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ORIGINAL ARTICLE

Negative pressure therapy versus passive open abdominal drainage for the treatment of septic peritonitis in dogs: A randomized, prospective study

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Abstract

Objective: To compare passive open abdominal drainage (POAD) and negative-pressure abdominal drainage (NPAD) using the ABThera™ system in the treatment of septic peritonitis.

Study design: Randomized prospective clinical trial.

Animals: Dogs (n = 16) with septic peritonitis.

Methods: Dogs with septic peritonitis were randomly assigned to one of two treatment protocols: NPAD versus POAD. Anesthesia time, operating time, duration of drainage, costs, survival, and complications were compared between techniques. Hematological and biochemical parameters in blood and abdominal fluid, and histopathological findings of omentum and abdominal wall tissue samples were compared between NPAD and POAD at time of initial surgery and at time of closure.

Results: Overall survival was 81%. Treatment costs, anesthesia and operating time, drainage time, survival, and postoperative complications were similar between techniques. Loss of total plasma protein and decreased inflammation-related factors in abdominal fluid at time of closure were noted in all patients. Neutrophilic inflammation was greater in abdominal wall samples after NPAD. POAD patients showed discomfort during bandage changes and had frequent leakage of abdominal fluid outside of the bandage.

Conclusion: NPAD is an effective alternative to POAD for treatment of septic peritonitis, based on costs and survival. NPAD resulted in less abdominal fluid leakage, and evidence of superior healing on histological evaluation of abdominal tissues.

1 | INTRODUCTION

Septic peritonitis is a life-threatening disease, requiring immediate stabilization and surgical intervention. Reported survival in dogs and cats varies from 27% to 80%.[1-5] Secondary peritonitis is most commonly caused by gastro-intestinal leakage in companion animals.[6,7] Surgery aims at identifying and controlling the source of contamination. After resolving the cause of contamination, extensive abdominal lavage is combined with local debridement of severely affected

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tissues, to reduce contamination and release of endotoxins.[8,9] However, the postoperative management of septic peritonitis remains controversial in terms of primary closure or continued abdominal drainage. Current abdominal drainage techniques include active closed suction drainage (Jackson Pratt-type drains), passive open abdominal drainage (POAD), and negative pressure abdominal drainage (NPAD).[9] Current literature consists primarily of retrospective studies/case series with no differences in survival rates between postoperative treatment modalities, but potential biases due to preselection.[1,2,4,5,9-11]

In man, open abdominal drainage in indicated to treat abdominal compartment syndrome, damage control for polytrauma, abdominal injuries, and severe intra-abdominal sepsis.[12-14] The mortality rate of abdominal sepsis reaches 20%-60%,[15,16] prompting research to refine the decision making related to open abdominal drainage in patients with septic peritonitis. The rationale for this approach is based on treating the abdominal cavity as an abscess cavity.[17] Improved survival rates and shorter hospital stays have been documented after open abdominal drainage.[18,19] The decision to start postoperative drainage therapy in septic peritonitis is often based on the surgeons's assessment of intraoperative findings consistent with severe generalized septic peritonitis: amount of free abdominal fluid, obvious widespread inflammatory changes of the peritoneum, source of contamination, and gross evidence of contamination.[2,5,20-22] However, in both human and veterinary medicine no uniform objective guidelines are described to support the indications for drainage.

The perioperative care and monitoring requirements for a patient with septic peritonitis are high, regardless of the treatment modality. Until recently, POAD was the standard of care for generalized septic peritonitis in our institution. In our experience, PAOD requires a high workload and the need of experienced intensive care personnel for frequent and often complicated bandage changes.[2] POAD can also be uncomfortable for the patient, bandage changes create concerns for nosocomial infections.[2,3] Active closed suction drains (Jackson Pratt drains) have been proposed as an alternative but may be less ideal because abdominal drainage is limited in severely contaminated cases. Indeed, drain openings can be easily sealed by omental tissue and these drains carry bacterial contamination within 24 hours after placement in up to 90% of the cases.[2,4,10]

In human medicine, open abdominal drainage is associated with complications such as enteroatmospheric fistula formation, fluid and protein losses, extended hospital stay, increased costs and loss of abdominal wall domain.[14] To address those problems, POAD has been replaced by negative pressure techniques because it was less labor intensive, resulted in reduced hospital stay, was more cost-effective, and improved the monitoring of fluid production.[18,19] Initial negative pressure therapies were limited by uneven distribution of negative pressure in the abdominal cavity. Subsequent improvements led to a new NPAD system (ABThera™, KCI-medical, Houten, the Netherlands), addressing several limitations of open abdominal drainage and negative pressure therapy systems.[14] The risk of abdominal herniation in man was successfully reduced by faster closure of the abdominal surgical wound through stimulation of wound retraction by the negative pressure therapy.[23] Also, the drainage time was reduced and a lower amount of enteroatmospheric fistulae were observed.[24] The uniform distribution of negative pressure created by the NPAD through the abdominal cavity improves the removal of peritoneal fluid compared to other techniques.[14] This approach has been introduced in veterinary with promising results, documenting the feasibility of this technique for managing septic peritonitis.[11,25]

The aim of this study was to compare the outcome, advantages, and disadvantages of the POAD technique with NPAD for postoperative drainage in dogs with septic peritonitis. We hypothesized that NPAD would improve abdominal drainage and patient well-being, and reduce labor, treatment duration, and costs in patients with septic peritonitis compared to POAD.

