45-54

[5] Junkin J, Selekof JL.Prevalence of incontinence and associated skin injury in the acute care inpatient. J Wound Ostomy Continence Nurs. 260-9

[6] Rapportage resultaten Landelijke Prevalentiemeting Zorgproblemen 2006. Halfens RJG. Janssen MAP. Meijers JMM September 2006 Universiteit Maastricht, Zorgwetenschappen, sectie Verplegingswetenschap. www.nursingscience.nl/LPZ.

[7] Bos WH, Koning J de. A senile gluteal dermatosis caused by friction. European J Dermatol 1992;2:157-9

[8] Brienza DM, Geyer MJ, Karg P. White Paper on Pressure Management www.rercwm.pitt.edu Accessed june 2006

[9] Bliss MR, Aetiology of pressure sores. Review Clin Geront 1993;3:379-97

[10] Grey JE, Harding KG, Enoch S. Pressure ulcers. BMJ 2006;332:472-475

[11] Sivamani RK, Goodman J, gitis NV, Maibach HI. Coefficient of friction: tribological studies in man- an overview. Skin Res Techn. 2003;9:227-234

[12] Lowthian PT. Trauma and thrombosis in the pathogenesis of pressure ulcers Clin Dermatol 2005;23:116-123

[13] Naylor PFD. The skin surface and friction br J dermatol 1955;67:239-48

[14] Bennett L, Kavner D, Lee BK, et al. Shear vs pressure as causative factors in skin blood flow occlusion. Arch Phys Med Rehabil 1979;60:309- 14.

[15] Goldstein B, Sanders J. Skin response to repetitive mechanical stress: a new experimental model in pig. Arch Phys Med Rehabil. 1998 Mar;79(3):265-72.

[16] Goossens RH, Zegers R, Hoek van Dijke GA, Snijders CJ. Influence of shear on skin oxygen tension. Clin Physiol. 1994 Jan;14(1):111-8

[17] Bronneberg D, Bouten C, Oomens C, Kemenade P, Baaijens F. An in vitro Model System to Study the Damaging Effects of Prolonged Mechanical Loading of the Epidermis. Annals of Biomedical Engineering. 2006;34(3):506-14

[18] Witkowski JA, Parish LC. Histopathology of the decubitus ulcer. J Am Acad Dermatol. 1982 Jun;6(6):1014-21

[19] Dinsdale SM. Decubitus ulcers in swine: light and electron microscope study of pathogenesis. Arch Phys Med Rehabil 1973;54:51- 6.

[20] Daniel RK, Priest DL, Wheatley DC. Etiologic factors in pressure sores: an experimental model. Arch Phys Med Rehabil 1981;62:492- 8.

[21] Salcido R, Donofrio JC, Fisher SB, LeGrand EK, Dickey K, Carney JM, Schosser R, Liang R. Histopathology of pressure ulcers as a result of sequential computer-controlled pressure sessions in a fuzzy rat model. Adv Wound Care. 1994;7(5):23-4, 26, 28 passim

[22] Sulzberger MB, Cortese,TA Jr, Fishman L, Wiley HS. Studies on blisters produced by friction. I. Results of linear and twisting technics. J Invest Dermatol 1966;47:456-65

[23] Kligman AM. The chronic effects of repeated mechanical. trauma to the skin. Am J indust med 1985;8:257-264

[24] Silver FH, Siperko LM, Seehra GP. Review. Mechanobiology of force transduction in dermal tissue Skin Res Techn. 2003;9:3-23

[25] Ryan TJ. Cellular responses to tissue distortion. In: Bader DL, editor. Pressures sores: clinical practice and scientific approach. London: Macmillan Pr; 1990. p 141-52.

[26] Montagna W, Carlisle K. Structural changes in ageing skin. Br J dermatol 1990;122(S35):61-70

[27] Ryan T. The ageing of the blood supply and the lymphatic drainage of the skin Micron 35 2004;35:161–71

[28] Burgesons RE, Christiano AM. The dermal-epidermal junction. Curr Opinion Cell Biol 1997:9;651-8

[29] Bader Dl, White SH. Soft tissues in elderly subjects undergoing surgery Age and Ageing 1998;27:217-21

[30] Braverman IM, Fonferko E. Studies in Cutaneous Aging: I. The Elastic Fiber Network J Invest Dermatol 1982;78: 434–443

[31] Ek AC, Lewis DH, Zetterqvist H, Svensson PG. Skin blood flow in an area at risk for pressure sore. Scand J Rehabil Med. 1984;16(2):85-9

[32] Dalton SJ, Mitchell DC, Whiting CV, Tarlton JF. Abnormal extracellular matrix metabolism in chronically

ischemic skin: a mechanism for dermal failur in leg ulcers. J invest Dermatol 2005 125:373-9
[33] Bickers DR, Athar M. oxidative stress in the pathogenesis of skin disease. J Invest Dermatol 2006:126;2565-75
[34] Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. Pathophysiology of premature skin aging induced by ultraviolet light.N Engl J Med. 1997;337(20):1419-28.
[35] Chang E, Yang J, Nagavarapu U, Herron S. Ageing and survival of cutaneous microvasculature J Invest dermatol 2002:118(5);752-8
[36] Wlaschek, M., and Scharffetter-Kochanek, K. Oxidative stress in chronic venous leg ulcers. Wound Repair Regen. 2005;13: 452,
[37] Sanders JE, Goldstein BS, Leotta DF. Skin response to mechanical stress: adaptation rather than breakdown-a review of the literature. J Rehabil Res Dev. 1995 Oct;32(3):214-26.
[38] Meulenbelt HEJ, Geertzen JHB, Dijkstra PU, Jonkman MF. Skin problems in lower limb amputees: an overview by case reports. J. Eur Ac Derm Ven. 2007;21:1-9
[39] Atherton DJ. A review of the pathophysiology, prevention and treatment of irritant diaper dermatitis. Curr Med Res Opin. 2004 May;20(5):645-9
[40] Ersser SJ, Getliffe K, Voegeli D, Regan S. A critical review of the inter-relationship between skin vulnerabilityand urinary incontinence and related nursing intervention. Int J Nurs Stud. 2005 Sep;42(7):823-35.
[41] Margesson LJ. Contact dermatitis of the vulva. Dermatol Ther 2004;17:20-7.
[42] Robson KJ, Maughan JA,Purcell SD, Petersen MJ, Haefner HK, Lowe L. Erosive papulonodular dermatosis associated with topical benzocaine: A report of two cases and evidence that granuloma gluteale, pseudoverrucous papules, and Jacquet's erosive dermatitis are a disease spectrum. J Am Acad Dermatol 2006;55:S74-80
[43] Andersen PH, Bucher AP, Saeed I, Lee PC, Davis JA, Maibach HI. Faecal enzymes: in vivo human skin irritation. Contact Dermatitis. 1994;30(3):152-8.
[44] Defloor T. Pressure reduction and positioning to prevent pressure ulcers (Drukreductie en wisselhouding in de preventie van decubitus). Thesis,Ghent University, Ghent, Belgium, 2000.
[45] Bates-Jensen B, Alessie CA, Al-Samarrai NR, Schnelle JF. The effects of an exercise and Incontinence Intervention on Skin health Outcomes in Nusing Home Re sidents. J Am Geriatr Soc 2003;51:348-55
[46] Hogkinson B, Nay R, wilson J. A systemic review of topical skin care in aged care facilities. J Clin Nursing 2006;16:129-36
[47] Lyder C, Clemes-Lowrance C, Davis A, Sullivan L, Zucker A. A structured skin care regimen to prevent perineal dermatitis in the elderly. J ET Nurs. 1992;12:12–16
[48] Teunissen TAM, van Weel C, Lagro-Janssen ALM. Prevalence of urinary-, fecal and double incontinence in the elderly living at home. Int Urogynecol J 2004; 15(1):10-3
[49] Black J, Baharestani M, Cuddigan J, et al. National Pressure Ulcer Advisory Panel's Updated Pressure Ulcer Staging System. Urol Nurs. 2007;27(2):144-150
[50] Shea JD. Pressure sores-classification and management. Clin Orthop Relat Res 1975;112:89 - 100
[51] http://npuap.org/ Classification system Accessed 11 july 2007
[52] http://www.epuap.org/ Classification system Accessed 11 july 2007
[53] Bethell E. Controversies in classifying and assessing grade I pressure ulcers. J Wound Care. 2003;12(1):33-6
[54] Dealey C. Review of advances in pressure ulcer management since 1992. In : M. Clark ed. Pressure Ulcers: Recent advances in tissue viability. 2004 blz 3-8
[55] Parish LC, Lowthian PT, Witkowski JA.Brouhaha across the atlantic: decubitus ulcers defy description. Skinmed. 2005 Sep-Oct;4(5):262-4
[56] Donnelly J. Should we include deep tissue injury in pressure ulcer staging systems? The NPUAP debate J Wound Care 2005;14(5):207-10
[57] Baumgarten M, Margolis D, Doorn van C, gruben-Baldini AL, Hebel JR, Zimmerman S, Magaziner J. Black/White differences in pressure ulcer incidence in nursing home residents. JAGS 2004;52(8):1293-8
[58] Lowthian P. the distinction between superficial pressure ulcers and moisture lesions. Skin Med 2007:6(3);111-2
[59] Parish LC, Witkowski JA.Controversies about the decubitus ulcer. Dermatol Clin. 2004 Jan;22(1):87-91
[60] Clark M. What drives pressure ulcer classification- scientific knowledge or fear of litigation? J Tissue Viability 2005;15(2):2
[61] Defloor T, Schoonhoven L, Vanderwee K, Westrate J, Myny D. Reliability of the european pressure advisory panel classification system. J Adv nursing 2006;54(2):189-98
[62] Torra i Bou JE, García-Fernández FP, Pancorbo-Hidalgo PL, Furtado K. Science Risk Assessment Scales for Predicting the Risk of Developing Pressure Ulcers. In Science and Practice of Pressure Ulcer Management eds Marco Romanelli et al. 2006 Springer London. pg43-57

