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Randomized Clinical Trial

Effect of peritoneal and wound lavage with super-oxidized solution on surgical-site infection after open appendicectomy in perforated appendicitis (PLaSSo): randomized clinical trial

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Abstract

Background: Surgical-site infection following open appendicectomy for perforated appendicitis increases length of hospital stay and treatment costs while compromising patients' quality of life. Data from randomized clinical trials (RCTs) evaluating the role of super-oxidized solution in perforated appendicitis are lacking. The study objective was to determine the effect of peritoneal and wound lavage with super-oxidized solution in reducing risk of surgical-site infection following open appendicectomy for perforated appendicitis.

Methods: In this multicentre RCT conducted between September 2020 and March 2022, patients aged 13 years and older with perforated appendicitis undergoing open appendicectomy were randomly assigned to receive peritoneal and wound lavage with either super-oxidized solution or normal saline. The primary outcome was surgical-site infection within 30 days after surgery. Randomization was computer-generated, with allocation concealment by opaque, sequentially numbered, sealed envelope. The patients, surgeons, outcome assessors and statisticians performing the analysis were blinded to treatment assigned.

Results: A total of 102 consecutive patients (51 in the super-oxidized solution group and 51 in the normal saline group) were randomized and included in the intention-to-treat analysis. The super-oxidized solution group showed a significant reduction in overall surgical-site infection (8 (15.6%) *versus* 19 (37.2%); relative risk (RR) 0.42; 95% c.i. 0.20 to 0.87; $P = 0.014$), and superficial surgical-site infection (5 (9.8%) *versus* 18 (35.3%); RR 0.28; 95% c.i. 0.11 to 0.69; $P = 0.002$), with a number-needed-to-treat of four patients. There were no adverse events in either group.

Conclusions: Peritoneal and wound lavage with super-oxidized solution is superior to normal saline in preventing surgical-site infection after open appendicectomy for perforated appendicitis.

Trial Registration: ClinicalTrial.gov Identifier: NCT04512196

Introduction

Appendicitis is among the most common surgical emergencies, with a lifetime risk of 6.7–9.9%[1,2], and perforated appendicitis accounts for 20.8–38.5% of these cases[3,4]. Incidence of surgical-site infection after open appendicectomy for perforated appendicitis remains high at between 23.9% and 50%[5–8], leading to an increase in length of hospital stay and incurring higher treatment costs[9,10].

Laparoscopic appendicectomy in perforated appendicitis significantly lowered the risk of surgical-site infection to 7.2–15.2%[5–7] as compared to open surgery. However, large population-based studies showed that the prevalence of open surgery and conversion from initial laparoscopic approach to open for perforated appendicitis remains high, ranging from 22.4 to24% in America and Europe[11–13] and 66.2% in Asia[14]. Furthermore, open appendicectomy is more prevalent in developing and resource-limited regions in the world.

Several prospective studies looked at factors that determine incidence of surgical-site infection, with use of chlorhexidine–alcohol for skin antisepsis[15], wound edge protectors[4,16], peritoneal and wound lavage[17,18], and delayed wound closure[8]; however, the outcomes were not consistent.

The 2016 WHO global guidelines for prevention of surgical-site infection recommend lavage of clean and clean–contaminated incisional wounds with aqueous povidone iodine, while concluding that antibiotic wound lavage does not confer any benefit. Although povidone iodine contains antimicrobial properties, it impairs wound healing due to its cytotoxic nature[19]. Conversely, peritoneal lavage

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with antibacterial and non-antibacterial solutions such as gentamicin, kanamycin, metronidazole and povidone iodine confers no benefit in reducing surgical-site infection rates[20].

Previous work demonstrated a significant reduction in surgical-site infection rates with peritoneal lavage using super-oxidized solution compared to normal saline in patients with peritonitis; however, subgroup analysis showed no benefit in patients with perforated appendicitis[18].