2 | MATERIALS AND METHODS

This prospective study was performed from October 2012 till October 2014 at the University clinic for companion animals of Utrecht University. The institutional ethical committee approved the study protocol; owners were required to provide informed consent before participation to the study.

2.1 | Patient selection

Dogs diagnosed and surgically treated for generalized septic peritonitis were included in the study. Initial diagnosis of septic peritonitis was based on cytological criteria (ie, presence of inflammatory cells, toxic and degenerated neutrophils, and intracellular bacteria or plant material), a blood to abdominal fluid glucose difference of more than 20 mg/dL (1.1 mmol/L) and a blood to abdominal fluid lactate difference of more than −18 mg/dL (–2 mmol/L).[26,27] This presumptive diagnosis had to be confirmed with a positive bacteriological culture of abdominal fluid taken during surgery. Decision to perform drainage was subjectively made by the surgeon, taking into account several parameters of generalized septic peritonitis: the amount of free abdominal fluid present; the aspect of abdominal fluid (ie, serous, turbid, purulent); inflammatory changes of the peritoneal cavity including hyperemia, fibrin depositions, and adhesions; the source of contamination (bile, stomach, small bowel, large bowel, etc); and macroscopically visible contamination.

Dogs with septic peritonitis were included in the study protocol if the underlying cause was treated during surgery and survived the surgery.

2.2 | Randomization and blinding

Randomization was performed prior to the trial and group assignment (POAD or NPAD) and documented in a closed and numbered envelope (1-16). After fulfilling the initial inclusion criteria, the envelope was opened by the anesthetist in the final stage of the surgery (just before closure) for each individual dog.

2.3 | Surgical procedure

All dogs underwent abdominal exploratory surgery through a midline celiotomy and the source of bacterial contamination was treated accordingly. Subsequent routine lavage of the abdomen was performed intensively until abdominal fluid was macroscopically clear before proceeding to partial closure of the abdomen.

2.4 | Passive open abdominal drainage technique

For POAD, the abdominal wall was partially closed in 3 layers, leaving the midline incision open over a length of 15-20 cm. A 0 (USP) monofilament polydioxanone continuous suture line was loosely placed in the external abdominal fascia allowing the wound edges to separate 3-5 cm. The open surgical wound was covered by a sterile absorptive bandage secured by a tie-over bandage.[28] An abdominal bandage was used to protect the surgical wound.

2.5 | Negative pressure abdominal drainage technique (the ABThera™ system)

For NPAD, the abdominal wall was partially closed in 3 layers leaving an opening of 12-15 cm in length. The spider-shaped ABThera™ dressing consisting of polyurethane foam enclosed in a perforated protective polyurethane sheet was placed in the abdomen between the abdominal organs and abdominal wall (Figure 1A-C). A piece of polyurethane foam was fitted to the abdominal defect maintaining 3-5 cm width and was placed in the abdominal wound, covering the center of the spider-shaped abdominal dressing, maintaining close contact with the abdominal dressing, to obtain equal distribution of the negative pressure (Figure 1D). The surrounding skin was prepared using ether and an adhesive spray. The entire NPAD construction and the surrounding skin were covered with an occlusive adhesive film creating an airtight seal with the surrounding skin (Figure 1E). A 2.5-3 cm round hole was created in the occlusive film layer (Figure 1F), centrally located over the polyurethane foam in the abdominal wound, on which the track pad of the suction device was applied (Figure 1G). The suction device with collection canister applied a continuous negative pressure of 125 mm Hg, which has been shown to be effective and safe for abdominal drainage (Figure 1H).[11,14,25,29]

2.6 | Postoperative care

After surgery, patients were hospitalized at the intensive care unit, receiving fluid therapy, antibiotic treatment, gastroprotective medication, analgesia according to the need, and additional treatment if indicated. Standard monitoring consisted of measurement of body weight, heart rate, respiratory rate, body temperature, and invasive arterial blood pressure, and fluid balance over time. Clinical signs such as vomiting/regurgitation, diarrhea, and edema formation were recorded.

With POAD, the bandage was changed at least twice daily with new sterile absorptive bandages, generally without additional sedation. The patient was placed in dorsal recumbency with 2 assistants holding the patient while a surgeon changed the bandage. Two plastic-covered cushions were used to support the shoulders and pelvis of the dog to facilitate bandage changes. Omental and body wall adhesions blocking the abdominal opening were gently loosened by digital manipulation using sterile gloves. Drainage production was measured by weighing the bandages after each bandage change. Abdominal fluid was collected daily with a sterile polyurethane urinary catheter introduced through the abdominal drainage opening for cytology.

With NPAD, the collection canister of the ABThera™ system (Figure 1H) was replaced with a new canister when full. The canister was also changed for collection of "fresh" abdominal fluid so abdominal fluid analysis could be performed daily for the study. Care was taken to maintain negative pressure. As a rule, any loss of negative pressure due to device malfunction or air leakage of the bandage should be resolved within 2 hours. If not, the entire NPAD bandage was replaced to prevent negative effect on the wound environment, according to the manufacturer.