[63] *Versluysen M. Pressure sores in elderly patients. The epidemiology related to hip operations. J Bone Joint Surg Br 1985;67:10-3*
[64] *Cullum N, Deeks J, Fletcher A, Long A, Mouneimne H, Sheldon T et al. The prevention and treatment of pressure sores: How effective are pressure-relieving interventions and risk assessment for the prevention and treatment of pressure sores? Effective Health Care 1995; 2(1):1-16*
[65] *Schoonhoven L. Prediction of pressure ulcers: problems and prospects. Thesis,Utrecht University, Utrecht, The Netherlands, 2003*
[66] *Pancorbo-hidalgo PL, Garcia-fernandez FP, lopez-Medina IM, Alvarez-Nieto CA. risk assessment scales for pressure ulcer prevention: a systematic review. J Adv Nurs 2006:54(1);94-110*
[67] *Vanderwee K, Grypdonck M, Defloor T. Non-blanchable erythema as an indicator for the need for pressure ulcer prevention: a randomized-controlled trial Journal of Clinical Nursing 2007;16: 325–35*
[68] *CBO Richtlijn Decubitus (tweede herziening 2002) Kwaliteitsinstituut voor de Gezondheidszorg CBO, [Dutch institute for Healthcare CBO] Utrecht 2002*
[69] *Nixon, J. The pathophysiology and aetiology of pressure ulcers In Morison, M.J. (Ed.) The Prevention and Treatment of Pressure Ulcers, Mosby, Edinburgh. 2001 ;17-36*
[70] *Marum RJ, Meijer JH, Ooms ME, Kostense PJ, van Eijk JT, Ribbe MW. Relationship between internal risk factors for development of decubitus ulcers and the blood flow response following pressure load.Angiology. 2001 Jun;52(6):409-16*
[71] *Nixon J, Cranny G, Bond S. Skin alterations of intact skin and risk factors associated with pressure ulcer development in surgical patients: A cohort study. Int J Nurs Stud. 2007;44(5):655-63*
[72] *Berlowitz DR, Wilking SV. Risk factors for pressure sores: A comparison of cross-sectional and cohort-derived data. J Am Geriatr Soc 1989;37:1043-1050*
[73] *Bergstrom N, Braden B. A prospective study of pressure sore risk among institutionalized elderly. J Am Geriatr Soc 1992;40:747-758*
[74] *Langer G, Schloemer G, Knerr A , Kuss O, Behrens J. Nutritional interventions for preventing and treating pressure ulcers. Cochrane Database Syst Rev. 2003;(4):CD003216*
[75] *Thomas DR, Goode PS, Tarquine PH, Allman R. Hospital acquired pressure ulcers and risk of Death. J Am Geriatr Soc 1996;44:1435-1440*
[76] *Pinchcofsky-Devin G, Kaminski M. Correlation of pressure sores and nutritional status. J Am Geriatr Soc 1986;34:435-440*
[77] *Thomas DR. Improving the outcome of pressure ulcers with nutritional intervention: review of the evidence. Nutrition 2001;17:121-125*
[78] *Kruizenga HM, Wierdsma NJ, van Bokhorst MA, de van der Schueren, et al. Screening of nutritional status in The Netherlands. Clin Nutr. 2003;22(2):147-52.*
[79] *Thompson C, Furhman P. Nutrition and wound healing: Still searching for the magic bullet. Nutr Clin Pract 2005;20(3):331-47*
[80] *Bonjour JP, Schurch MA, Rizzoli R. Nutritional aspects of hip fractures. Bone 1996;18:139S-144S*
[81] *Avenell A, Handoll HH Nutritional supplementation for hip fracture aftercare in older people. Cochrane Database Syst Rev. 2005;18;(2):CD001880*
[82] *Delmi M, Rapin CH, Bengoa JM, Delmas PD, Vasey H, Bonjour JP. Dietary supplementation in elderly patients with fractured neck of the femur. Lancet 1990 Apr 28;335(8696):1013-6.*
[83] *Hartgrink HH, Wille J, Konig P, Hermans J, Breslau PJ. Pressure sores and tube feeding in patients with a fracture of the hip: a randomized clinical trial. Clin Nutr 1998;17:287-92.*
[84] *Bourdel-Marchasson I, BarateauM, RondeauV, Dequae-Merchadou L, Salles-Montaudon N, Emeriau JP, Manciet G, Dartigues JF. A multi-center trial of the effects of oral nutritional supplementation in critically ill older inpatients. GAGE Group. Groupe Aquitain Geriatrique d'Evaluation. Nutrition 2000;16(1):1-5.*
[85] *Mullineaux J. Cutting the delay reduces the risk. Assessment of the risk of developing pressure sores among elderly patients in A&E. Prof Nurse. 1993;9(1):22-30.*
[86] *Grous CA, Reilly NJ, Gift AG. Skin integrity in patients undergoing prolonged operations. J Wound Ostomy Continence Nurs 1997; 24(2):86-91.*
[87] *Haydock DA, Hill GL. Improved woundhealing response in surgical patients receiving intravenous nutrition. Br J Surg. 1987 ;74(4):320–323.*
[88] *Thomas DR. Prevention andTreatment of Pressure Ulcers J Am Med Dir Assoc 2006; 7: 46-59*
[89] *Mathus-Vliegen EMH Old Age, Malnutrition, and Pressure Sores: An Ill-Fated Alliance. J Gerontol A Biol Sci Med Sci Gerontol 2004;59(4): 355-60.*
[90] *Finucane TE, Christmas C, Travis K. Tube Feeding in Patients With Advanced Dementia A Review of the Evidence JAMA. 1999;282:1365-1370*
[91] *Thomas DR. The role of nutrition in prevention and healing of pressure ulcers. Clin Geriatr Med 1997:13:497-511.*

