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No benefit of additional treatment with exenatide in patients with an acute myocardial infarction☆

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ABSTRACT

Objectives: This double blinded, placebo controlled randomized clinical trial studies the effect of exenatide on myocardial infarct size. The glucagon-like peptide-1 receptor agonist exenatide has possible cardioprotective properties during reperfusion after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction.

Methods: 191 patients were randomly assigned to intravenous exenatide or placebo initiated prior to percutaneous coronary intervention using 10 μg/h for 30 min followed by 0.84 μg/h for 72 h. Patients with a previous myocardial infarction, Trombolysis in Myocardial Infarction flow 2 or 3, multi-vessel disease, or diabetes were excluded. Magnetic resonance imaging (MRI) was performed to determine infarct size, area at risk (AAR) (using T2-weighted hyperintensity (T2W) and late enhancement endocardial surface area (ESA)). The primary endpoint was of 4-month final infarct size, corrected for the AAR measured in the acute phase using MRI.

Results: After exclusion, 91 patients (age 57.4 ± 10.1 years, 76% male) completed the protocol. There were no baseline differences between groups. No difference was found in infarct size corrected for the AAR in the exenatide group compared to the placebo group (37.1 ± 18.8 vs. 39.3 ± 20.1%, $p = 0.662$). There was also no difference in infarct size (18.8 ± 13.2 vs. 18.8 ± 11.3% of left ventricular mass, $p = 0.965$). No major adverse cardiac events occurred during the in-hospital phase.

Conclusion: Exenatide did not reduce myocardial infarct size expressed as a percentage of AAR in ST elevated myocardial infarction patients successfully treated with percutaneous coronary intervention.

1. Introduction

ST elevated myocardial infarction is a leading cause of mortality and morbidity, caused by acute occlusion of one or more of the epicardial coronary arteries. Therapy is focussed on fast restoration of antegrade flow preferably by means of a primary percutaneous coronary intervention [1,2]. Successful reperfusion however, paradoxically also induces death of cardiomyocytes. This is mediated by a multitude of factors that eventually culminate in loss of mitochondrial integrity and hypercontracture, leading to cardiomyocyte death [3]. This phenomenon is called reperfusion injury and contributes for up to 40% to the final myocardial infarct size [4], which is an important determinant of clinical outcome in patients with ST elevated myocardial infarction [5]. Therapies to prevent reperfusion injury are therefore of utmost importance.

Glucagon-like-peptide-1 (GLP-1) is an incretin hormone with insulinotropic and insulinomimetic properties. The GLP-1 receptor is also present on cardiomyocytes and infusion of GLP-1 has been shown to activate anti-apoptotic pathways and increase myocardial metabolic efficiency in preclinical and clinical studies [6–8].

Exenatide is a long acting GLP-1 receptor agonist and is used widely for improving glycemic control in patients with type 2 diabetes mellitus [9]. In preclinical models of myocardial ischaemia and reperfusion

Abbreviations: AAR, area at risk; EDV, end diastolic volume; ESA, endocardial surface area; ESV, end systolic volume; GLP-1, glucagon-like-peptide-1; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MSI, myocardial salvage index; MVO, microvascular obstruction; T2 W, T2 weighted.

☆ TOC: Clinical study, arteriosclerosis, randomized clinical trial.

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injury exenatide reduces myocardial apoptosis and oxidative stress, resulting in reduced infarct size and preserved cardiac function [10,11].

Recently, exenatide therapy was shown to increase myocardial salvage [12] and decrease final infarct size [13] in ST elevated myocardial infarction patients successfully treated with percutaneous coronary intervention. Exenatide is therefore considered one of the most promising compounds to reduce infarct size [14]. The current study was designed to investigate the effect of exenatide on myocardial infarct size as a percentage of the area at risk (AAR) in patients with ST elevated myocardial infarction who underwent successful percutaneous coronary intervention.

2. Methods

2.1. Overview

The study protocol has been published previously [15]. This multi-centre, prospective, randomized, placebo controlled clinical trial was executed at the VU University Medical Centre, Amsterdam, and the University Medical Centre Utrecht, Utrecht, the Netherlands. All patients gave oral informed consent prior to percutaneous coronary intervention and written informed consent after percutaneous coronary intervention. The local ethics committees approved of the protocol. This study was performed in accordance to the declaration of Helsinki. No financial support was provided from the manufacturer. The study was registered at https://clinicaltrial.gov identifier: NCT01254123.