In the study centre, patients who underwent open appendicectomy for perforated appendicitis received peritoneal and wound lavage with normal saline; however, the incidence of surgical-site infection remained high at 34%. To bridge this research gap, the study team designed a randomized clinical trial to test the hypothesis that peritoneal and wound lavage with super-oxidized solution is superior to normal saline 0.9% in preventing surgical-site infection after open appendicectomy for perforated appendicitis.

Method

Study design

The Peritoneal Lavage with Super-oxidized Solution (PLaSSo) trial is a prospective, pragmatically designed, triple-blinded, randomized, placebo-controlled trial. This study was carried out at the surgical departments of Queen Elizabeth Hospital and Queen Elizabeth II Hospital in Kota Kinabalu, Malaysia between September 2020 and March 2022. This study was designed to assess the superiority of the intervention compared to placebo. The patients, surgeons, outcome assessors and statisticians performing the analysis were blinded to treatment assigned.

Patients

All participants provided written informed consent upon recruitment, and those below 18 years old were consented by their parents or legal guardians. Patients aged 13 years and above diagnosed with perforated appendicitis intraoperatively and who underwent open appendicectomy *via* a Lanz incision were enrolled by the study team. Patients who required conversion to mid-line laparotomy or were on steroids or immune-suppressant therapy were excluded.

Due to heterogeneity in definition, perforated appendicitis was strictly defined intraoperatively when there was evidence of a defect in the wall of the appendix, extraluminal faecolith and/or frank pus or abscess surrounding the appendix, which fulfilled the criteria of 'dirty' surgery. Gangrenous, suppurative and exudative appendicitis, which are associated with a significantly lower incidence of surgical-site infection, were excluded[21–24].

Trial interventions

Enrolled patients were randomly assigned to receive either the intervention (super-oxidized solution (Hydrocyn Aqua®, Vigilenz MD, Penang, Malaysia)) or placebo (normal saline 0.9%). A computer-generated random sequence with a block size of eight and allocation ratio of 1:1 was produced. Allocation sequence was concealed from surgeons and investigators in sequentially numbered, opaque, sealed envelopes prepared by an administrative staff member who was not part of the clinical team.

All study participants underwent peritoneal toilette with suction and dry swabbing followed by peritoneal lavage before wound closure. The envelope with the allocation was opened by a circulating theatre nurse not involved in the clinical management of the patient. The intervention group received super-oxidized solution whereas the control group received normal saline 0.9% solution for peritoneal lavage (9 ml per kg body weight for 3 min) and wound lavage (1 ml per kg body weight for 2 min). The study solutions were clear and colourless, and came in an identical 500-ml plastic bottle with a code printed on a detachable label that was removed before bringing the bottle into the operating theatre. The odour was very faint and could only be detected when held close to the nose without a mask, and hence indiscernible in the operating theatre setting.

Primary and secondary end points

The primary end point was the incidence of surgical-site infection within 30 days after surgery, diagnosed by investigators based on the definition developed by the Centre for Disease Control (CDC)[25] (*Supplementary materials*).

The secondary end points included duration of ileus (time from end of surgery to passing flatus or bowel opening), the preoperative C-reactive protein (CRP) trend, and the postoperative CRP trend at 24 and 48 h.

Procedures

Preoperative evaluation included a thorough history, physical examination, blood investigations and imaging by ultrasound and/or CT scan when there was a diagnostic uncertainty. Empirical antibiotics with intravenous cefuroxime and metronidazole were initiated upon diagnosis of perforated appendicitis. Standard skin preparation with chlorhexidine gluconate 2% with isopropyl alcohol 70%, infection-prevention measures based on WHO guidelines and operative techniques were used. The peritoneal cavity was suctioned and swabbed dry until the gauze was free of pus or slough followed by saline irrigation till clear effluent. Peritoneal lavage followed by fascial closure and wound lavage was performed based on the study protocol. Skin was sutured using non-absorbable sutures in a simple interrupted fashion. Antibiotic therapy was administered for a total of 7 days and converted to oral route upon discharge.