[92] *http://www.epuap.org/guidelines/ accessed june 4 2007*
[93] *Milne AC, Avenell A, Potter J. Meta-analysis: protein and energy supplementation in older people. Ann Intern Med 2006;144: 37-48.*
[94] *Tippett AW. Wounds at the end of life. Wounds 2005;17(14):91–98.*
[95] *McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital BMJ 1994;308(9):945-8*
[96] *Griffiths RD, Bongers T. Nutrition support for patients in the intensive care unit Postgrad Med J 2005;81:629-636*
[97] *Reifsnyder J, Magee HS. Development of Pressure Ulcers in Patients Receiving Home Hospice Care. Wounds 2005;17(4):74-79*
[98] *Nijs KA, Graaf de C, Kok FJ, Staveren van WA. Effect of family style mealtimes on quality of life, physical performance, and body weight of nursing home residents: cluster randomised controlled trial BMJ 2006;332:1180-1184*
[99] *McCord JM. Oxygen derived free radicals in postischemic tissue injury. N Eng J Med 1985; 312: 159-163*
[100] *Bulkley GB Free radical-mediated reperfusion injury: A selective review. Br j Cancer 1987:55(suppl VIII);66-73*
[101] *Daniel RK, Priest DL, Wheatley DC. Etiologic factors in pressure sores: an experimental model. Arch Phys Med Rehabil 1981;62:492- 8.*
[102] *Dinsdale SM. Decubitus ulcers in swine: light and electron microscope study of pathogenesis. Arch Phys Med Rehabil 1973;54:51- 6.*
[103] *Groth KE. Klinische beobachtungen und experimentelle studien uber die entstehung des dekubitus. Acta Chir Scand 1942;LXXXVII (Suppl 76).*
[104] *Kosiak M. Etiology and pathology of ischemic ulcers. Arch Phys Med Rehabil 1959;40:62- 9.*
[105] *Taylor R, James T. The role of oxidative stress in the development and persistence of pressure ulcers. In: Pressure Ulcer Research Current and Future Perspectives ed D. Bader. C.Bouten, D.colin, C. Oomens Springer Berlin Heidelberg New York 2005; 205-32*
[106] *Wang Y, Sanders J Skin model studies in Pressure Ulcer Research Current and Future Perspectives. ed D. Bader. C.Bouten, D.colin, C. Oomens Springer Berlin Heidelberg New York 2005; 263-85*
[107] *Salcido R, Fisher SB, Donofrio JC, Bieschke M, Knapp C, Liang R, LeGrand EK, Carney JM. An animal model and computer-controlled surface pressure delivery system for the production of pressure ulcers. J Rehabil Res Dev. 1995;32(2):149-61.*
[108] *Peirce SM, Skalak TC, Rodeheaver GT. Ischemia-reperfusion injury in chronic pressure ulcer formation: a skin model in the rat. Wound Repair Regen 2000;8:68-76.*
[109] *Seiler WO, Stahelin HB. Recent findings on decubitus ulcer pathology: implications for care. Geriatrics. 1986;41(1):47-50*
[110] *VandeBerg JS, Rudolph R. Pressure (decubitus) ulcer: variation in histopathology-a light and electron microscope study. Hum Pathol. 1995;26(2):195-200*
[111] *Witkowski JA, Parish LC. Histopathology of the decubitus ulcer. J Am Acad Dermatol. 1982;6(6):1014-21*
[112] *Bohm E, Kuhlman I, Bótel U. Das druckgeschwür bei Querschnittgelähmten- eine vergleicehnde klinisch-histologische Untersuchung. Unfallchirurgie 1988;14(6):335-42*
[113] *Jong de BD. Decubitus bij lijders aan dwarslaesie (Decubitus in patients with paraplegia) Thesis Rijksuniversiteit Utrecht. Utrecht The Netherlands 1965*
[114] *Salcido R, Donofrio JC, Fisher SB, LeGrand EK, Dickey K, Carney JM, Schosser R, Liang R.Histopathology of pressure ulcers as a result of sequential computer-controlled pressure sessions in a fuzzy rat model. Adv Wound Care. 1994;7(5):23-40*
[115] *Coleridge Smith PD. Deleterious effects of white cells in the course of skin damage in CVI. Int Angiol. 2002;21(2 Suppl 1):26-32*
[116] *Weiss SJ.Tissue destruction by neutrophils. N Engl J Med. 1989;320(6):365-76.*
[117] *Novelli GP Adembri C, Gandini E, et al. Vitamin E protects human skeletal muscle from damage during surgical ischemia-reperfusion. Am J Surg. 1997;173(3):206-9*
[118] *Formigli L, Ibba Manneschi L, Tani A, Gandini E, Adembri C, Pratesi C, Novelli GP, Zecchi Orlandini S. Vitamin E prevents neutrophil accumulation and attenuates tissue damage in ischemic-reperfused human skeletal muscle. Histol Histopathol. 1997l;12(3):663-9.*
[119] *Sundin BM, Hussein MA, Glasofer S, El-Falaky MH, Abdel-Aleem SM, Sachse RE, Klitzman B. The role of allopurinol and deferoxamine in preventing pressure ulcer in pigs. Plast reconstr Surg 2000;105(4):1408-21*
[120] *Şener G, Sert G, Sehiri AO, Arbak S, Gedik N, Ayanoglu-Dulger G. Melatonin protects against pressure ulcer-induced oxidative injury of the skin and remote organs in rats J Pineal Res 2006;40:280-7*
[121] *Peirce SM, Skalak TC, Rieger JM, Macdonald TL, Linden J. Selective A(2A) adenosine receptor activation reduces skin pressure ulcer formation and inflammation Am J Physiol Heart Circ Physiol. 2001;281(1):H67-74)*

[122] *Marum RJ, Meijer JH, Ooms ME, Kostense PJ, van Eijk JT, Ribbe MW. Relationship between internal risk factors for development of decubitus ulcers and the blood flow response following pressure load.Angiology. 2001;52(6):409-16.*

[123] *Devasagayam TP , Tilak JC, Tilak+JC, Boloor KK, Sane KS, Ghaskadbi SS ,Lele RD. Free radicals and antioxidants in human health: Current status and future prospects J. Assoc. Phys. India 2004;52:794-804*

[124] *Polidori MC. Antioxidant Micronutrients in the Prevention of Age-related Diseases. JPGM 2003;49(3);229-35)*

[125] *Lee, BY, Hogan DJ, Ursine S, Yanamandra K, Bocchini JA. Personal observation of skin disorders in malnutrition. Clin Dermatol 2006;24:222-7*

[126] *Goode HF, Burns E, Walker BE. Vitamin C depletion and pressure sores in elderly patients with femoral neck fractures. BMJ 1992;305:925-7*

[127] *Arnold M, Barbul A. Nutrition and Wound Healing. Plastic & Reconstructive Surgery. 2006:117(7S) ;42S-58S*

[128] *Norris JR, Reynolds RE. The effect of oral zinc sulfate therapy on decubitus ulcers. J Am Geriatr Soc 1971;19:793-7.*

[129] *Taylor TV, Rimmer S, Day B, Butcher J, Dymock IW. Ascorbic acid supplementation in the treatment of pressure-sores. Lancet 1974 Sep 7;2(7880):544-6.*

[130] *Riet ter G, Kessels AG, Knipschild PG. Randomized clinical trial of ascorbic acid in the treatment of pressure ulcers. J Clin Epidemiol 1995;48:1453-1460.*

[131] *Benati G, Delvecchio S, Cilla D, Pedone V. Impact on pressure ulcer healing of an arginine-enriched nutritional solution in patients with severe cognitive impairment.Arch Gerontol Geriatr Suppl. 2001;7:43-7.*

[132] *Thiele J, Elsner P. (eds): oxidants and antioxidants in cutaneous biology. Curr Probl Dermatol. Basel, Karger, 2001, vol 29*

[133] *Thiele JJ, Schroeter C, Hsieh SN, Podda M, Packer L. The antioxidant network of the stratum corneum. In: Detection of antioxidants in Skin and antioxidant response to environmental stress. Thiele J, Elsner P. (eds): oxidants and antioxidants in cutaneous biology. Curr Probl Dermatol. Basel, Karger, 2001, vol 29.pp 26-42*

[134] *Green MF, Exton-Smith AN, Helps EP, et al. Prohylaxis of pressure sores using a new lotion. Modern Geriatr. 1974;4:376-82*

[135] *Torra i Bou JE, Segovia Gómez T, Verdú Soriano J, Nolasco Bonmatí A, Rueda López J, Arboix i Perejamo M.The effectiveness of a hyperoxygenated fatty acid compound in preventing pressure ulcers. J Wound Care. 2005;14(3):117-21*

[136] *van der Cammen TJ, O'Callaghan U, Whitefield M. Prevention of pressure sores. A comparison of new and old pressure sore treatments. Br J Clin Pract. 1987;41(11):1009-11*

[137] *Meaume s, Colinn D, Barrois B, Bohbots S, Allaert F.A. Preventing the occurrence of pressure ulceration in hospitalised elderly patients. J of Woundcare 2005;14(2):78-82*

[138] *Reddy M, Gill S, Rochon PA. Preventing pressure ulcers: a systematic review. JAMA 2006;296: 974-984.*

[139] *Halliwell B.The antioxidant paradox. Lancet 2000; 355: 1179–80*

[140] *Halliwell B Antioxidants in human health and disease. Annu Rev Nutr.1996;16:33-50*

[141] *Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention Systematic Review and Meta-analysis. JAMA. 2007;297:842-857*

[142] *Bast A, Haenen GR. The toxicity of antioxidants and their metabolites. Environ Toxicol Pharmacol. 2002;11:251-8*

[143] *Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients.J Parenter Enteral Nutr. 2003;27(5):355-73.*

[144] *Heyland DK, Dhaliwalm R, Day A, Drover J, Cote H, Wischmeyer P. Optimizing the dose of glutamine dipeptides and antioxidants in critically ill patients: a phase I dose-finding study.*
J Parenter Enteral Nutr. 2007;31(2):109-18.