2.2. Patient population

Consecutive adult patients with ST elevated myocardial infarction with a symptom duration of less than 6 h were enrolled in the study. Exclusion criteria were primarily: a known history of diabetes mellitus, prior myocardial infarction or coronary artery bypass grafting, a clinically unstable patient (i.e. cardiac shock, ventricular rhythm disorders and Killip class > 1 excluded) and any known contra-indications to magnetic resonance imaging. Randomization took place using envelops, created by the primary investigator, in block sizes of 6. A research nurse was unblinded upon enrolment of a patient to prepare the study medication. The study medication was then transferred to a blinded nurse, who administered the study medication to the patient. Investigators, patients and other care providers remained blinded. After randomization to placebo or exenatide, patients were treated with percutaneous coronary intervention and standard drug therapy according to local and hospital guidelines valid at the time of admission. Prior to or during percutaneous coronary intervention, additional exclusion criteria could arise; patients were excluded if they had multi-vessel disease in need of acute coronary artery bypass grafting or additional percutaneous coronary intervention, because significant multi-vessel disease could potentially have impact on the AAR assessment. Patients were also excluded if no culprit lesion was found or if the culprit vessel had Thrombosis in Myocardial infarction 2/3 flow. In these patients, treatment using exenatide or placebo was discontinued immediately upon reaching one of the angiographic exclusion criteria. The study protocol was continued in patients that remained eligible for the study after primary percutaneous coronary intervention. The current study also includes patients enrolled in our pilot safety study [16]. These patients met the same in- and exclusion criteria.

2.3. Treatment protocol

On admission, patients were immediately randomized to double-blind treatment with exenatide or placebo. The study medication was prepared as follows: a 50 ml syringe was filled with 49 ml of NaCl 0.9% and 1 ml human serum albumin with or without 15 μg of exenatide, leading to a concentration of 0.3 μg/ml. All patients received a loading dose (5 μg) in 30 min using a 33.3 ml/h intravenous infusion, followed by a 2.8 ml/h (20 μg/day) infusion for the remainder of the 3 days. The syringe was replaced every 8 h.

2.4. Study endpoints

The primary endpoint of this study was final infarct size measured by magnetic resonance imaging at 4 months after myocardial infarction, expressed as a percentage of the area at risk (AAR) measured with T2W magnetic resonance imaging in the first week after ST elevated myocardial infarction (Fig. 1). Secondary endpoints included final infarct size, myocardial salvage index (MSI), ejection fraction at baseline and 4 months assessed by magnetic resonance imaging and major adverse cardiac events (major adverse cardiac events, defined as cardiac death, myocardial infarction, coronary artery bypass grafting or repeat percutaneous coronary intervention) in 4 months. Creatine kinase muscle brain was measured on admission and every 6 h following percutaneous coronary intervention. In the first 20 patients treated with exenatide, plasma levels of exenatide were measured 4 h and 24 h after lowering the initial study medication infusion rate.

2.5. Magnetic resonance imaging

Magnetic resonance imaging was performed at 3–7 days after ST elevated myocardial infarction and at 4 months of follow-up. The protocol included Cine, T2 weighted (T2W) and late gadolinium enhancement (LGE) imaging [15]. Parameters acquired consisted of left ventricular function (ejection fraction, volumes and left ventricular mass), area at risk using T2W and the endocardial surface area (ESA), microvascular obstruction (MVO) and infarct size at baseline. MVO was defined as the low signal intensity region within the high intensity infarct zone on LGE images. At follow-up, left ventricular function and infarct size were measured. Parameters were indexed for body surface area and calculated as percentage of left ventricular mass where applicable. The MSI was calculated in 2 ways: using the AAR measured with T2W imaging (MSI_{T2W}) [17] at baseline and ESA measured on LGE baseline images (MSI_{ESA}) [18]. The formula to determine MSI was (AAR-infarct size)/AAR. Infarct size was measured in the acute phase (baseline) and at 4 months of follow-up magnetic resonance imaging using LGE images.