Clinical assessment

All data were collected by the study team and entered into a case report form. All study participants were followed-up by a clinician at 10 days post-surgery for suture removal and at 30 days post-surgery to assess for signs of surgical-site infection. Patients who developed wound-related complications in the interim or were unable to attend the scheduled clinic at the trial centre had their wounds assessed by their primary care physicians, who then updated the study coordinator. Appropriate imaging by ultrasound and/or CT abdomen was ordered to look for intra-abdominal collection or abscess, which was treated with drainage, or with a longer course of antibiotics if not amenable to drainage. Pus and/or wound swab samples were cultured to determine causative microorganism and antibiotic sensitivity.

Trial safety and oversights

The study was approved by the Medical Research and Ethics Committee Ministry of Health Malaysia and was registered with National Medical Research Registry Malaysia (NMMR-ID-16-2905-30891) and ClinicalTrial.gov (NCT04512196). This study was funded by the Ministry of Health Research Grant. All adverse events including skin irritation and allergic reaction were documented and reported.

Statistical analysis

The incidence of surgical-site infection after open surgery for perforated appendicitis at the study centre was 34%. Based on

the results of studies by Kubota *et al.*[17] and Garg *et al.*[18], the anticipated incidence of surgical-site infection in the intervention group was 10%. The study needed to enrol 92 participants in order to have 80% power to detect a 24% decrease in the rate of surgical-site infection, at a two-tailed significance level of 0.05. To accommodate 10% loss to follow-up, 102 participants were enrolled, 51 in each group.

Primary data were analysed using an intention-to-treat principle. Preventive measures were taken to minimize loss to follow-up and missing data. Categorical data were analysed using Chi-square test or Fisher's exact test. Parametric continuous variables were analysed using Student's *t*-test whereas non-parametric continuous variables were analysed using Mann–Whitney U test. Kaplan–Meier estimates with log-rank test were used to compare time to first surgical-site infection. $P < 0.05$ was considered statistically significant, with a relative risk (RR) or mean difference within a 95% confidence interval. All statistical analyses were performed using IBM SPSS Statistics Version 26 (IBM Corp.; Armonk, New York, USA).

Results

Patients

A total of 102 patients were enrolled and randomly assigned, 51 to the super-oxidized solution group and 51 to the normal saline 0.9% group as described in the CONSORT flow diagram (*Fig. 1*). All 102 patients received their allocated intervention and were included in the intention-to-treat analysis. Three patients were lost to follow-up at 30 days after surgery, one in the super-oxidized solution group and two in the normal saline 0.9% group.

The median (i.q.r.) age was 26 (18–41) years and 76 participants (74.5%) were male. Baseline demography, risk factors for surgical-site infection and surgical characteristics were generally well balanced between the two treatment groups (*Table 1*). None had a penicillin allergy, hence all patients received standard antibiotic therapy with cefuroxime and metronidazole.

Primary outcome

In the intention-to-treat population, 8 patients (15.6%) in the super-oxidized solution group and 19 patients (37.2%) in the