[145] *Thompson C, Furhman P. Nutrition and wound healing: Still searching for the magic bullet. Nutr Clin Pract 2005;20(3):331-47*

[146] *Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutritioon become routine in critically ill patients. A systemic review of the effidence JAMA 2001;286(8):944-53*

Summary

Pressure ulcers (PU), also called bedsores or decubitus, present a significant problem in healthcare **(chapter 1)**. PU are suffered mainly, but not exclusively, by the elderly, the bedridden, the wheelchair bound or the severely ill. Increased longlivity and associated morbidity are also likely to lead to an increase in the prevalence of PU. PU are associated with pain, discomfort, and social isolation for the patient. In addition, they constitute a burden to the community in terms of healthcare and finances. PU are mostly preventable, if appropriate measures are taken in time. Prevention is not only important for the patient, but also important to reduce the high costs for the community. A PU is an area of localised damage to the skin and underlying tissue caused by pressure, shear or fiction or a combination of these forces. Pressure on skin, usually over bony prominences as heels, sacrum and hips can result in ulceration. This varies from a non-blanchable erythema of intact skin to extensive destruction of muscle or even bone. Although the main cause for the development of PU is always dependent on sustained mechanical loads, other factors play a role as well. While some patients develop PU when subjected to a certain pressure, others do not. Many factors are known to increase the risk of developing PU; however, they have no defined place in pathofysiological mechanisms.
It is quite obvious that many of our preventive strategies are based on daily practice rather than research. To obtain an evidence-based tool to measure the effectiveness of the different preventive strategies, more insight in the complex aetiology of PU is necessary. Such fundamental work is required but often overlooked in the rush to compare the effects of different interventions on the prevention and treatment of PU.

This thesis addresses some aspects of the aetiology of superficial and deep PU. The possible benefit of therapeutical interventions with nutrional supplementation and the use of a risk assessment tool are evaluated. The role of reactive oxygen species in the pathogenesis of pressure ulcer coupled with possible therapeutical interventions with antioxidant drugs, being protective against reactive oxygen species, is the main topic of this thesis.

Patients with incontinence often suffer from superficial skin defects on their buttocks. By introducing the diagnosis " moisture lesions" attempts have been made to single out this superficial skin loss as a distinct entity, different from early stages of PU.
Moisture is considered as the main cause, so treatment guidelines are different from those of PU. Singling out moisture lesions, from the PU classification system influences the PU prevalence figures. However, the introduction of the diagnosis "moisture lesion"

and treatment guidelines are solely based on expert opinions, without scientific justification.

Chapter 2 describes the results of a clinical-pathological study of skin samples in patients with incontinence and so-called moisture lesions. Histopathological examination shows two distinct patterns. One pattern with damage due to an ischemic process, and one with a hyperplastic epidermis with partial skin loss without ischemia. It was impossible to predict the histopathological pattern on the basis of the clinical features. Shearing forces seem to be essential in the etiology; moisture is only an attributing factor. Based on these results there is no justification for a distinction between moisture lesions and superficial pressure ulcers. In prevalence figures they have to be considered as a grade 2 or 3 PU. Preventive measures to avoid deterioration of the condition of the skin should include proper skin care, incontinence management, frequent change of pads, and drying the skin to the air, **and** relief of pressure.

Prevention of the development of PU is expensive and labour intensive and should therefore be applied to people who are actually at risk. This notion led to the development of PU risk assessment scales (PURAS) entailing an enumeration of factors, which could be attributed to the chance of getting decubitus. A PURAS with high-sensitivity and specificity enables to determination of patients for whom preventive measures are required or not.

In **chapter 3** we evaluated the sensitivity and specificity of a risk assessment tool in relation to 121 hip fracture patients. We found a high occurrence of PU, despite the use of preventive measures. In this patient group, prolonged stays in an emergency and radiology ward and prolonged surgical procedures are the only risk factors that predicted an increased likelihood of developing PU with any accuracy. The used PURAS seemed to be of limited value, and was unable to predict the likelihood of developing PU, even in this selected patient population. As the occurrence of PU in these patient populations has proven to be high, our advice would be to give all hip fracture patients maximum PU preventive measures. We recommend that the use of pressure-reducing mattresses should start immediately at admission as well as the application of pressure-reducing positions during operation.

Malnutrition is an important risk factor for the development of PU. Patients with fractured proximal femur are often undernourished. In **chapter 4** we studied the effect of nutritional supplementation on the prevention of the development of PU. Hip fracture patients (n=103) after the surgical procedure received 400ml daily of a high-protein supplementation, enriched with arginin, zinc and antioxidants (Cubitan®) or a non-caloric, water-based placebo supplement. We did not find a statistical positive effect on

the occurrence of PU with the nutritional supplement in comparison with the placebo. The reason may be that the supplementation was started only after the critical moment of PU formation because, as shown in chapter 3, the onset of PU is started before and/or during surgery.

In **chapter 5** we studied the effects of pressure with a new computer-controlled pressure device applied in an animal model. After the application of pressure on the trochanteric region of pigs, we investigated the damage in muscle, subcutis and cutis. Histological specimen taken immediately after cessation of the pressure showed no damage at all. The first signs of beginning damage appear after two hours of pressure relief. The severity of the damage was not dependant of the duration of the pressure. The noted histopathology, in combination with the required pressure relief time for this pathology, indicates that reperfusion is a necessary contributing factor. Electron- and light microscopic examination and biochemical analyses point to the role of reactive oxygen species (ROS) in the process of inflammation during ischemia-reperfusion (I/R). Under normal circumstances ROS are buffered by so-called scavengers. However, when there is a shortness of scavengers or when ROS are present in excess, this can result in inflammation and tissue necrosis. Pre-treatment with a scavenger prevents the excess production of ROS during reperfusion and diminishes the tissue damage. As a conesquence of the beneficial effect of an antioxidant in the avoidance of the development of PU, there seemed to be cause to further investigate this apparent correlation.

In **chapter 6A** we present the findings of a systematic survey of the literature about the effects of topical application of dimethyl sulfoxide (DMSO) on the skin as an anti-inflammatory agent. DMSO has multiple applications for instance as a vehicle for drug therapy and as an anti-inflammatory agent. No pharmaceutical company was able to get an exclusive patent for DMSO and, as a consequence, for studies on its use as a drug component were performed. Since it is known to be a powerful hydroxyl-inactivating compound, it can be assumed that it has beneficial effects on PU development.
First we have evaluated the literature on the efficacy of DMSO in various concentrations on wound healing and as an anti-inflammatory drug administered by topical application. A Medline literature research was carried out and three independent reviewers scored the articles found. The conclusion from the evaluation was that it appears to be safe for use in a low concentration on the human skin and could be effective in the prevention of PU.

Chapter 6B describes the results of a randomised double-blinded study, performed to assess the effects of massage with or without DMSO cream in three intervention groups in two locations, buttocks or heel and ankle. For the buttocks there was no difference in

PU incidence between the three interventions. Surprisingly, however, massage with the topical 5% DMSO cream showed an increase in occurrence of superficial PU for the heel and ankle region. A possible explanation for this unexpected detrimental effect could be a result of the complex mechanism of action of DMSO. Scavengers can have an antioxidant, neutral, or (paradoxically) pro-oxidant role. Prevention of the cell response to stress, by up-regulating its anti-oxidants effects, could be an explanation.