2.7 | Re-exploration and timing of surgical abdominal closure

The timing of abdomen closure was based on a steady decrease in drainage fluid production, significantly reduced or absence of signs of septic inflammation on abdominal fluid cytology, combined with improved clinical signs (general health status, appetite, responsiveness, circulatory and respiratory stability, or improving laboratory parameters, eg, albumin). A second surgery/re-exploration of the abdomen was considered when abdominal fluid production did not

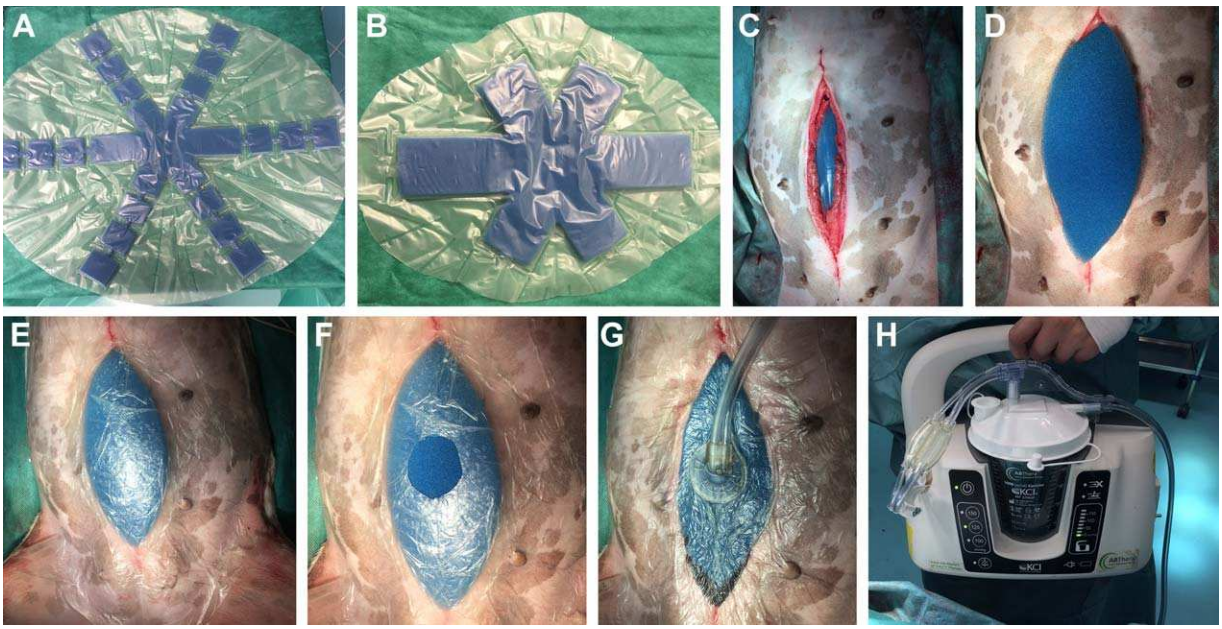

FIGURE 1 Negative pressure abdominal drainage in a dog. A, Spider-shaped ABThera™ dressing. B, The dressing is cut to fit the patient. C, Placement of the dressing in the abdomen, between the abdominal organs and wall. D, Placement of polyurethane foam in the abdominal defect, covering the center of the dressing; direct contact between the dressing and the foam is important for efficient drainage. E, Coverage of the entire NPAD construction with an occlusive adhesive film to create an airtight seal. F, The track pad connected to a suction device is installed by creating a 2.5 cm hole in the occlusive film. G, The NPAD system is complete and a continuous negative pressure of 125 mm Hg is applied. H, The NPAD system connected to a suction device and canister allows collection of abdominal fluid

decrease or increased, and/or obvious intracellular bacteria and degenerated/toxic neutrophils were found on cytology, in combination with lack of clinical improvement or clinical decline.

2.8 | Data collection

Collected data included breed, age, weight, cause of septic peritonitis, anesthesia time, and operating time of the initial surgery, any re-exploratory surgery and final abdominal closure surgery, total hours of drainage, and material costs used for each drainage technique. Material costs for the NPAD system consisted of an ABThera™ drainage system, ABThera™ canisters, and one bandage change. The costs for the ABThera™ drainage system are €447 (478 $), the costs for the ABThera™ canisters are €8 (8.6 $). Material costs for the POAD system consist of time and materials needed to perform the 2-daily bandage changes.

Hematological and plasma parameters were measured at the time of initial surgery (T_0) and at the time of closure (T_1), including: hematocrit, sodium, potassium, chloride, calcium, urea, creatinine, glucose, lactate, total protein, albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, bile acids, amylase, lipase, activated partial thromboplastin time, prothrombin time, and fibrinogen. Biochemical parameters were measured in the abdominal fluid at the time of initial surgery (T_0) and at the time of closure (T_1), including: sodium, potassium, chloride, urea, creatinine, glucose, lactate, total protein, albumin, amylase, and lipase.

Bacteriological cultures were performed of abdominal fluid samples taken at the time of initial surgery (T_0) and at the time of closure (T_1).