2.6. Sample size

With a 5% type 1 error risk, a power of 90% and an anticipated dropout of 10%, 108 patients (54 per group) were needed to detect a 15% improvement of the primary endpoint.

2.7. Statistical analysis

All patients were analysed using intention to treat protocol. Data was tested for normal distribution using kurtosis and skewness, values between −2 and 2 were considered to be normally distributed data. Independent sample *t*-test was used for continuous variables. Chi square test and Fisher's exact were used for categorical data. 1-way ANOVA with Bonferroni post-hoc testing was used to compare subgroups of the study population. Kolmogorov–Smirnov testing was performed when applicable for nonparametric data.

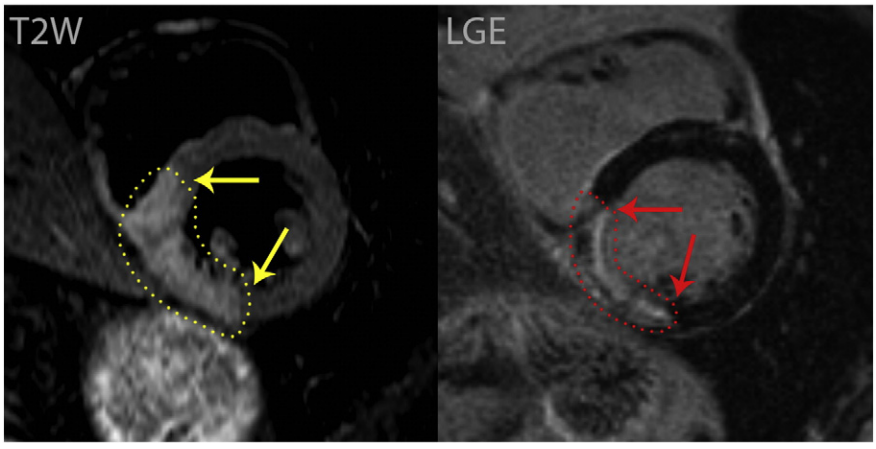

Fig. 1. Measurement of the primary endpoint. The primary endpoint of final infarct size as percentage of the AAR was calculated using T2W images at baseline and LGE images at follow-up. Contours delineate myocardial oedema (yellow) and infarct size (red). Arrows point to the region of interest. The computer calculated oedema and infarct size within the region of interest.

3. Results

3.1. Study population

Between November 2009 and September 2014, a total of 191 out of 412 screened patients with ST elevated myocardial infarction undergoing primary percutaneous coronary intervention fitted the pre-angiographic inclusion criteria and were randomly assigned to treatment with exenatide or placebo. After percutaneous coronary intervention, 108 patients (51 exenatide, 57 placebo) remained in the study due to exclusion criteria met during angiography. At follow-up, a 19% drop-out led to 91 patients (42 exenatides, 49 placebos) that completed the study protocol. Most dropouts were due to insufficient imaging quality available for analysis of the primary endpoint (Fig. 2). The trial was ended as sufficient patients were included before MRI analysis took place.

There were no baseline differences between both groups (Table 1). The mean age was 57.4 years and 76% of patients were male. Symptom-to-balloon time was 170 ± 83 vs. 188 ± 91 min ($p = 0.35$) for exenatide and placebo respectively. The left anterior descending artery was culprit artery in 30% of patients. Unfractionated heparin together with a loading dose of a P2Y12 inhibitor and intravenous aspirin were administered prior to percutaneous coronary intervention in all patients according to current European Society for Cardiology guidelines [18]. Glycoprotein IIb/IIIa inhibitors were administered in 30% of patients. Most percutaneous coronary intervention procedures (90%) resulted in final Thrombolysis in Myocardial Infarction 3 flow. A complete overview of procedural data is provided in Table 2.

3.2. Myocardial infarct size and myocardial salvage

The primary endpoint of infarct size as a percentage of the AAR did not differ between patients treated with exenatide and placebo (37.1 ± 18.8 vs. 39.3 ± 20.1%, $p = 0.662$). There was also no difference in final infarct size and myocardial salvage. (Table 3). Infarct location, body mass index, gender and initial therapeutic treatment differences showed no confounding effects.