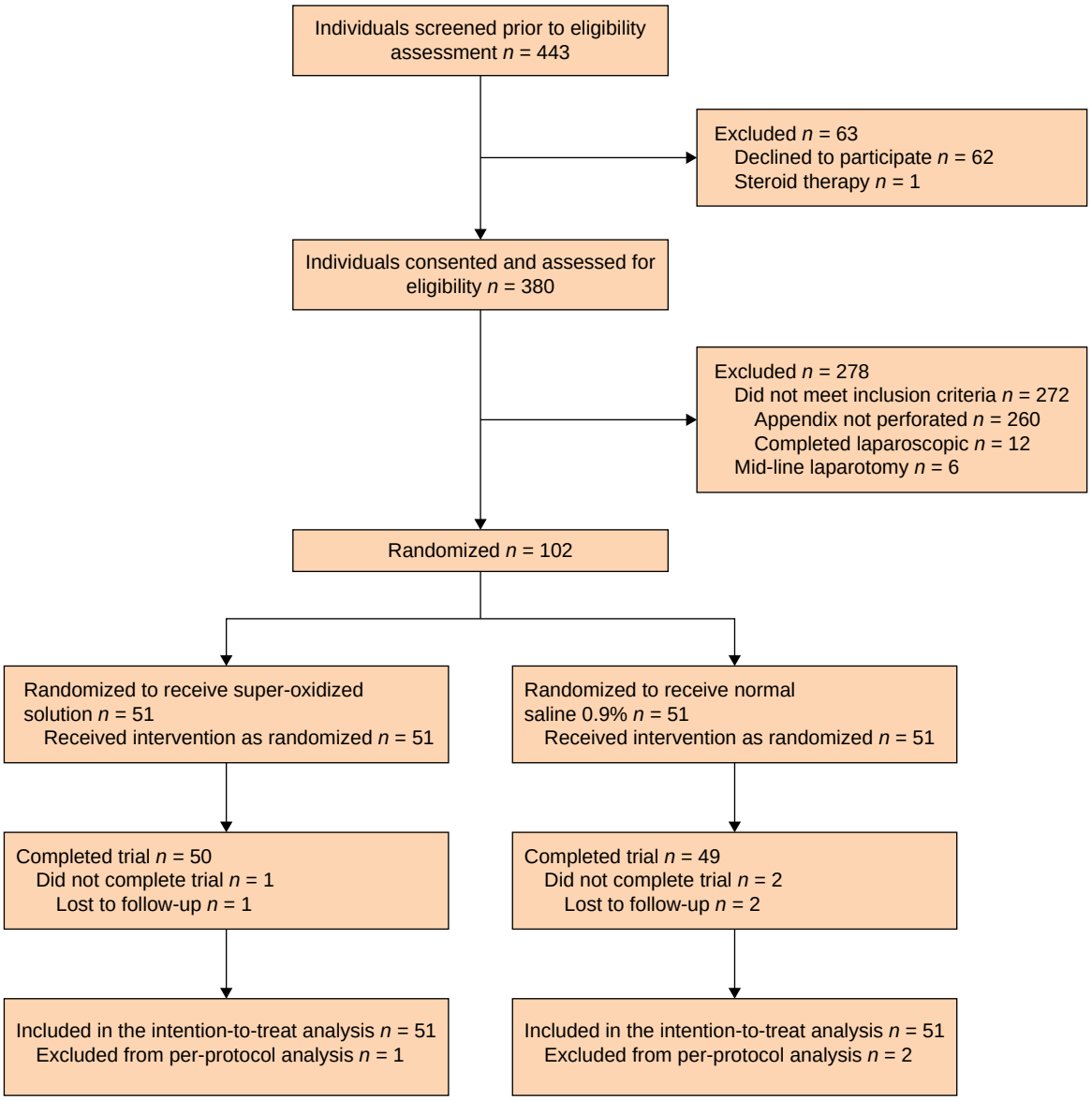

Fig. 1 CONSORT flow diagram—randomization and follow-up of study participants

normal saline 0.9% group were diagnosed with surgical-site infection (RR 0.42; 95% c.i. 0.20 to 0.87; $P = 0.014$). The incidence of superficial surgical-site infection was 9.8% in the super-oxidized solution group and 35.3% in the normal saline 0.9% group (RR 0.28; 95% c.i. 0.11 to 0.69; $P = 0.002$). Absolute risk reduction for superficial surgical-site infection was 25.5%. To prevent one case of superficial surgical-site infection, the number needed to treat (NNT) was four patients. There were no patients with deep surgical-site infections in either group and no significant differences between groups in the incidence of organ space infection (RR 3.00; 95% c.i. 0.32 to 27.89; $P = 0.617$; *Table 2*). Per-protocol analysis yielded similar results (*Supplementary materials*, *Table S1*).