Incisional biopsies were collected from omentum and abdominal wall at initial surgery (T_0) and at time of abdominal closure (T_1) for histological examination. Biopsies were fixed in 10% formaldehyde for further analysis.

2.9 | Histology

Tissue samples were embedded in paraffin according to standard procedures and cut into 4 μm tissue sections. Sections were stained with hematoxylin and eosin (Klinipath, Duiven, the Netherlands). Immunohistochemistry for Tomato lectin (LEA) was performed on subsequent sections to visualize vascular endothelium. Mouse anti-smooth muscle actin antibody (Biogenex, Fremont, California) was used as the primary antibody and dog anti-mouse/biotin (Vector Laboratories, Peterborough, UK) as the secondary antibody according to the manufacturers' instructions.

Tissues were examined by one veterinary pathologist (RT), blinded for patient data and time of collection (T_0 or T_1). Abdominal wall samples were scored at 2 levels: the superficial mesothelial surface with associated adipose tissue and the deeper layers of the abdominal wall musculature

with associated connective tissue fascia. Tissues were scanned at low magnification to identify areas of higher cell density: 3 high-power fields per tissue were selected and subjectively assessed for the degree and distribution of neutrophilic inflammation, the presence and amount of associated granulation tissue, edema, superficial necrosis, and hemorrhage. The distribution of neutrophilic infiltrate was scored (0 = within normal limits, 1 = scattered individual cells or small groups, 2 = nodular to confluent, 3 = diffuse). The degree of the neutrophilic inflammation was scored based on the density of neutrophils within the inflamed regions (0 = within normal limits, 1 = mild inflammation, 2 = moderate inflammation, 3 severe inflammation). Granulation tissue was defined as the proliferation of fibroblasts in a collagenous matrix and presence of small caliber vasculature arranged perpendicularly to the surface of the tissue. Immunohistochemistry with LEA was used to facilitate identification of microvasculature. The presence and amount of granulation tissue in the identified areas of inflammation was scored (0 = absent, 1= mild, 2 = moderate, 3 = abundant). The extent of associated edema was scored (0 = absent, 1 = mild, 2 = moderate, 3 = severe), as identified by the presence of increased spaces and wispy eosinophilic material between cells and collagen bundles, dilated superficial lymphatics, and foamy macrophages. The degree of necrosis, defined as loss of cell detail, formation of an eosinophilic or amphophilic coagulum, and nuclear streaming, was assessed in the superficial aspect of areas of inflammation. Necrosis was scored (0 = no necrosis, 1 = focal necrosis, 2 = nodular necrosis, 3 = diffuse necrosis tracking along the entire mesothelial surface). Severity of hemorrhage was scored (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

2.10 | Statistical analysis

Statistical analysis was performed with SPSS Statistics 23. A power analysis was performed prior to the study, using estimated values to determine the number of dogs needed in the experiment (paired samples; $\beta = 0.20$; $\alpha = 0.05$; standard deviation of 20%; estimated difference of 30%).[30] A minimum number of 7 patients per group was required. All parameters were tested for normality of their distribution using a Shapiro-Wilk test. Normally distributed variables were assessed using parametric tests (*t* test and paired samples *t* test) and results displayed as mean ± 95% confidence interval (CI). Non-normal distributed variables were assessed using nonparametric tests (Mann-Whitney *U* test and Wilcoxon signed rank test) and results displayed as median and interquartile range (IQR). Survival and complications were compared between techniques using a chi-square test. A significance level of $P < .05$ was established for all analyses.

3 | RESULTS

3.1 | Patients

Sixteen patients (Table 1) were enrolled: 8 patients underwent treatment with the POAD and 8 with the NPAD technique. The main cause for septic peritonitis was gastrointestinal perforation (n = 12), other causes were hepatobiliary (n = 2), pyometra (n = 1), and abscess formation due to migrating corpus alienum (n = 1). All patients had a positive culture of the abdominal fluid that was collected during the first operation, confirming septic peritonitis, with the exception of a dog having bile peritonitis (Table 1 patient N°6). Nevertheless, this dog was kept in the study because cytology showed degenerated neutrophils and (intracellular) bacteria and sufficient lactate and glucose differences.

Mean overall operating time for initial surgery was 160 minutes (CI 122-198 minutes) and mean overall operating time for closure was 39 minutes (CI 28-49 minutes). Thirteen patients (81%) survived until discharge. Mean drainage time was 66 hours (CI 52-80 hours).

3.2 | Passive open abdominal versus negative pressure abdominal drainage

Patient demographics did not differ between groups. For the POAD group, mean age was 7.2 years (CI 3.5-10.8) and mean body weight was 24.6 kg (CI 15.2-34.1), for the NPAD group mean age was 7.0 years (CI 3.5-10.4) and mean body weight was 28.3 kg (CI 19.8-36.7). Breeds represented in the POAD group included one of each: mixed breed, Golden Retriever, Labrador Retriever, Border Collie, West Highland White Terrier, Shetland Sheepdog, German Shepherd, and Cane Corso. Breeds represented in the NPAD group included 2 Labrador Retrievers and one of each: mixed breed, Beauceron, Australian Shepherd, Dalmatian, Rottweiler, and Labradoodle.