3.3. Other endpoints

There were no differences in baseline and follow-up left ventricular volumes, functional parameters and occurrence of MVO. A significant difference in left ventricular mass was found, patients that received exenatide had higher left ventricular masses, but this difference disappeared after adjusting for body surface area (Table 3). Creatine kinase muscle brain-max was 239 ± 146 and 249 ± 191 μg/l ($p = 0.39$) for exenatide and placebo respectively. Median plasma levels of exenatide 4 h after percutaneous coronary intervention were 0.14 [0.01–1.73] nmol/l.

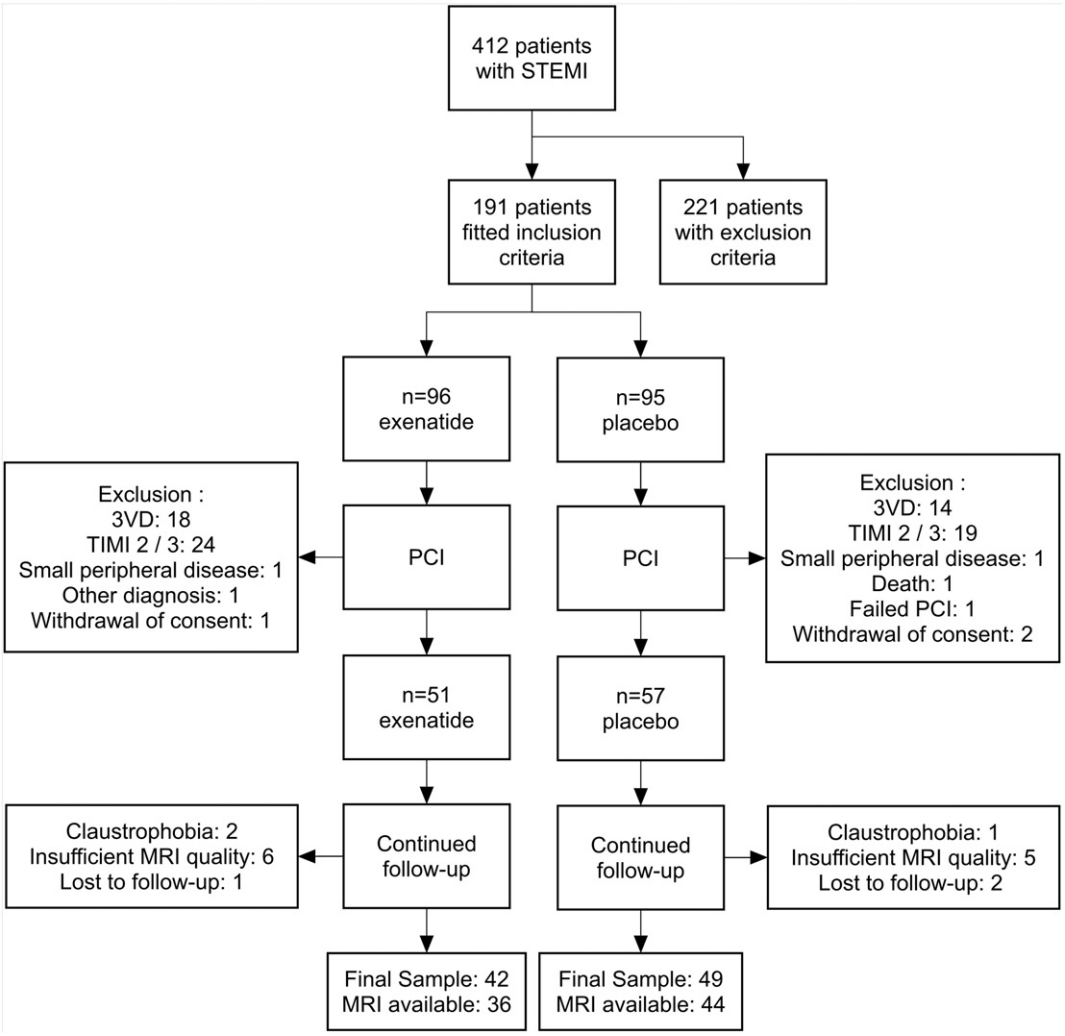

Fig. 2. Study flowchart.