Kaplan–Meier estimates of risk of surgical-site infection showed a longer time-to-infection in the super-oxidized solution group than in the normal saline 0.9% group (*Fig. 2*). The median time (i.q.r.) to develop surgical-site infection was 10 days (7–14) in the super-oxidized solution group, and 7 days (5–9) in the normal saline 0.9% group (hazard ratio 0.35; 95% c.i. 0.15 to 0.79, log-rank $P = 0.008$).

Table 1 Baseline characteristics of patients in the super-oxidized solution and normal saline groups

Characteristics	Super-oxidized solution ($n = 51$)	Normal saline 0.9% ($n = 51$)	P
Sex			0.821
Male	39 (76.5)	37 (72.5)	
Female	12 (23.5)	14 (27.5)	
Age (years), median (i.q.r.)	26 (18–41)	24 (17–41)	0.618
Diabetic	4 (7.8)	4 (7.8)	1.000
BMI (kg/m^2), mean(s.d.)	23.2(4.6)	24.1(5.1)	0.456
Preop. CRP (mg/l), mean(s.d.)	162.3(91.9)	166.8(94.2)	0.816
Surgeon experience			0.808
Medical Officer	12 (23.5)	14 (27.4)	
Registrar	36 (70.6)	33 (64.7)	
General Surgeon	3 (5.9)	4 (7.8)	
Initial approach			0.419
Open	28 (54.9)	33 (64.7)	
Laparoscopic with conversion	23 (45.1)	18 (35.3)	
Duration of surgery (min), mean(s.d.)	128.0(49.9)	125.7(39.6)	0.769
Degree of contamination			0.626
Peri-appendiceal	8 (15.7)	8 (15.7)	
Pelvis	39 (76.5)	36 (70.6)	
Generalized	4 (7.8)	7 (13.7)	
Wound depth (cm), mean(s.d.)	2.5(1.3)	2.4(0.9)	0.481
Wound length (cm), mean(s.d.)	6.9(1.8)	7.1(1.7)	0.486
Organism cultured			0.530
Escherichia coli	20/39 (51.3)	24/40 (60.0)	
Klebsiella pneumonia	4/39 (10.3)	4/40 (10.0)	
Pseudomonas aeruginosa	2/39 (5.1)	4/40 (10.0)	

Values are *n* (%) unless otherwise indicated. BMI, body mass index; CRP, C-reactive protein.

Secondary and additional outcomes

There were no significant differences in duration of ileus (mean difference −1.41; 95% c.i. −4.84 to 2.03; $P = 0.415$), changes to CRP trend at 24 h *versus* 48 h (mean difference 1.54; 95% c.i. −9.38 to 12.46; $P = 0.783$), length of hospital stay (mean difference 0.00; 95% c.i. −0.48 to 0.48; $P = 1.000$) and hospital readmission rates (RR 0.75; 95% c.i. 0.18 to 3.18; $P = 1.000$) between the groups randomized to super-oxidized solution and normal saline 0.9% (*Table 3*). There were no documented adverse reactions in either group.

Subgroup analysis based on initial surgical approach, open or laparoscopy converted to open was performed. In the open approach, 3 patients (10.7%) in the super-oxidized solution group and 14 patients (42.4%) in the normal saline 0.9% group were diagnosed with superficial surgical-site infection (RR 0.25; 95% c.i. 0.08 to 0.79; $P = 0.006$; *Supplementary materials*, *Table S2*). Also, in the open approach, the risk of overall surgical-site infection in the intervention *versus* control arm was 17.9% *versus* 42.4% (RR 0.42; 95% c.i. 0.17 to 1.02; $P = 0.053$). In the laparoscopy converted to open approach, the risk of overall surgical-site infection in the intervention *versus* control arm was 13.0% *versus* 27.8% (RR 0.47; 95% c.i. 0.13 to 1.71; $P = 0.267$), whereas superficial surgical-site infection was 8.7% *versus* 22.2% (RR 0.39; 95% c.i. 0.08 to 1.90; $P = 0.377$). Given the small number of patients in each subgroup, the study was underpowered to show the difference between groups in the laparoscopy converted to open subgroup (*Supplementary materials*, *Table S2*).