Since under normal circumstances large quantities of antioxidants are provided to the organism by means of the diet, a poor nutritional condition could be associated with a deficit of antioxidants. This emphasises the role of nutrition, with a focus on vitamins and tracer elements, in a rational therapy for PU prevention. However, the results of the intervention study (chapter 4) with the administration of a mixed nutritional supplement enriched with anti-oxidants, showed no convincing preventive effect when compared with the administration of a placebo.

Conclusions

In the general discussion (**chapter 7**) we endeavour to answer the questions addressed in chapter 1, the aims of this thesis. The results and implications for PU care or further research in relation to the studies of chapter 2 up to 6 are discussed in this chapter.

Do moisture lesions exist as a separate entity?

Based on the results of chapter 2 it can be concluded that the influence of urine and/or faeces per se is not sufficient to cause epidermal skin loss, but that shearing forces are an essential etiologic factor in moisture lesions. In immobile and incontinent elderly patients the skin has a diminished tolerance for tissue loading, which can result in subepidermal skin loss. Methods and effectiveness of proper skin care on prevention and treatment of skin damage in individuals prone to develop PU deserves more research, attention and education. There is no justification to consider moisture lesions as a clinical entity different from superficial PU. A sore and odorous skin loss in the incontinent elderly seems to indicate a lack of proper quality of care. The guidelines on prevention and treatment of skin lesions in incontinent patients should be based on three main interventions: managing the incontinence problem, adequate skin care **and** diminishing tissue loading.

Do risk assessment tools really identify patients at risk?

The results showed that it is not possible to identify patients at risk for PU solely on the basis of the use of a risk assessment tool.

A risk assessment tool should be used as a tool to observe a patient according to a specific protocol and, obviously, an increased PU risk should alert a clinical team. The identification of a patient at risk, should be based on the combination of the following items 1) a pressure ulcer risk assessment tool 2) the clinical judgement of the medical and nursing personnel 3) the prognosis of the underlying disease and mobility 4) the discomfort of the patient **and** 5) inspection and palpation of the threatened area (skin assessment). Skin assessment seems to be a useful tool and deserves more research, attention and education.

Can nutritional supplements prevent the development of PU?
The fact that both undernutrition and PU frequently coexist in the same persons, in itself does not necessarily imply a causal relation. The scientific relationship between nutrition and the development of PU is often assumed but is based on limited evidence. We found no statistically significant positive effect of extra nutritional supplementation by drink foods in the prevention of PU. Before advocating the use of extra nutrional supplements in PU prevention, further research is required. This does not imply that until such evidence is provided, no attention has to be given to the nutritional state of the patient. However, intervention with drink foods especially can interfere with the normal daily intake, are expensive and do not integrate physical care with measures to improve quality of life. Food adjustments by offering healthy and tasty food of good quality in a social ambiance should be the first objective.

Is ischemia-reperfusion injury the main underlying cause of PU?
Although other mechanisms as occlusion of lymphatics and sustained deformation of cells can contribute to the development of PU, our studies showed that reperfusion injury plays an important role in the pathophysiology of PU.

Is it possible to reduce the extent of the tissue damage in PU by means of antioxidants?
We have shown that it is possible to reduce the extent of the tissue damage in PU by means of antioxidants in an animal model. However, we were not able to demonstrate a significant effect of adding nutrional supplements, enriched with antioxidants in humans. Moreover, we even demonstrated a detrimental effect on the occurrence of PU on the heels in humans with a locally applied antioxidant.
However, although the use of antioxidants seems promising, no studies with a positive result on the prevention or treatment of PU in humans are known. As synthetic antioxidant supplements may increase mortality, and a locally applied antioxidant contributes to increased occurrence of PU, more animal and human studies are required to establish the safety and effectiveness of antioxidantal therapy.

Nederlandse samenvatting

Inleiding

Decubitus, in de volksmond doorliggen genoemd, is een belangrijk probleem in de gezondheidszorg. Doorliggen wordt veelal gesignaleerd bij langdurig zieke, bedlegerige personen, maar ook bij patiënten die in een rolstoel zitten, bijvoorbeeld na een dwarslaesie. Ook kan een kortdurende druk op de operatietafel leiden tot decubitus. Decubitus gaat vaak gepaard met pijn, ernstig ongemak of leed, met kans op sociale isolatie. Daarnaast geeft decubitus hoge kosten voor de gezondheidszorg. De meeste decubituswonden kunnen voorkomen worden als preventieve maatregelen worden genomen. Voorkomen van decubitus is niet alleen belangrijk voor de patiënt, maar ook belangrijk voor de maatschappij vanwege de hoge kosten. Reden waarom de overheid zich de laatste jaren actief bezighoudt met het probleem van decubitus.

De definitie van decubitus luidt: elke degeneratieve verandering die wordt veroorzaakt door op weefsels inwerkende druk- schuif- en/of wrijfkrachten. Langdurige druk op huid, onderhuidweefsel en spieren kan leiden tot het afsterven hiervan. De meest gevoelige plaatsen op het lichaam zijn plaatsen waar bot relatief vlak onder de huid ligt, zoals hielen, stuit en heupen. De ernst van een decubituswond wordt ingedeeld in vier graden, variërend van een paarsrode verkleuring van de huid (graad 1) tot een diepe wond tot op het bot (graad 4). Deze indeling wordt gebruikt als leidraad voor de behandeling, en bij de jaarlijkse metingen hoe vaak decubitus voorkomt (prevalentie meting). Naast de belasting van huid en spieren, zijn er factoren die patiënten extra gevoelig maken voor het krijgen van decubitus. Van veel van deze factoren is onbekend waarom zij een patiënt gevoeliger maken. Dit komt omdat er een gebrek aan kennis is over de oorzaken en de mechanismen achter de ontwikkeling van decubitus. Hierdoor kunnen we niet goed voorspellen wie extra gevoelig is voor het krijgen van decubitus. De preventieve maatregelen die we momenteel geven berusten nog steeds meer op ervaring dan op wetenschappelijk bewijs.

De artikelen in dit proefschrift gaan over de ontstaanswijze van diepe en oppervlakkige decubitus. Het effect van een voedingssupplement op het voorkomen van decubitus werd onderzocht. De rol van toxische zuurstofmetabolieten (radicalen) bij het ontstaan van decubitus, en de mogelijkheid deze radicalen onschadelijk te maken met zogenaamde anti-oxidanten is het hoofdonderwerp van dit proefschrift.

Incontinente bedlegerige patiënten hebben vaak oppervlakkige wonden op de billen, deze letsels werden tot dusver als een oppervlakkige vorm van decubitus gezien. Sinds kort

worden door sommigen deze huidafwijkingen echter als een apart ziektebeeld beschouwd, vocht -of incontinentieletsel genaamd. Volgens hen worden deze huidletsels veroorzaakt door de inwerking van vocht op de huid en niet, zoals bij decubitus, door druk- schuif- en/of wrijf krachten. Behandelingsrichtlijnen zijn anders dan voor decubitus en in de jaarlijkse metingen worden zij niet meer als decubitus meegeteld. De diagnose vochtletsel en de geadviseerde behandelingsrichtlijnen zijn echter niet gebaseerd op wetenschappelijk onderzoek, maar berusten op een mening van deskundigen op decubitus gebied.

In **hoofdstuk 2** wordt een onderzoek beschreven met als doel inzicht te verkrijgen in de ontstaanswijze van zogenoemde vochtletsels. Bij 12 patiënten met vochtletsels werden kleine stukjes huid afgenomen voor microscopisch onderzoek. Onder de microscoop werden twee soorten beelden gezien. Bij eenderde van de patiënten was er schade aan de huid door een tekort aan zuurstof (ischemie), een gevolg van druk- of schuifkrachten. Bij de andere patiënten bleek zuurstoftekort geen rol te spelen. Er werd een beeld gezien dat waarschijnlijk veroorzaakt wordt door een uitwendige schuifkracht, zonder dat er ischemie optreedt. Op het klinisch beeld bleek het niet mogelijk te voorspellen of de schade een gevolg was van het zuurstof tekort of werd veroorzaakt door schuif- en/of wrijfkrachten zonder een ischemisch proces. De invloed van vocht bleek slechts een bijdragende factor. De resultaten van dit onderzoek hebben consequenties voor de behandeling en preventie van een dergelijk letsel. Naast aandacht voor de incontinentieproblematiek, moet met name aandacht worden besteed aan drukontlastende maatregelen. In de jaarlijkse decubitusmetingen moeten dergelijke letsels worden meegeteld bij voorkeur als graad 2 of 3 decubitus, zoals we voor 2004 deden.