Table 1
Baseline characteristics.

	Exenatide (n = 42)	Placebo (n = 49)	p
Age (years)	57.23 (±10.2)	57.48 (±10.1)	0.906
Male (%)	33 (79%)	36 (73%)	0.576
BMI (kg/m^2)	27.47 (±4.1)	26.39 (±3.2)	0.167
Body surface area	2.57 (±0.22)	1.99 (±0.20)	0.311
Risk factors			
Past/current smoker	18 (45%)	26 (55.3%)	0.688
Hypertension	9 (22.5%)	6 (13.3%)	0.274
Hypercholesterolemia	9 (23.1%)	12 (27.9%)	0.622
Positive family history	18 (43.9%)	26 (56.5%)	0.245
Laboratory results			
Haemoglobin (mmol/l)	9.01 (±0.8)	8.87 (±1.6)	0.593
CRP (mg/l)[a]	3.98 (±3.8)	7.67 (±22.6)	0.357
Cholesterol (mmol/l)	5.56 (±1.1)	5.96 (±1.0)	0.084
Creatinin (μmol/l)	78.9 (±19.0)	77.8 (±23.4)	0.822
eGFR MDRD (ml/min/1.73 m^2)	93.8 (±22.4)	94.4 (±33.9)	0.919
NTproBNP (ng/l)[a]	75.2 (±138.2)	145.9 (±407.8)	0.294
CK-MB max (μg/l)[a]	326 (±593)	249 (±191)	0.389
CK Max (U/l)[a]	2510 (±1888)	2650 (±2076)	0.738
Troponin T max (VUmc) (ng/l)	4690 (±4000)	4310 (±5600)	0.76
Troponin I max (UMCU) (ng/l)	36.6 (±38.2)	43.6 (±40.0)	0.694
Blood glucose (mmol/l)[a]	8.20 (±1.8)	8.01 (±2.1)	0.655
HbA1c (mmol/mol)[a]	38.59 (±4.4)	39.56 (±5.4)	0.363

Numbers as 'mean (±SD)' or 'n (%)' where applicable. N = number, SD = standard deviation, BMI = body mass index, Hb = haemoglobin, CRP = C-reactive protein, eGFR MDRD = estimated glomerular filtration rate modification of diet in renal disease, CK-MB = creatine kinase muscle brain, CK = creatine kinase, HbA1c = haemoglobin A1c.
[a] Nonparametric Kolmogorov–Smirnov test was used.

3.4. Side effects and safety

Nausea, a notorious side effect of exenatide, occurred significantly more often in patients receiving exenatide (38 vs 8%, p = 0.001). No changes had to be made to the infusion rate of study medication in these patients. Hypoglycaemic episodes occurred equally between groups (24 vs 18%, p = 0.53), but hyperglycaemia occurred more often in the placebo treatment arm (7 vs 20%, p = 0.064) (Table 4). Two patients receiving exenatide developed an exanthema after >36 h of infusion, resulting in the preventive cessation of study therapy and successful administration of an antihistaminic agent. At 4 months of follow-up, no major adverse cardiac events had occurred. One patient had received a pacemaker due to AV block.

Table 2
Procedural data from PCI.

	Exenatide (n = 42)	Placebo (n = 49)	p
Treatment pre-PCI			0.451
Heparin	42	49	
Aspegic	42	49	
Clopidogrel	14 (33%)	11 (22%)	
Prasugrel	15 (36%)	25 (51%)	
Ticagrelor	13 (31%)	13 (27%)	
GP IIb/IIIa treatment	12 (32%)	13 (28%)	0.635
Procedural data			
Symptom-to-balloon time (min)	170 (±83)	188 (±91)	0.345
FMC-to-balloon time (min)	73 (±15)	84 (±18)	0.588
Door-to-balloon time (min)	41 (±12)	49 (±19)	0.058
Thrombosuction	36 (86%)	36 (71%)	0.101
Culprit artery			0.585
LAD (%)	13 (31%)	14 (29%)	
RCX (%)	6 (14%)	10 (20%)	
RCA (%)	23 (55%)	25 (51%)	
TIMI grade before procedure			0.738
0 (%)	37 (88%)	42 (86%)	
1 (%)	5 (12%)	7 (14%)	
TIMI grade after procedure			1.0
2 (%)	4 (9%)	5 (10%)	
3 (%)	38 (90%)	44 (90%)	
Stent type			0.524
BMS (%)	10 (24%)	9 (18%)	
DES (%)	32 (76%)	40 (82%)	