Discussion

The effectiveness of super-oxidized solution in reducing surgical-site infection after open appendicectomy for perforated appendicitis still remains uncertain due to lack of strong evidence[17,18]. This pragmatic, randomized, triple-blind, placebo-controlled trial clearly demonstrates the superiority of super-oxidized solution in reducing the incidence of surgical-site infection when compared to normal saline 0.9% when used for peritoneal and wound lavage after open appendicectomy for perforated appendicitis. The risk of overall surgical-site infection (superficial, deep and organ-space) was reduced by 58% ($P = 0.014$), whereas the risk of superficial surgical-site infection was reduced by 72% ($P = 0.002$, NNT = 4). Patients assigned to the super-oxidized solution group showed a longer time-to-infection compared to the normal saline 0.9% group ($P = 0.008$).

Super-oxidized solution significantly reduced the risk of overall surgical-site infection to 15.6% *versus* 37.2% and superficial surgical-site infection to 9.8% *versus* 35.3%. This finding is

Table 2 Proportion of patients with surgical-site infection by intention-to-treat population

Grade of infection	Super-oxidized solution ($n = 51$)	Normal saline 0.9% ($n = 51$)	Relative risk (95% c.i.)	P
Overall SSI	**8 (15.7)**	**19 (37.3)**	**0.42 (0.20,0.87)**	**0.014**
Superficial SSI	**5 (9.8)**	**18 (35.3)**	**0.28 (0.11,0.69)**	**0.002**
Deep SSI	0	0		
Organ space SSI	3 (5.9)	1 (2.0)	3.00 (0.32,27.89)	0.617

Values are *n* (%) unless otherwise indicated. Statistically significant values are highlighted in bold. SSI, surgical-site infection.

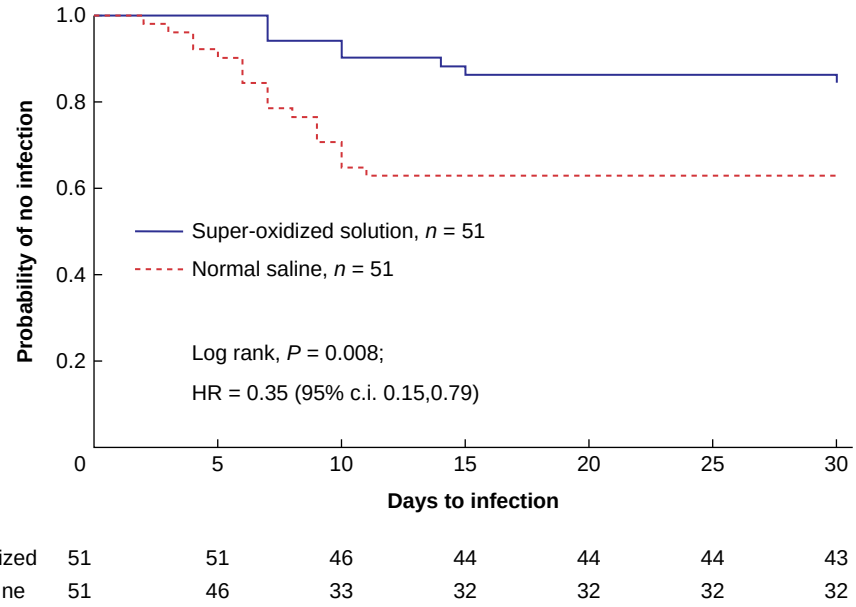

Fig. 2 Kaplan–Meier curve for freedom from surgical-site infection (intention-to-treat population) showing time to infection in the super-oxidized solution and normal saline 0.9% group

The median time (i.q.r.) to develop surgical-site infection was 10 days (7–14) in the super-oxidized solution group, and 7 days (5–9) in the normal saline 0.9% group (hazard ratio 0.35; 95% c.i. 0.15 to 0.79, log-rank $P = 0.008$).