De maatregelen om decubitus te voorkomen zijn kostbaar en arbeidsintensief, echter nog altijd goedkoper dan behandeling van een al opgetreden decubitus. Preventieve maatregelen moeten worden toegepast bij die mensen die daadwerkelijk risico lopen. Om deze redenen zijn zogenaamde decubitus-risico-score-lijsten ontwikkeld. Dit zijn opsommingen van factoren die mogelijk de kans op decubitus vergroten. Met behulp van een betrouwbare scorelijst kan goed worden voorspeld welke patiënt wel - en welke patiënt geen preventieve maatregelen nodig heeft. Hiermee zou het mogelijk moeten zijn preventie efficiënt en kosten effectief toe te passen.

In **hoofdstuk 3** werd de betrouwbaarheid van een risicoscorelijst geëvalueerd, bij 121 patiënten opgenomen wegens een gebroken heup. Ondanks het gebruik van preventieve maatregelen vonden wij, net als anderen, een hoge decubitus incidentie. Met de risicoscorelijst bleek het niet mogelijk te voorspellen of iemand wel of geen decubitus zou

krijgen. Van alle afzonderlijke risicofactoren, waarvan we vermoeden dat die de kans op decubitus vergroten, bleek alleen de duur van het verblijf op de eerste hulp, röntgen afdeling en de duur van de operatieve ingreep van voorspellende waarde te zijn. Op grond van deze bevindingen moet geadviseerd worden, bij patiënten met een gebroken heup al op de eerste hulp afdeling drukontlastende maatregelen te nemen. Ook op de röntgenafdeling en de operatietafel moet aandacht besteed worden aan anti-decubitus maatregelen.

Tot de risicofactoren voor het krijgen van decubitus behoort een slechte voedingstoestand. Deze risicofactor lijkt, in tegenstelling tot de andere risicofactoren, relatief eenvoudig te corrigeren. Patiënten die een heupfractuur oplopen blijken vaak een slechte voedingstoestand te hebben.

Hoofdstuk 4 is een studie naar het preventieve effect van extra voeding op het voorkomen van decubitus. Patiënten (n=103) met een heupfractuur kregen na de operatie een speciaal voor decubitus patiënten ontwikkelde drinkvoeding (Cubitan®) of een placebo (nepmiddel). Dagelijks werden de patiënten gecontroleerd op eventuele decubitus laesies. Het resultaat was teleurstellend. De patiënten die de speciale drinkvoeding kregen, ontwikkelden bijna net zoveel decubitus als patiënten die een placebo kregen. Het negatieve resultaat is mogelijk een gevolg van het late tijdstip van het starten van de drinkvoeding, namelijk na de operatie. Wellicht hadden de patiënten toen al de eerste schade opgelopen. In de general discussion wordt verder ingegaan op de mogelijke rol van voeding op de preventie van decubitus.

In een proefdiermodel in **hoofdstuk 5** hebben we het effect van druk onderzocht. Voor dit doel werd een apparaat ontwikkeld, waarmee door middel van twee stempels een computergestuurde hoeveelheid druk gegeven kon worden. Deze drukstempels werden aangebracht op de dijbenen bij onder narcose gebrachte varkens. Na het stoppen van de druk hebben we de schade in huid en spieren, microscopisch, elektronenmicroscopisch en biochemisch onderzocht. Er werd geen schade gevonden aan het weefsel indien dit direct na het stoppen van de druk werd onderzocht. De eerste tekenen van schade werden pas gevonden als er 2 uur geen druk gegeven werd. Het gegeven dat niet het stoppen van de circulatie (ischemie) maar het opnieuw op gang komen van de circulatie (reperfusie) nodig is voor schade, staat bekend als ischemie-reperfusie schade. Ook bij het hart- en herseninfarct speelt dit fenomeen een belangrijke rol. De ischemie-reperfusie weefsel schade wordt verklaard door het ontstaan van toxische afbraakproducten van zuurstof. Deze afbraakproducten, radicalen genoemd, worden gevormd tijdens de recirculatie, na een periode van zuurstof tekort. Radicalen kunnen via een cascade van reacties tot een

potentieel verwoestend proces leiden. Normaliter worden zij onschadelijk gemaakt door beschermende stoffen, scavengers of anti-oxidanten genaamd. Echter bij een over-productie van radicalen, of als er een tekort aan scavengers is, ontstaat een ontstekings-reactie die tot celdood kan leiden. Zowel elektronen- en lichtmicroscopisch onderzoek als de biochemische analyse, gaven aanwijzingen dat ischemie-reperfusie schade een belangrijke rol speelt bij de pathofysiologie van decubitus. Indien de varkens enkele dagen voor de proef een antioxidant (vitamine-E) met de voeding toegediend kregen, trad beduidend minder schade aan de spieren op. Dit ondersteunt de theorie van ischemie-reperfusie, en belangrijker, biedt perspectieven voor een mogelijke therapie ter voorkoming van decubitus. Door het toedienen van extra anti-oxidanten via de voeding zou de gevoeligheid voor decubitus verminderd kunnen worden. Dit positieve resultaat was aanleiding voor vervolgonderzoeken naar het mogelijk preventieve effect van anti-oxidanten op decubitus.

Anti-oxidanten kan men via voeding of pillen toedienen, maar ook met een smeersel aanbrengen. **Hoofdstuk 6A** laat de resultaten zien van een systematisch literatuur onderzoek, naar het ontstekings remmend effect van lokaal dimethyl sulfoxide (DMSO). DMSO wordt in de dermatologie al jaren gebruikt vanwege zijn uitstekende penetrerende vermogen. Er is relatief weinig onderzoek verricht naar de therapeutische mogelijkheden van DMSO, omdat geen enkele farmaceutisch bedrijf een exclusief patent wist te krijgen. In de reguliere geneeskunde en als zelfzorg medicatie wordt DMSO soms gebruikt vanwege de mogelijk ontstekingsremmende werking. Dit zou berusten op het onschadelijk maken van radicalen, die een belangrijke rol spelen bij ontsteking. Ondanks het jarenlang gebruik van dit middel is relatief weinig onderzoek verricht naar de precieze werking. DMSO is een krachtige antioxidant, met name gericht tegen de hydroxylradicaal. Deze radicaal speelt een belangrijke rol bij ischemie-reperfusie schade. Uit de bestaande literatuur bleek dat DMSO in lage concentratie veilig is en mogelijk een preventieve werking zou kunnen hebben op het ontstaan van decubitus.

Dit onderzoek vormde de basis van een studie naar het preventieve effect van een 5% DMSO crème, op het voorkomen van decubitus (**hoofdstuk 6B**). Uit verschillende verpleeghuizen werden 79 personen ingedeeld in 3 groepen. De ene groep kreeg gedurende 4 weken, 4 maal daags een 5% DMSO crème op voor decubitus gevoelige plekken als stuit, hiel en enkel. Een andere groep kreeg een crème zonder DMSO (placebo groep). Een derde groep (controle) werd toegevoegd om een eventueel positief of negatief effect van het aanbrengen van een crème uit te sluiten.
Helaas werd in deze studie geen positief effect gevonden van het lokale antioxidant. Integendeel, er bleek meer decubitus op te treden aan de enkels en hielen in de DMSO

groep, in vergelijking met de patiënten uit de placebo- of controle groep. Het is niet eenvoudig een verklaring te vinden waarom het wegvangen van radicalen juist meer decubitus veroorzaakt. Het is echter bekend dat radicale zuurstof metabolieten naast een schadelijke ook een nuttige werking hebben. Het wegvangen van deze radicalen kan zo een tegengesteld effect veroorzaken, bekend als het *pro-oxidant effect*.

De in **hoofdstuk 4** beschreven drinkvoeding (Cubitan®) was speciaal voor patiënten met decubitus ontwikkeld. Naast een verrijking met energie en eiwit zijn ook ingrediënten toegevoegd die mogelijk een positief effect hebben op de doorbloeding van de huid (arginine), en invloed hebben op het door radicalen veroorzaakte ontstekingsproces (anti-oxidanten). Zoals hierboven beschreven bleek het niet mogelijk om het aantal decubitus gevallen te verlagen met de speciale drinkvoeding, in vergelijking met de placebo.