Numbers as 'mean (±SD)' or 'n (%)' or 'mode [±range]' where applicable. N = number, SD = standard deviation, PCI = percutaneous coronary intervention, FMT = first medical contact, LAD = left anterior descending, RCX = right circumflex, RCA = right coronary artery, TIMI = thrombolysis in myocardial infarction, BMS = bare metal stent, DES = drug eluting stent, GP IIb/IIIa = glycoprotein IIb/IIIa.

Table 3
Imaging results MRI and primary endpoint.

	Exenatide	Placebo	p
LV-EDV (ml, n = 87)	184.15 (±38.44)	174.89 (±40.07)	0.277
LV-ESV (ml, n = 91)	84.54 (±30.71)	81.23 (±34.17)	0.630
LV mass (g)	115.65 (±29.55)	107.46 (±25.27)	0.172
LV-EDV indexed	88.13 (±13.58)	87.61 (±16.64)	0.875
LV-ESV indexed	40.51 (±13.82)	40.65 (±16.30)	0.964
LV mass indexed	55.33 (±11.55)	53.78 (±11.11)	0.529
LV SV (ml)	91.53 (±19.97)	85.54 (±19.16)	0.240
LV EF (%, n = 86)	52.18 (±7.25)	51.17 (±7.35)	0.525
MVO present (n = 79)	19 (50%)	22 (54%)	0.745
AAR_{T2W} (g, n = 66)	36.79 (±17.54)	31.72 (±18.95)	0.267
MSI_{ESA} (n = 73)	0.59 (±0.21)	0.55 (±0.22)	0.491
MSI_{T2W} (n = 66)	0.63 (±0.19)	0.61 (±0.20)	0.662
Follow-up LV-EDV (ml, n = 87)	196.34 (±36.95)	180.72 (±39.33)	0.075
Follow-up LV-ESV (ml, n = 91)	94.78 (±27.98)	87.47 (±29.92)	0.272
Follow-up LV mass (g)	104.46 (±26.08)	89.77 (±22.67)	0.010
Follow-up LV SV (ml)	99.10 (±17.31)	92.65 (±19.62)	0.218
Follow-up LV EF (%, n = 86)	52.42 (±8.34)	52.66 (±8.35)	0.897
Follow-up LV-EDV indexed	93.58 (±14.66)	91.39 (±16.09)	0.532
Follow-up LV-ESV indexed	45.20 (±12.95)	44.01 (±13.59)	0.696
Follow-up LV mass indexed	49.56 (±10.29)	45.31 (±10.05)	0.073
Final infarct size (g, n = 77)	13.12 (±9.21)	12.75 (±9.41)	0.868
Final infarct size as % of LV mass	13.30 (±8.97)	15.06 (±10.53)	0.460
Final infarct size as % of AAR_{T2W}	37.08 (±18.78)	39.27 (±20.12)	0.662

Numbers as 'mean (±SD)' or 'n (%)' or 'mode [±range]' where applicable. N = number, SD = standard deviation, BSA = body surface area, LV = left ventricle, EDV = end diastolic volume, ESV = end systolic volume, EF = ejection fraction, MVO = microvascular obstruction, AAR = area at risk, ESA = endocardial surface area. EDV, ESV and mass are corrected for BSA.

4. Discussion

In contrast to previous clinical trials using exenatide in ST elevated myocardial infarction patients, our trial shows no benefit of using exenatide on top of primary percutaneous coronary intervention in ST elevated myocardial infarction patients. This may indicate that the cardioprotective effect of exenatide is less than previously thought, or that it depends on several specific conditions. Therefore, it is of utmost importance to understand the differences between this trial and the previous studies.