Treatment variables did not differ between groups (Table 2). One dog in the NPAD group underwent abdominal re-exploration, based on an increase in the amount of abdominal fluid production, large amount of intracellular bacteria on cytology of abdominal fluid, and a gradual decline in clinical condition of the patient. A dehiscence of a jejunal end-to-end anastomosis was repaired and a second period of abdominal drainage was initiated using the NPAD technique, leading to clinical recovery and long-term survival of the patient.

Postoperative complications (Table 2) included vomiting/regurgitation (n = 7), diarrhea (n = 5), hypoproteinemia (n = 15), and development of generalized peripheral edema (n = 12) and were not significantly different between groups. Problems specifically related to the POAD technique were leakage of abdominal fluid outside the bandage and obvious

TABLE 1 Source of contamination, bacteriology before treatment (T_0) and at abdominal closure (T_1), and surgical treatment in dogs treated with POAD and NPAD

Dog	Contaminating source	Bacteriology at T_0	Bacteriology at T_1	Surgical treatment	Treatment
1	GI*	*Escherichia coli, Streptococcus* group D Multiresistant	*Escherichia coli, Streptococcus* group D (moderate amount) multiresistant	Enterectomy	NPAD**
2	Liver (hepatocellular carcinoma)	*Escherichia coli*		Liver lobectomy	POAD***
3	GI	Mixed culture (5 bacteria), fecal flora	Mixed culture (3 bacteria), fecal flora	Enterectomy	POAD
4	GI	*Escherichia coli* Multiresistant	*Escherichia coli* (moderate amount) Multiresistant	Partial gastrectomy	NPAD
5	Uro-genital (ruptured pyometra)	*Streptococcus* group G	No bacteria	Ovariohysterectomy	NPAD
6	Liver (bile duct rupture)	No bacteria	No bacteria	Cholecystectomy	POAD
7	GI	*Staphylococcus* coagulase negative Multiresistant	*Candida glabrata* Mixed culture (3 bacteria)	Partial gastrectomy	NPAD
8	GI	Mixed culture, fecal flora	No bacteria	Colotomy	POAD
9	GI	*Escherichia coli*		Pylorectomy (Billroth-1)	NPAD
10	Abscess, migrating corpus alienum	Anaerobe mixed culture	No bacteria	Drainage + removal corpus alienum	NPAD
11	GI	*Candida albicans*	*Candida albicans* (through accumulation)	Enterectomy	POAD
12	GI	Mixed culture, fecal flora	*Clostridium perfringens* (through accumulation)	Enterectomy (cecum)	POAD
13	GI	Mixed culture, fecal flora	*Staphylococcus* coagulase negative (through accumulation)	Partial colectomy	POAD
14	GI	Anaerobe mixed culture		Partial pylorectomy	NPAD
15	GI	*Escherichia coli* Multiresistant	*Escherichia coli* Multiresistant	Enterectomy	NPAD
16	GI	*Escherichia coli, Streptococcus*	*Streptococcus* group D Multiresistant	Enterectomy (cecum)	POAD

*GI = gastrointestinal; **NPAD = negative pressure abdominal drainage; ***POAD = passive open abdominal drainage.

patient discomfort during the bandage change. In the NPAD group, no air or fluid leakage of the bandages occurred. Workload was higher in the POAD group due to frequent bandage changes.

Difference in plasma and abdominal fluid parameters at any of the measurement time points are summarized in Table 3. At T_0, total protein concentration in abdominal fluid was lower in the NPAD group than the POAD group. At T_1, glucose concentration was lower and lactate higher in the abdominal fluid of the NPAD group in comparison with the POAD group.

Temporal changes in abdominal fluid and plasma parameters between T_0 and T_1 in all patients are displayed in Table 4. Concentrations of total plasma protein, total abdominal fluid protein, and abdominal fluid lipase decreased over time. Temporal changes in all abdominal fluid and serum parameters between T_0 and T_1, including total protein, were not different between treatment groups (Table 5). There was

TABLE 2 Treatment variables in dogs treated with POAD and NPAD

	NPAD	PAOD	*P*-value
Operating time for initial surgery	135 min (CI 54-215)	182 min (CI 137-226)	.29
Anesthesia time for initial surgery	206 min (CI 88-324)	264 min (CI 229-300)	.18
Postoperative drainage time	70 h (CI 34-105 h)	64 h (CI 48-79)	.17
Operating time for surgical closure	29 min (CI 17-40)	47 min (CI 32-62)	.33
Anesthesia time for surgical closure	73 min (CI 47-99)	92 min (CI 70-115)	.91
Overall bandage costs	€493 (IQR 0)	€405 (IQR 163)	.07
Survival	6 (75%)	7 (87.5%)	.52
Diarhea	1/8	4/8	.11
Edema	7/8	5/8	.25
Vomiting/regurgitation	3/8	4/8	.61

no significant difference in survival between the treatment modalities (Table 2). One patient in the POAD group was diagnosed with hepatocellular carcinoma and died 19 hours postoperatively during hospitalization. Two patients in the NPAD group were diagnosed with pyloric ulcerations and underwent reconstructions (one Billroth-1 and one Heineke-Mikulicz pyloroplasty). The patient with the Billroth-1 reconstruction died within 24 hours postoperative and the patient with the partial pyloric resection was euthanized 24 hours after surgery because the owners refrained from further treatment. None of the dogs underwent necropsy because owners declined permission.