Conclusies

In **hoofdstuk 7** (general discussion) worden de resultaten van de studies van hoofdstuk 2 t/m 6 besproken, en vergeleken met eerdere studies die op dit gebied zijn verricht. De in de inleiding **(hoofdstuk 1)** gestelde vragen worden beantwoord.

Is vochtletsel een aparte diagnose, anders dan decubitus?

Op basis van het resultaat van hoofdstuk 2 kan geconcludeerd worden dat vochtletsels niet alleen door vocht worden veroorzaakt, maar vooral een gevolg zijn van belasting van de huid. Wel is de huid mogelijk extra gevoelig door de inwerking van vocht. "Vochtletsels" moeten daarom beschouwd worden als een graad 2 of 3 decubitus, en meegeteld worden in de prevalentie- of incidentie metingen. Meer onderzoek naar de belastbaarheid van deze gevoelige huid is nodig, om tot goede therapeutische en preventieve richtlijnen te komen. In deze richtlijnen moet aandacht worden besteed aan 1) de incontinentie problematiek 2) juiste wijze van verzorging van de huid en 3) de gevolgen van belasting op deze gevoelige huid.

Voorspellen decubitus-risico-score-lijsten wie gevoelig is voor het krijgen van decubitus?

Zoals ook is gebleken uit andere onderzoeken, is het met decubitus-risico-score-lijsten niet mogelijk te voorspellen wie extra gevoelig is voor het krijgen van decubitus. Voor de praktijk zijn deze lijsten nuttig als hulpmiddel om op gestructureerde wijze naar een patiënt te kijken. De beste manier om in te schatten of een patiënt een groter risico heeft op het krijgen van decubitus, is door het combineren van 1) een decubitus-risico-score-lijst 2) het klinische oordeel van het verzorgende en medische personeel 3) de prognose van de onderliggende ziekte en mobiliteit 4) het aangeven door de patiënt dat het

bedreigde gebied gevoelig is 5) het inspecteren en palperen van de huid op zoek naar aanwijzingen voor beginnende schade. Dit laatste aspect, in het Engels "skin-assessment" genaamd, verdient veel meer aandacht, instructie en onderzoek bij de preventie van decubitus.

Kunnen voedingspreparaten verrijkt met extra energie en eiwit, decubitus voorkomen?
Ondervoeding is een voorspellende factor voor het krijgen van decubitus. Een bewezen wetenschappelijk verklaring, waarom ondervoeding en decubitus gerelateerd zijn is er echter niet. Het zij ondervoede mensen zijn minder mobiel, waardoor zij de huid meer belasten, of weefsel van ondervoede mensen is gevoeliger voor belasting. In ons onderzoek kon, evenals bij andere onderzoeken, geen overtuigend bewijs geleverd worden dat extra voeding doormiddel van een drinkvoeding van nut is bij het voorkomen van decubitus. Voordat in deze situatie drinkvoeding als regel geadviseerd gaat worden, zal eerst meer onderzoek verricht moeten worden. Aandacht voor ondervoeding is echter wel van belang, aangezien het leidt tot toename van ziekte en sterfte, opname duur, infectie kans en vertraging in de wondgenezing. Een eiwit- en energie verrijkte voeding, in een klein volume, lekker èn smaakvol opgediend, samen met anderen genuttigd in een eetlust stimulerende omgeving, gecombineerd met tussendoortjes, verdient de voorkeur boven duurdere, minder lekkere en niet gezondere drinkvoeding.

Speelt ischemie-reperfusie schade een belangrijke rol als oorzaak van decubitus?
Alhoewel ook andere oorzaken, zoals afsluiting van lymfevaten en vervorming van cellen door druk, van invloed kunnen zijn op het ontstaan van decubitus, speelt ischemie-reperfusie een belangrijke rol.

Kan een antioxidant de schade aan weefsels bij decubitus voorkomen?
Een anti-oxidant (vitamine-E) bleek in staat de schade ten gevolge van reactieve zuurstof metabolieten in een proefdier model te verminderen. Een lokaal aangebracht anti-oxidant bleek bij mensen echter juist *meer* decubitus op de huid te veroorzaken. Anti-oxidanten verwerkt in een drinkvoeding bleken geen positief effect te hebben op het voorkomen van decubitus. Alhoewel de mogelijkheid van therapeutische interventies in het proces van oxidatieve stress bij decubitus interessant kan zijn, zijn veel meer studies nodig om de effectiviteit en veiligheid te bewijzen. Synthetische antioxidanten kunnen mogelijk leiden tot een verhoogde mortaliteit. Het gebruik van deze middelen in de preventie van decubitus, lokaal of in hoge dosis oraal, moet afgeraden worden.

Nawoord

Dit proefschrift is het resultaat van 18 jaar verwondering over decubitus. Behandeling en voorkomen van decubitus vergt een multidisciplinaire benadering, helaas zijn weinig artsen hier bijzonder in geïnteresseerd. Ik heb vanuit mijn specialisme, de dermatologie, op mijn manier naar het probleem gekeken. Weer anders dan andere onderzoekers als verplegingswetenschappers, technisch en biomedisch ingenieurs, of artsen van andere disciplines. Soms ben ik tot andere dan de heersende conclusies gekomen. Als dit kan leiden tot wetenschappelijke discussies en aanleiding is voor verder onderzoek, dan zou dat prachtig zijn.

Verwonderen en het bedenken van ideeën en oplossingen is het creatieve en leuke deel van wetenschappelijk werk. Het uitwerken van de resultaten echter is een zware opgave, zeker in combinatie met het gewone werk als dermatoloog. Dat ik niet in verwondering ben blijven steken, maar toch tot een afronding gekomen ben, is door de bijdrage van velen. Ik wil iedereen hiervoor van harte bedanken, een aantal mensen wil ik in het bijzonder noemen.

Als eerste wil ik de patiënten bedanken, die hebben meegedaan met de onderzoeken.

Prof. dr. J.R.E. Haalboom, beste Jeen. Ik mocht tijdens mijn opleiding deel uitmaken van de AZU decubitus werkgroep. Sinds die tijd heeft decubitus mijn bijzondere belangstelling. Jouw kennis en inzicht in de grote verscheidenheid van de problematiek van decubitus, jouw enthousiasme en vasthoudendheid, zijn in die 18 jaar niet minder geworden. Ik vind het een grote eer dat ik bij jou mag promoveren.
Prof. dr. C.A.F.M. Bruijnzeel-Koomen, beste Carla. Ik dank je zeer voor het in mij gestelde vertrouwen. Hierdoor heb ik de mogelijkheid gekregen om mijn medische studie te kunnen afronden in Utrecht, de stad waar ik 31 jaar geleden met die opleiding begonnen ben.
Prof. dr. J.W. Arends, beste Jan Willem. Jouw gave als opleider en het vertrouwen dat je me schonk, kwamen op het juiste moment. Zonder jouw inzet en betrokkenheid was het niet gelukt.
De leden van de beoordelingscommissie: Prof. dr. J.J.M. Marx, Prof. dr. M. Kon, Prof. dr. Chr. van der Werken, dr. B.S. van Asbeck en Prof. dr. T. Defloor, ben ik erkentelijk voor het kritisch beoordelen van mijn manuscript.
dr. Wil van der Zwet, wil ik danken voor zijn hulp bij de statistiek. De aanwezigheid van een wetenschapscoördinator in een STZ ziekenhuis is een duidelijk voordeel.

Een lagere incidentie van decubitus in Nederland is zeker mogelijk. Als voorbeeld het Deventer Ziekenhuis door de tomeloze, non-conformistische inzet van Eddy Koopman. Eddy veel dank.
Alle medeauteurs van mijn artikelen dank ik voor hun hulp en inspiratie. Iedereen die geholpen heeft bij de onderzoeken, als laborant, dierenverzorger, verpleegkundige, instrumentenmaker heel veel dank. Familie, vrienden, "mijn" assistentes, Yvette Jonasse, Max Overgoor, Joyce von Oerthel, Marian Muller-Boerstoel, Cees Oomens, Coen Teunissen, Ruud Halfens, Hans van Rossum, de afdeling pathologie van het DZ, Kees van Ginkel, Martijn van de Scheur en Jurr Boer, Michiel Schoemaker en Reinier Nijmeijer allen hebben mij geholpen en gesteund.
Mijn ouders dank ik voor mijn opvoeding en hun vertrouwen in mij. Een van de mores thuis; " Je moet afmaken waar je aan begint" kwam mij nu van pas.