4.1. Trial differences

Two previous trials investigated the cardioprotective effect of exenatide in patients with ST elevated myocardial infarction undergoing primary percutaneous coronary intervention and reported a beneficial effect on myocardial salvage in a Danish study [12] and final infarct size in a Korean study [13]. Most baseline clinical characteristics,

Table 4
Adverse events.

	Exenatide (n = 42)	Placebo (n = 49)	p
Nausea	16 (38%)	4 (8%)	0.001
Need for anti-emetics	14 (33%)	3 (6%)	0.001
Hypoglycaemic episode	10 (24%)	9 (18%)	0.530
Hyperglycaemic episode	3 (7%)	10 (20%)	0.064
MACE	2 (5%)	2 (4%)	0.876

Numbers as 'mean (±SD)' or 'n (%)' or 'mode [±range]' where applicable. MACE = major adverse cardiac events.

procedural characteristics and average AAR are comparable with the Danish and Korean studies. Another report by Lønborg et al. in 2012 showed that exenatide reduced infarct size in patients with a short system delay, i.e. <132 min, and not in patients with a system delay >132 min [20]. Most likely the ischaemic area is beyond repair if the ischaemic duration is too long. In our trial the system delay was shorter (76 min vs 132 min) and the symptom-to-balloon time was comparable with the Danish trial. Despite the short system delay, we were not able to confirm a cardioprotective effect of exenatide. Other factors must have played a role.

For example, in our study few patients with anterior infarctions were included. While the average infarct size as a percentage of AAR (38%) and final infarct size (13 g) were similar to the previously published trials, patients included in our trial suffered from anterior infarctions in only 30% of cases, which was 40% in the Danish trial [12]. In the Danish trial, myocardial salvage was more pronounced in anterior MI than in non-anterior infarct location. This might be of interest in determining the exact subgroup of patients with myocardial infarction that benefits from exenatide treatment.

Our study also included more smokers (Table 1) and fewer patients were treated with glycoprotein (GP) IIb/IIIa inhibitors in our study compared to the Danish study (30% vs 90%; no data provided in the Korean study). We did not observe an interaction between smoking and GPIIb/IIIa inhibitors and infarct size, but a relationship cannot be ruled out because our study was not powered for subgroup analysis. GP IIb/IIIa inhibitors can be considered in patients if no-reflow occurs after percutaneous coronary intervention [2]. There is evidence for reduced infarct size in ST elevated myocardial infarction patients receiving abciximab [19]. A potential synergistic effect between abciximab (or other GP IIb/IIIa inhibitors) and exenatide could explain the difference in outcome between our study and the Danish study.

4.2. Diabetes

Patients with known diabetes mellitus were excluded from our study, for the arbitrary reason to exclude a potential effect from glucose control instead of a direct effect on apoptosis. Exenatide might be more effective in patients with diabetes mellitus, as glucose control might contribute to an improved clinical outcome [21]. Because of the preclinical evidence, and the relatively low number of patients with diabetes mellitus in the previous trials (4–9% in the Danish and 25–28% in the Korean) it is unlikely that exenatide mediated cardioprotection is exclusively present in patients with diabetes mellitus. Consequently, this does not explain the different outcomes between the clinical trials.

4.3. Underestimation of effect

Furthermore, potential favourable effects of exenatide in this study might have been underestimated, because of the assessment of the AAR using T2W magnetic resonance imaging. This modality of AAR assessment is based on myocardial oedema. Since exenatide might also reduce myocardial oedema, the AAR could have been underestimated in the exenatide treatment arm, and therefore the infarct size in relation to the AAR was overestimated. This effect might be enhanced by the time-dependence of oedema in the first week after ST elevated myocardial infarction that adds to the large variability of AAR assessment using T2W imaging [22]. Lønborg et al. however used the same modality and observed a favourable effect of exenatide. Also, the ESA does not have these limitations and also did not show a difference between our patient groups.

