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The Impact of Intraoperative Fluid Therapy and Body Temperature on Surgical Site Infection – Re-Assessment of a Randomized Trial

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Rezumat

Impactul terapiei lichidiene intraoperatorii și a temperaturii corporale asupra infecției plăgii chirurgicale - reevaluare a unui studiu clinic randomizat

Contextul: Utilizarea oxigenului suplimentar în timpul intervenției chirurgicale pentru a reduce incidența infecțiilor plăgii chirurgicale (IPC) a fost studiată în cadrul studiului clinic PROXI, care nu a descoperit o frecvență redusă a infecțiilor. Ulterior, s-a sugerat că terapia lichidiană restrictivă și hipotermia în cazul unor pacienți ar putea explica lipsa efectelor benefice a administrării oxigenului suplimentar. Am evaluat asocierea incidenței IPC și doi factori perioperatori, volumul fluidului administrat și temperatura corporală.

Metode: Am folosit informații din studiul clinic PROXI, care a inclus 1.386 de pacienți supuși laparotomiei, cărora li s-a administrat randomizat 80% sau 30% oxigen în timpul intervenției chirurgicale. S-a calculat un index al lichidelor administrate pentru fiecare pacient: volumul lichidelor administrate/ greutate corporală / durata operației.

Rezultate: Au suferit de IPC: 18,9% din pacienții cu un indice scăzut (RR (risc relativ)=0.86; P=0.41), 20,4% din pacienții cu indice crescut (RR =1.49; P=0.05), 19,7% din pacienții cu hipotermie (RR =1.28; P=0.25) și 25,0% din pacienții cu hipertermie

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(RR =1.26; P=0.52). Un risc crescut de IPC (RR =3.15; P=0.01) a fost identificat la pacienții care au suferit de hipotermie și intervenție chirurgicală de urgență.

Concluzii: S-a observat un trend crescător al apariției IPC la pacienții care au primit o cantitate mai mare de lichid intravenos. Nu s-a identificat nici o asociere între temperatura corporală și IPC.

Cuvinte cheie: Infecția plăgii chirurgicale, oxigen suplimentar, laparotomie, terapie lichidiană intraoperatorie, temperatură corporală perioperaorie, studiu clinic PROXI

Abstract

Background: Use of supplemental oxygen during surgery to reduce the incidence of SSI was investigated in the PROXI trial, which found no reduced frequency of SSI. Subsequently, it has been suggested that a restrictive fluid regimen and hypothermia in some patients could explain why no beneficial effect of supplemental oxygen was found. We evaluated the association between the occurrence of SSI and two perioperative factors, volume of infused fluid and body temperature (BT). **Methods:** We used data from the PROXI trial including 1,386 patients undergoing laparotomy randomly assigned to receive 80% or 30% oxygen during surgery. A fluid infusion index (FII) was calculated for each patient as the volume of infused fluids/body weight/duration of surgery.

Results: SSI occurred in 18.9% of the patients in the lower FII tertile group (OR=0.86; P=0.41), in 20.4% in the upper FII tertile group (OR=1.49; P=0.05), in 19.7% of the patients with hypothermia (OR=1.28; P=0.25) and in 25.0% with hyperthermia (OR=1.26; P=0.52). An increased risk of SSI (OR=3.15; P=0.01) was found in patients having both hypothermia and emergency surgery.

Conclusion: A trend towards an increased risk of SSI was seen in patients who received a greater volume of intravenous fluid. No association was found between BT and SSI.

Key words: Surgical site infection, supplemental oxygen, laparotomy, intraoperative fluid therapy, perioperative body temperature, the PROXI trial

Introduction

Surgical site infection (SSI) is a common complication following surgical procedures, leading to antibiotic therapy, reoperations, prolonged hospitalization, higher mortality, and increased hospital costs (1-3).

The most important defence against surgical pathogens is mediated by neutrophils' oxidative killing. This process depends on the partial pressure of oxygen in the wound, which may be improved by increasing the concentration of inspired oxygen (4-6). Accordingly, the frequency of SSI might be reduced by supplemental oxygen during surgery. This concept has been tested in many randomized trials (7). One of the largest of these trials, the Danish PROXI trial, included 1,386 patients undergoing elective or

emergency laparotomy. Patients were randomized to receive 80% or 30% oxygen during surgery and for the first two hours after surgery. The study found no statistically significant differences in the incidence of SSI between the groups (8).

An increase in oxygen tension in a wound secondary to a higher inspiratory oxygen fraction requires adequate perfusion. A randomized trial by Greif et al in 2000 found that use of high inspired oxygen fraction (80% vs. 30%) during and after colorectal surgery significantly reduced the risk of SSI (9). In order to maintain a sufficient perfusion to the wound all patients were aggressively hydrated intraoperatively with intravenous fluid administration equivalent to 15 mL/kg/hr ("liberal" fluid therapy). Hunt et al addressed that fluid

volumen administered in the PROXI trial were smaller (“restrictive” fluid therapy) (10). Normothermia is also important in maintaining peripheral perfusion (10). It was thus hypothesized that some patients in the PROXI trial had lower oxygen tension in the surgical wound, thereby impeding the oxidative bacterial killing by neutrophils. Accordingly, the intravenous fluid regimen and the fact that it was not possible to maintain normothermia in all patients during surgery, might explain why the frequency of SSI was not reduced in the group of patients assigned to 80% compared with 30% oxygen in the PROXI trial.