En tenslotte wil ik mijn meisjes bedanken aan wie ik dit boekje opdraag:
Lieve Marita, Maite, Tanne en Fiore, jullie liefde en vrolijke gezelligheid zijn het belangrijkste in mijn leven. Het was mijn bedoeling om stiekem te promoveren, zonder dat jullie het zouden merken. Dat is niet gelukt. Vanaf nu zal ik altijd luisteren, en lekke banden en vastgelopen computers fluitend repareren.
Lieve Maite, ik hoop dat je in de toekomst de weg naar het UMCU nog heel vaak mag afleggen. Zingend, net zoals wij samen vroeger op de fiets deden, op die zelfde weg.
Lieve Tanne, we weten het nu zeker: ook jij bent veroordeeld door je talent. Volg je gevoel, dan komt alles goed.
Lieve Fiore, ooit verzuchtte je "papa, je bent leuker als je *niet* aan het promoveren bent" Erewoord, ik zal het nooit weer doen! Zoals beloofd, het boekje met varkentje, *ons* varkentje! Dit als ode aan haar zusjes en broertjes die mee hebben geholpen aan hoofdstuk 5.
Lieve Marita, zo het schrijven niet aan onze meisjes voorbij is gegaan, aan jou zeker niet. Al hebben nog zoveel mensen geholpen, zonder jou was dit boekje nooit verschenen.
Gelukkig laat jij me altijd zien wat echt belangrijk is in het leven. Love you!

List of publications

Patch test results with standard allergens over a decade. Young E, Houwing RH. Contact Dermatitis 1987;17:104-7.

Huidnecrose na vasopressine. Houwing RH, Leguit P. Ned Tijdschr Geneeskd 1987;131:2149-52.

Rothmund-Thomson syndrome. Houwing RH, Oosterkamp RF, Berghuis M, Beemer FA, Van Vloten WA. Br J Dermatol 1991;125(3):279-80.

Antiseptische wondbehandelingsmiddelen; een overzicht. Houwing RH, de Wit RF. Ned Tijdschr Geneeskd 1991;135:1908-11.

Pressure sores are caused by oxygen free radicals. Haalboom J, van Asbeck S, Houwing R, Jonasse Y. Eur J Clin Invest 1991;21:58

Acute febriele neutrofiele dermatose (morbus Sweet).Houwing RH., Boer J. ,Smeenk G. Ned. Tijdschr. Dermatovenereologie 1996:11;286

Nut en gevaren van op de huid toegepaste antibiotica en desinfectantia. Smeenk G, Sebens FW, Houwing RH.Ned Tijdschr Geneeskd. 1999;143:1140-3. .

Pressure-induced skin lesions in pigs: reperfusion injury and the effects of vitamin E. Houwing R, Overgoor M, Kon M, Jansen G, van Asbeck BS, Haalboom JR. J Wound Care. 2000;9:36-40

A Systematic Review of the Efficacy of Topical Skin Application of Dimethyl Sulfoxide on Wound Healing and as an Anti-Inflammatory Drug. Duimel-Peeters IGP, Houwing RH, Teunissen CP, Berger MPF, Snoeckx LHEH, Halfens RJG, Wounds 2003;15:361-370

A randomised, double-blind assessment of the effect of nutritional supplementation on the prevention of pressure ulcers in hip-fracture patients. Houwing RH, Rozendaal M., Wouters-Wesseling W, Beulens JWJ, Buskens E, Haalboom JRE. Clinical Nutrion 2003;22:401-405

Pressure ulcer risk in hip fracture patients. Houwing RH, Rozendaal M, Wouters-Wesseling W, Buskens E, Keller P, Haalboom J. Acta Orthop Scand. 2004;75:390-3.

Pimecrolimus creme 1% in atopic dermatitis: A 6-month open-label trial in pediatric patients. Houwing RH, Svensson Å, Song M, Hofmann H, et al. X World Congress of Pediatric Dermatology Rome, 7-10 July 2004

Safety, Efficacay, and dosage of 1% Pimecrolimus Cream for the treatment of Atopic dermatitis in daily Practice. Lübbe J, Friedlander S.F., Cribier B., Morren MA, Garcia-Díez A,Gelmetti C, Hofmann H, Houwing RH. et al. Am J Clin Dermatol 2006;7(2):121-131

Ulcus venosum van de onderarm. Pennings MCP, Houwing RH, Sluiter HE, van Ginkel CJW. Ned. Tijdschr. Dermatovenereologie 2006;16:150-2

Vochtigheidsletsel is 'gewone' decubitus. Houwing RH, Koopman E, Haalboom JRE Medisch Contact 2007;62(3):103-5

Bullosis diabeticorum in combinatie met onychodystrofie. Bijen CBM, Houwing RH, Toonstra J. Ned. Tijdschr. Dermatovenereologie 2007;17:78-80

Is the distinction between superficial pressure ulcers and moisture lesions justifiable? A clinical-pathological study. Houwing RH, Arends JW, Canninga- van Dijk MR, Koopman E, Haalboom JRE. Skinmed 2007;6:113–117

Druk op vochtletsels. Koopman E, Houwing RH. WCS nieuws 2007:23;20-1

Epidermodysplasia verruciformis unsuccessfully treated with imiquimod.
Janssen K, Lucker GPH, Houwing RH, van Rijssel R. Int J dermatol Accepted for publication.

An unexpected detrimental effect on the incidence of heel pressure ulcers after local 5% DMSO cream application.A randomised double-blinded study with massaging DMSO in patients at risk for pressure ulcers. Houwing R.H., van der Zwet W.C., van Asbeck B.S.E., Halfens R.J.G., Arends J.W. Accepted for publication.

Curriculum vitae

Ronald Han Houwing werd geboren op 2 januari 1958 te Dordrecht. Na het behalen van het VWO diploma aan het Gemeentelijk Lyceum te Dordrecht, ging hij geneeskunde studeren aan de Rijks Universiteit Utrecht. Na het behalen van zijn artsexamen in 1986, heeft hij gewerkt als arts-assistent chirurgie niet in opleiding in het Gemeente Ziekenhuis Arnhem (opleider dr. W.F. Eggink). In 1987 is hij gestart met de opleiding tot dermato-venereoloog in het Academisch Ziekenhuis Utrecht (opleider prof. dr. W.A. van Vloten). Prof. dr. J.R.E. Haalboom, dr. B.S. van Asbeck en prof. dr. M. Kon gaven hem de mogelijkheid onderzoek te doen naar de pathofysiologie van decubitus bij varkens.
Sinds het beëindigen van zijn opleiding in 1991 is hij als dermatoloog werkzaam in het Deventer Ziekenhuis te Deventer. Tevens is hij medisch directeur van de cosmetische laserkliniek Care4Skin. Naast het werk als dermatoloog heeft hij wetenschappelijk onderzoek verricht naar verschillende klinische en etiologische aspecten van decubitus. In 2003 ontving hij de "Jozef prijs", de jaarlijkse wetenschapsprijs van het Deventer Ziekenhuis.

Abbreviations

ADL	activities of dailey living
CBO	Dutch Consensus Meeting
CI	confidence interval
C-I	critical illness
DEJ	dermo-epidermal-junction
DMSO	dimethyl sulfoxide
DPA	data presentation and analysis
EPUAP	European Ulcer Advisory Panel
GCP	good clinical practice
GSH	Reduced glutathione
H_20_2	hydrogen peroxide
H-F	hip-fracture patients
I/R	ischemia reperfusion
IAD	incontinence-associated dermatitis
ICD	international classification of diseases
I-R	ischemia-reperfusion
K	Kappa
MASD	moisture-associated skin damage
N	Newton
NPUAP	National Pressure Ulcer Advisory Panel
OR	odds ratio
PU	pressure ulcer
PURAS	pressure ulcer risk assessment scale
QoL	quality of life
Ref	reference group
ROS	reactive oxygen species
SD	standard deviation
WHO	world health organization