Table 3 Secondary and post-hoc additional outcomes by intention-to-treat population

Outcomes	Super-oxidized solution ($n = 51$)	Normal saline 0.9% ($n = 51$)	Mean difference/relative risk (95% c.i.)	P
Secondary outcomes				
Duration of ileus (h), mean(s.d.)	14.88(7.60)	16.29(9.53)	−1.41 (−4.84,2.03)	0.415
ΔCRP at 24 h *versus* 48 h (mg/l), mean(s.d.)	32.42(30.34)	30.88(20.69)	1.54 (−9.38,12.46)	0.783
Additional outcomes				
Length of stay (days), mean(s.d.)	4.00(0.96)	4.00(1.46)	0.00 (−0.48,0.48)	1.000
Hospital readmission	3 (5.9)	4 (7.8)	0.75 (0.18,3.18)	1.000
Adverse events	0	0		

Values are *n* (%) unless otherwise indicated. CRP, C-reactive protein.

consistent with the results reported by Garg *et al.* in 2013, in a randomized controlled trial published in a non-indexed journal, who found that super-oxidized solution applied during peritoneal lavage for peritonitis of any cause significantly reduced superficial surgical-site infection rate compared to saline: 14% *versus* 40% (RR 0.35; 95% c.i. 0.16 to 0.75; $P = 0.003$)[18]. However, the study population was heterogeneous and a subgroup analysis showed a significant reduction in surgical-site infection rates only in patients with gastric and duodenal perforations, whereas there was no difference in perforated appendicitis. Only 5% of 100 trial participants had perforated appendicitis, hence the study is likely underpowered to show a difference in this subgroup of patients[18].

Previous studies have shown a significant reduction in superficial surgical-site infection rates after peritoneal lavage alone[17,18]. In contrast, a recent study by Mueller *et al.* showed no significant difference in risk of surgical-site infection between intraoperative irrigation of laparotomy wounds with polyhexanide compared to saline or no irrigation[26]. The PLaSSo trial employed both wound and peritoneal lavage, which led to the reduction in superficial surgical-site infection rates; however, no difference in deep or organ-space infection were seen. The primary source of contamination originates from the peritoneal cavity and extends into the exposed wound edges. Hence sequential irrigation of the peritoneal cavity followed by rectus closure and wound irrigation reduces microbial load and decreases the risk of superficial surgical-site infection. Peritoneal fluid has the potential to seep into the subcutaneous wound, which, being relatively less vascular, gives rise to the risk of superficial surgical-site infection. Therefore, peritoneal lavage does reduce the microbial load and subsequent risk of superficial surgical-site infection.

The results are also in keeping with the findings published by Kubota *et al.* in 2014 on the use of strong acid electrolyzed water (SAEW) compared to saline for peritoneal lavage in the treatment of perforated appendicitis in children: 0% *versus* 20% ($P < 0.05$). However, only 44 children were randomized whereas 34 were excluded for receiving antibiotics prior to surgery or had an abscess formation. In clinical practice, empirical antibiotic therapy will be initiated prior to surgery upon a diagnosis of perforated appendicitis. This explains their very low incidence of surgical-site infection rates likely due to a selection bias by excluding patients with clinically apparent perforated appendicitis diagnosed prior to surgery. Furthermore, strong acid electrolyzed water has a pH of 2.5–2.7 and a hypochlorous acid concentration of 0.004%, whereas the super-oxidized solution used in this study has a neutral pH and a hypochlorous acid concentration of 0.003%. Hence, the results of Kubota *et al.*'s study cannot be directly translated to reflect the clinical effectiveness of super-oxidized solution in reducing surgical-site infection[17].