Twelve of the bacteriological cultures of abdominal fluid taken during final abdominal closure were positive. Four samples had a negative culture (2 NPAD and 2 POAD). The microorganisms cultured at T_1 were comparable to those cultured at T_0 for 3 NPAD and 1 POAD case, in which bacteria showed multiresistant at both T_0 and T_1. All other positive cultures at T_1

TABLE 3 Results of biochemical analyses of abdominal fluid and plasma in dogs before POAD or NPAD (T_0), and at abdominal closure (T_1)

	NPAD	POAD	*P*-value
T_0			
Total protein (g/L) plasma	46 (CI 38-54)	47 (CI 37-56)	.73
Total protein (g/L) abdominal fluid	28 (CI 21-35)	37 (CI 31-42)	**.02**
T_1			
Total protein (g/L) plasma	35 (CI 29-41)	43 (CI 35-51)	.06
Total protein (g/L) abdominal fluid	19 (CI 13-25)	21 (CI 0-42)	.25
Glucose (mmol/L) abdominal fluid	1.6 (CI 1.2-4.4)	4.6 (CI 0.2-9.4)	**.05**
Lactate (mmol/L) abdominal fluid	8.9 (CI 1.5-16.3)	2.7 (CI 0.1-5.5)	**.03**
$T_0 \rightarrow T_1$			
Total protein difference plasma (g/L)	11 (CI 3-19)	4 (CI −9-16)	.23
Total protein difference abdominal fluid (g/L)	9 (CI 3-14)	11 (CI 1-22)	.38

TABLE 4 Biochemical analyses of plasma and abdominal fluid across time in the entire population

	Reference	T_0	T_1	*P*-value
Plasma				
Total protein (g/L)	54-70 g/L	46 (CI 41-51)	39 (CI 34-44)	**.03**
Amylase (IU/L)	<1200 IU/L	618 (IQR 1269)	919 (IQR 383)	.20
Lipase (IU/L)	<850 IU/L	66 (IQR 451)	22 (IQR 22)	.54
Abdominal fluid				
Total protein (g/L)		32 (CI 28-37)	23 (CI 17-28)	**.01**
Amylase (IU/L)		894 (IQR 2920)	632 (IQR 138)	.72
Lipase (IU/L)		455 (IQR 3760)	42 (IQR 80)	**.02**

revealed different bacteria compared to T_0 or mixed populations. Because of the 3 day delay to receive results of bacteriology, closure of the abdomen and postoperative treatment plan were based on abdominal fluid cytology and clinical parameters, as described above. None of the patients received antibiotic therapy longer than 7 days after discharge.

3.3 | Histology

Tissue samples were collected from 12 patients, 6 in each treatment group. Patients who died were excluded from the histopathology due to lack of T_1 samples and for 1 patient in the POAD group the sample was lost.

At T_0, no differences were found between techniques. At T_1, the distribution of inflammation in the superficial layer of the peritoneum and edema in the peritoneum was greater in the NPAD group compared to POAD (Table 5). Neutrophilic infiltration, necrosis, and edema increased across time (T_0 vs T_1) in the NPAD group (Table 6). Such differences were not noted in the POAD group.

4 | DISCUSSION

The results of this study support the application of NPAD using the ABThera™ system for the treatment of septic

TABLE 5 Histopathological findings in dogs treated with POAD and NPAD at abdominal closure (T_1)

	POAD	NPAD	*P*-value
Distribution of inflammation in the omentum	2.1 (CI 1.4-2.8)	2.2 (CI 1.5-2.8)	.89
Degree of inflammation in the omentum	1.6 (CI 1.1-2.0)	1.6 (CI 1.1-2.1)	.89
Distribution of inflammation in the superficial peritoneum	1.6 (CI 1.1-2.1)	2.6 (CI 2.3-3.0)	**.002**
Degree of inflammation in the superficial peritoneum	1.3 (CI 0.9-1.7)	1.8 (CI 1.3-2.3)	.07
Distribution of inflammation in the deep peritoneum	0.9 (CI 0.2-1.7)	1.1 (CI 0.5-1.8)	.68
Degree of inflammation in the deep peritoneum	0.6 (CI 0.0-1.4)	0.8 (0.4-1.2)	.68
Omental edema	1 (CI 0.5-1.5)	1.4 (0.7-2.1)	.28
Peritoneal edema	1.4 (CI 1.0-1.8)	2.2 (CI 1.9-2.5)	**.003**
Omental granulation tissue	1.8 (CI 0.9-2.7)	1.8 (CI 1.1-2.6)	.90
Peritoneal granulation tissue	1.8 (CI 0.6-3.0)	1.3 (CI 0.7-2.0)	.36
Omental hemorrhage	0.0 (IQR 0.1)	0.0 (IQR 0.1)	1.00
Peritoneal hemorrhage	0.0 (IQR 0.4)	0.0 (IQR 0.1)	.9
Omental necrosis	0.2 (IQR 1.0)	0.0 (IQR 1.2)	.79
Peritoneal necrosis	0.7 (IQR 1.7)	2.7 (IQR1.4)	.06