4.4. Treatment protocol

The most obvious difference between the trials is the exenatide treatment protocol. Our initial bolus dose was chosen based on our unpublished previous experience with healthy subjects and was demonstrated to be the highest well tolerated dose, not inducing severe nausea. The maintenance dose and duration were based on results of our previous preclinical study [11] and a clinical study with GLP-1 [7], in order to achieve a potential beneficial effect on metabolic efficiency and cardiac function. We previously demonstrated this protocol to be safe and feasible for application in patients with ST elevated myocardial infarction [16].

We administered an exenatide bolus of 5 μg in 30 min IV followed by an infusion of 20 μg per day for 3 days, whereas by Lønborg et al. an initial bolus of 1.8 μg IV (in 15 min) was given and another infusion of 15.5 μg over the next 6 h. These protocols resulted in exenatide plasma levels of 0.01–1.73 nmol/l (mean 0.14 nmol/l, measured 4 1/2 h after initiation of treatment) in our study and of 0.1–0.39 nmol/l (mean 0.177 nmol/l; measured 15 min after initiation of the treatment) in the Danish study. Unfortunately, plasma levels cannot be easily compared due to the different time points. Woo et al. treated patients with a 10 μg exenatide bolus intravenously and a 10 μg subcutaneous dose 5 min before reperfusion, followed by a 10 μg twice daily subcutaneous injection for three days, in accordance with our preclinical study [11], but plasma levels were not measured.

The cascade of events resulting in reperfusion injury is initiated in the first minutes after reperfusion [3]. Therefore it is important to obtain a therapeutic plasma level before the onset of reperfusion. In all 3 studies, the treatment was initiated before reperfusion. Woo et al. administered the highest intravenous dose before reperfusion (10 μg). In the Danish study, all participants received at least 1.8 μg before reperfusion. On average, our 42 patients in the treatment arm received 4.82 (±1.09) μg of exenatide prior to balloon inflation. Thus, a higher dose of exenatide was administered before reperfusion in our study than in the Danish study. Nonetheless, the Danish investigators observed a reduction in myocardial infarct size, whereas we did not. A biphasic dose–effect relationship of exenatide has been suggested for exenatide in an isolated rat heart model, with a loss of a cardioprotective effect with plasma levels exceeding 3.0 nmol/l [10]. Unfortunately, we do not have exenatide plasma levels available around the time of reperfusion. It cannot be ruled out that plasma levels were too high, possibly resulting in a loss of cardioprotection. However, in the Korean study by Woo et al. even a higher intravenous dose of 10 μg was administered before reperfusion. Although no correction was made for the AAR in this study, the reduction in final infarct size suggests a cardioprotective effect of exenatide using a very high bolus dose. Another possibility is that exenatide exerts its most important cardioprotective actions not so much in the first minutes, but in the first hours after reperfusion. Both Lønborg and Woo administered a higher total dose in the first 6 h after reperfusion than we did in the present study.

4.5. Tolerability

An important concern regarding a high treatment dose is the tolerability. Nausea is a well-known side effect of exenatide described to occur in up to 40–50% of the patients [23]. Severe nausea requiring the need for anti-emetics in most cases occurred in 38% of the patients receiving exenatide in this study, following the initial 30 min bolus dose, versus 8% in patients receiving placebo. The previous studies do not report data on the occurrence of nausea.

5. Limitations

Due to a higher dropout than expected the number of patients that was included in the final analysis was slightly lower than anticipated. However, the final endpoints are all comparable between exenatide and placebo without any trend towards a cardioprotective effect of exenatide. Expansion of the groups is therefore unlikely to change the interpretation of the results. A new power analysis based on the results from this study shows that a sample size of 1161 patients per group would be needed to meet a difference in the primary endpoint. Our

exclusion rate in this study is relatively high, due to the fact that we aimed to acquire a population without multiple confounding factors such as multi-vessel disease, in order to determine the maximum therapeutic effect of exenatide. Also, our initial dropout of 221 patients was mostly due to a high rate of patient refusal. These factors have caused our results to be only moderately applicable to the real world situation.

6. Conclusion

In this study, exenatide treatment did not result in reduction of myocardial infarct size as a percentage of the AAR in ST elevated myocardial infarction patients successfully treated with percutaneous coronary intervention. Additional studies are warranted to unravel the reasons for the ambiguous trial results and to identify an optimal treatment protocol.

Conflicts of interest

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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