There were no adverse events reported in either group in this study. This finding was concordant with the safety profile of super-oxidized solution reported in previous studies[27,28]. Super-oxidized solution contains hypochlorous acid (HOCl) 0.003%, a chemical compound also generated by neutrophils as part of the body's innate immunity[29]. These reactive species exhibit extensive bactericidal activity by altering the osmotic gradient, damaging the cell membrane integrity of single-celled organisms and subsequently denaturing its lipid and protein content. Multicellular organisms including human tissue are not susceptible to such changes in osmolarity, and hence are spared from damage[30].

The process of suctioning and swabbing followed by saline irrigation clears the peritoneal cavity from gross macroscopic contaminants. To exert maximal antimicrobial effect, the volume of super-oxidized solution required had to adequately soak the peritoneal and wound cavity. Super-oxidized solution has a rapid onset of antimicrobial action between 30 and 5 min, and demonstrates wound-healing properties[19]. The rapid onset of antimicrobial action has a direct impact on decreasing wound microbial load, which is reflected by the decrease in the incidence in surgical-site infection and a longer time to infection in the super-oxidized solution group in this study.

The strength of this study lies in its pragmatic design, triple-blinding and the application of an intention-to-treat protocol. The study protocol was designed to facilitate transition into clinical practice. In comparison to previous studies that required a high volume of 100 ml per kg body weight for lavage[17] and peritoneal drains that required clamping post-surgery[18], this study required 9 ml per kg body weight for peritoneal lavage with a 3-min soak time and 1 ml per kg body weight for wound lavage with a 2-min soak time, negating the need for drains. The NNT was four patients to prevent one case of superficial surgical-site infection. The additional cost incurred for the use of super-oxidized solution was US$8.50 per patient, whereas the median cost of treating surgical-site infection post-open appendicectomy was US$310[4]. This translates into a fast, convenient, cost-effective and easily replicable technique to significantly reduce surgical-site infection. Finally, randomization breaks confounding bias and triple-blinding minimized performance and detection bias, while the intention-to-treat analysis minimized attrition bias.

This trial has several limitations. First, this trial was conducted at two hospitals within the same locality, which potentially affects the generalizability of the findings. However, the study population was ethnically diverse with a mixed proportion of patients from several indigenous natives and Chinese origin. Second, a formal cost analysis was not performed in this study. The cost-effectiveness was extrapolated based on median cost of treating surgical-site infection post-open appendicectomy performed recently in a local institution. Third, there is a potential for recall bias as the patients were followed-up at day 10 and day 30 after surgery to assess for surgical-site infection. This was minimized as the patients and their primary care physicians updated the study coordinator when surgical-site infection occurred. Finally, the sample size was relatively small with 51 patients in each group, calculated based on anticipation of a large effect size based on previous studies. Despite this, there was clearly a significant difference in primary outcome between the two groups with a low rate of 2.9% lost to follow-up. Hence, the results of this study can be translated into clinically meaningful outcomes in patients undergoing open appendicectomy or initial laparoscopic with conversion to open in the form of a Lanz incision.

This randomized, triple-blind, placebo-controlled trial demonstrated that using super-oxidized solution for peritoneal and wound lavage following open appendicectomy for perforated appendicitis significantly lowers risk of surgical-site infection when compared to normal saline 0.9%.

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Disclosure

The authors declare that they have no conflicts of interest. Informed consent was obtained from all individual participants included in the study. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data that support the findings of the present study are available from the corresponding author upon reasonable request.

Author contributions

Harivinthan Sellappan (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing—original draft, Writing—review & editing), Dinesh Alagoo (Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Validation, Writing—review & editing), Christina Loo (Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Writing—review & editing), Kaesarina Vijian (Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Writing—review & editing), Rohamini Sibin (Conceptualization, Methodology, Project administration, Supervision, Validation, Writing—review & editing), and Jitt Chuah (Conceptualization, Methodology, Project administration, Supervision, Validation, Writing—review & editing)

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