TABLE 6 Histopathological findings over time in dogs treated with NPAD

NPAD	T_0	T_1	*P*-value
Distribution of inflammation in the omentum	1.7 (CI 0.9-2.5)	2.2 (CI 1.5-2.8)	.25
Degree of inflammation in the omentum	1.5 (CI 0.7-2.3)	1.6 (CI 1.1-2.1)	.64
Distribution of inflammation in the superficial peritoneum	1.4 (CI 1.1-2.7)	2.6 (CI 2.3-3.0)	**.05**
Degree of in the superficial peritoneum	0.8 (CI 0.1-1.5)	1.8 (CI 1.3-2.3)	**.03**
Distribution of inflammation in the deep peritoneum	0.4 (CI 0.0-1.1)	1.1 (CI 0.5-1.8)	**.03**
Degree of inflammation in the deep peritoneum	0.2 (CI 0.0-0.7)	0.8 (0.4-1.2)	**.03**
Omental edema	1.0 (CI 0.4-1.6)	1.4 (0.7-2.1)	.31
Peritoneal edema	1.3 (CI 0.5-2.1)	2.2 (CI 1.9-2.5)	**.03**
Omental granulation tissue	1.3 (CI 0.4-2.2)	1.8 (CI 1.1-2.6)	.39
Peritoneal granulation tissue	1.4 (CI 0.2-2.6)	1.3 (CI 0.7-2.0)	.93
Omental hemorrhage	0.7 (IQR 2.2)	0.0 (IQR 0.1)	.14
Peritoneal hemorrhage	0.0 (IQR 0.1)	0.0 (IQR 0.1)	1.00
Omental necrosis	0.0 (IQR 0.3)	0.0 (IQR 1.2)	.29
Peritoneal necrosis	0.5 (IQR 0.6)	2.7 (IQR1.4)	**.03**

peritonitis as an effective alternative to POAD, with similar survival, costs, and subjectively reduced workload.

Whereas NPAD improved the survival rate of human patients,[31] the present study did not show a positive effect of NPAD on patient recovery, treatment duration, or survival of one technique over POAD. However, the overall survival rate (81%) in the present study compared favorably to other studies in dogs (27%-80%),[1-5] and may have masked any additional positive effect of NPAD. The 2 patients that did not survive in the NPAD group were both initially diagnosed with perforated pyloric ulcers and treated by Billroth-1 and Heineke-Mikulicz pyloroplasty, respectively One was euthanatized and the other died during the drainage period due to severe clinical deterioration, which could in theory be due to a dehiscence of the gastro-duodenal anastomosis. This complication was most likely related to the anatomic site rather than the abdominal drainage technique. The limited accessibility to the pylorus and reconstruction options likely resulted in a more conservative (marginal) surgical approach, requiring healing of tissues where viability may have been less than in other intestinal sites allowing wide excision of diseased tissues. Some authors describe the prognosis after pyloric surgery as poor, while others describe it as dependent on the underlying disease like neoplasia, and preoperative weight loss.[32,33] However, specific data on prognosis in cases of septic peritonitis are lacking. Furthermore, NPAD using the ABThera™ system has been found to have no acute adverse effects on the healing of intestinal anastomoses in pigs.[34] Both dogs died within 24 hours after surgery, most probably because of severe sepsis-related circulatory compromise. The possibility of dehiscence of the surgical repair as a cause for death or clinical deterioration in these patients was considered very unlikely because of the short time span. The dog that died with to a hepatocellular carcinoma was found during surgery to have a lesion resembling a liver abscess rather than a tumor. Histopathological examination of the lesion was consistent with a hepatocellular carcinoma. We believe that the *E. coli* cultured in this case may have resulted from intestinal translocation and caused an abscess, due to lowered local immunity combined with tissue necrosis secondary to the hepatocellular carcinoma. *E. coli* can be found in the liver due to constant delivery of intestinal bacteria through the portal system, but are normally removed by the liver's mononuclear phagocytic system.

The intensive treatment necessary for patients with septic peritonitis using POAD demands a sufficient number of trained staff and a well-equipped intensive care unit, limiting the application of this technique in veterinary practice. NPAD provides constant active drainage without the need for bandage/system changes, reducing workload once the system is properly installed.[29] Furthermore, eliminating the need for twice-daily bandage changes associated with POAD, NPAD may reduce patient discomfort. Except for the bandage changes in the POAD group, analgesia seemed effective at maintaining all patients relatively comfortable during the study. In man, costs related to the ABThera™

device are offset by improved patient outcome, shorter hospital stay and lower morbidity.[24,35] Costs in the present study did not differ between the 2 treatment modalities, making NPAD a good alternative for POAD.

NPAD prevents leakage of abdominal fluid outside the bandage and contamination of the abdominal cavity through the wound by creating an air-tight seal under continuous negative pressure drainage. NPAD therefore probably improved hygiene for the patient, staff, and the environment. In addition, NPAD has been found to provide a more accurate and continuous measurement of abdominal fluid production in human medicine, facilitating the decision making regarding abdominal closure.[35] By contrast, abdominal drainage may be leaking out of the bandage during POAD, and fluid production can only be estimated intermittently by weighing bandages during bandage changes. In the present study, bandages were often not weighed correctly or not documented, leading to data loss. No nosocomial infection was diagnosed in our study. Although the use of the ABThera™ would be expected to decrease the risk of nosocomial infections, we believe that these are also rare with POAD in dogs. On the other hand, bacterial contamination of the abdomen was frequently present at time of closure in both groups, according to the bacteriology results (Table 1). It is important to emphasize that bacterial culture results lag behind treatment selection since results become available 3-5 days after submission of the sample to the laboratory. Therefore, all patients received standard antibiotherapy based on the source of the contamination at T_0 (ie, small bowel, large bowel, liver, etc). Closure of the abdomen (T_1) was based on clinical improvement and cytology of abdominal fluid that were consistent with eradication of abdominal sepsis and inflammation. Fluid samples for bacterial culture were taken at T_1 for study purposes only and culture results were not interpreted as ongoing infection, but rather as bacterial contamination. Such interpretation is further supported by the lack of complications after abdominal closure, despite short-term antibiotherapy (less than 7 days after discharge). Furthermore, several of the bacteria isolated from abdominal fluid samples were not sensitive to the administered antibiotic. Also, most of the bacteria cultured at T_1 included low numbers of colony forming units or were cultured after accumulation.

The preoperative (T_0) protein level in the abdominal fluid was lower in the NPAD group than in the POAD group, but the clinical implications of this finding remain unclear. Plasma protein levels and changes over time did not differ between groups, providing evidence that protein loss did not differ between treatments. Overall, all patients lost proteins over time, a well-established complication due to the leakage secondary to damaged or inflamed endothelial and peritoneal membranes in patients with peritonitis.[36,37] The reduction in total protein levels in abdominal fluid at T_1 in both groups probably result from decreased exudation of proteins as septic peritonitis cleared over time. The same process could explain the lower lipase levels in abdominal fluid at T_1 compared to T_0. However, other indicators of inflammatory response did not significantly change over time. High plasma lipase and amylase levels are known to accompany systemic inflammatory responses to tissue damage caused by, for example, gastro-enteritis, liver disease, renal failure, acute pancreatitis, or septic peritonitis.[38] A decrease in alkaline phosphatase across time may have been masked by a relatively short drainage period in the current study, based on a plasma half-life approximating 72 hours in dogs.[39,40] However, other measured parameters with short plasma half-lives should therefore be reliable for the time span in the present study. Lipase and amylase have a plasma half-life in dogs of 1-3 hours[41] and 5 hours,[42] respectively. Alanine transaminase and aspartate aminotransferase have a half-life of 2-4 hours and around 5 hours, respectively.[39] In humans, septic peritoneal fluid contains a high amount of proinflammatory mediators resulting in severe liver, kidney, intestinal, and even lung injury as a result of increased leukocyte infiltration into these organs.[43] Improved and faster removal of mediator rich peritoneal fluid may decrease the systemic inflammatory response. This reduction in systemic inflammatory response is supported by porcine studies in which the ABThera™ system significantly removed more abdominal fluid as compared to other negative pressures therapies or passive open abdominal drainage.[23,43] Systemic inflammation (eg, abdominal fluid levels of TNF-α, IL-1β, IL-6) was reduced in the ABThera™ group and was associated with significant improvement in intestine, lung, kidney, and liver histopathology.[43] Furthermore, the NPAD technique may also be associated with local augmentation of healing of abdominal tissue, as is described for the healing of soft tissue wounds with negative pressure wound therapy (NPWT).[44] As the healing of a septic abdomen is often compared to the healing of a septic wound, the increased inflammatory changes seen in peritoneum on histology in the NPAD group may be compared to the increased neutrophil infiltration that is found in infected wounds treated with NPWT compared to conventional wound treatment.[45] Thus, an increased local inflammatory response of the peritoneum on histology of the NPAD group may be expected as a sign of an improved healing compared to POAD.

High lactate and low glucose levels in the abdominal fluid of the NPAD group at T_1 may suggest ongoing bacterial contamination, although these parameters have been found unreliable indicators for postoperative sepsis.[46] Furthermore, the high lactate levels and low glucose levels measured in the abdominal fluid of the NPAD group at T_1 could have been the result of ongoing in vitro bacterial growth and metabolism in the NPAD fluid collection canister

from which fluid samples for analysis were taken. It was not possible to collect the fluid directly from the abdomen in the NPAD group because the constant negative pressure drainage limited the accumulation of fluid for abdominocentesis. By contrast, abdominal fluid from the POAD group was collected directly from the abdominal cavity during bandage change, allowing accurate measurements. Bacterial cultures were negative in one patient, but positive cytology justified inclusion of this case in the study. In addition, our laboratory does not routinely grow anaerobic cultures, and an anaerobic agent may therefore have been missed. Hepatobiliary causes for septic peritonitis are known to be associated with anaerobic bacteria.[47]

In conclusion, negative pressure therapy with the ABThera™ system is an effective alternative to PAOD to provide abdominal drainage in dogs with septic peritonitis. Clinical outcomes, including survival, time needed for drainage, and treatment costs were comparable between techniques. However, the authors recommend NPAD over POAD based on improved local healing response, decreased morbidity, and elimination of frequent bandage changes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this report.

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