The fluid regimen in the PROXI trial was chosen to ensure normovolaemia and specifically corresponded to the restrictive allocation arm in a randomized study, which concluded that such a regimen reduced the incidence of SSI (11). Nevertheless, it can be claimed that a high perioperative inspiratory oxygen fraction is only shown to prevent SSI under conditions with high tissue perfusion maintained using a “liberal” fluid regimen.

The aim of this study was to evaluate the possible association between the occurrence of SSI and two perioperative factors, namely volume of infused fluid and body temperature (BT) among the patients included in the PROXI trial. We hypothesized that a reduced frequency of SSI could be detected in patients who received a high volume of infused fluid and were normothermic during surgery.

Material and Method

We used data from the PROXI trial, which included patients aged 18 years and over admitted for an elective or emergency laparotomy (8). Only patients with suspected malignancy were included in cases where laparotomy was performed due to gynaecological disease (12). Patients were excluded in the following cases: general anaesthesia within 30 days, chemotherapy for malignancy within 3 months, inability to provide informed consent, and preoperative arterial haemoglobin oxygen saturation below 90% without supplemental oxygen assessed by pulse oximetry (8).

A restrictive fluid regimen was used, aiming at normovolaemia and a postoperative body weight increase less than 1 kg. No intravenous fluids were given preoperatively unless the patient had fluid deficit due to acute illness. During surgery, intravenous fluids were administered only to replace measured or calculated deficits in order to maintain a urinary output above 1 mL/kg/hr. A blood loss greater than 500 mL was replaced 1:1 with colloid and, if blood loss exceeded 20 mL/kg, blood transfusion was initiated (13).

During surgery, forced air warming and warmed fluids were used to avoid hypothermia. The patients’ BT (core) was measured continuously, most often in the nasopharynx, and it was aimed to maintain values between 36 and 37°C. BT was recorded at the end of the surgical procedure (13).

The patients included in the PROXI trial underwent different types of surgery with varying amounts of blood loss and, as a result, the intravenous fluid therapy given perioperatively varied considerably (8). To compare the administration of fluids among the patients, a individual fluid infusion index (FII) was calculated as the *volume of infused fluid/body weight/duration of surgery*. The *volume of infused fluid* was calculated by adding the *volume of blood products, the volume of infused colloids and one third of infused crystalloids minus the volume of blood loss*, assuming that 2/3 of the infused crystalloids leave the intravascular compartment.

Development of postoperative SSI was assessed daily by a surgical investigator blinded to allocation. After discharge, a follow-up visit was undertaken (8).

Statistical Analysis

The association between the volume of infused fluid and BT and the occurrence of SSI was assessed by logistic regression with adjustment for known predictive factors for SSI (daily smoking, obesity, duration of surgery, wound contamination) as well as allocation, emergency surgery, diabetes, and study centre.

The statistical analyses were performed

with the covariates FII and BT as both continuous and categorical variables. In the latter case, FII was classified in tertiles (FII < 2.71 mL/kg/hr; FII 2.71 - 5.64 mL/kg/hr; FII > 5.64 mL/kg/hr) and BT was categorised as hypothermia (BT ≤ 35.4°C), normothermia (BT 35.5°C - 37.5°C) and hyperthermia (BT ≥ 37.6°C). The middle tertile of FII and normothermia were used as reference groups. Additionally, univariable analyses were performed with data stratified according to the

type of surgery (elective and emergency).

P < 0.05 was considered statistically significant. Statistical software was SPSS version 20.0.

Results

Data regarding perioperative fluid administration were missing in 4 patients, impeding the calculation of FII in these cases. Additionally, BT was not recorded in 114 patients. Thus 1,382

Table 1. Patient characteristics and perioperative data

	Fluid infusion index			Body temperature ^a		
	< 2.71 mL/kg/h (n = 461)	2.71 - 5.64 mL/kg/h (n = 460)	> 5.64 mL/kg/h (n = 461)	≤ 35.4 °C (n = 203)	35.5 - 37.5 °C (n = 1013)	≥ 37.6 °C (n = 56)
Age, median (5%-95%), yrs	62 (29-82)	63 (31-84)	67 (31-87)	66 (42-86)	64 (30-85)	52 (21-78)
Males, n (%)	218 (47.3)	205 (44.6)	154 (33.4)	56 (27.6)	429 (42.3)	36 (64.3)
Body mass index, median (5%-95%) ^b	26 (20-39)	25 (19-35)	23 (17-32)	24 (18-31)	25 (18-36)	25 (18-38)
ASA physical status score, n (%)						
1	139 (30.2)	129 (28.0)	105 (22.8)	54 (26.6)	274 (27.0)	19 (33.9)
2	239 (51.8)	260 (56.5)	249 (54.0)	116 (57.1)	544 (53.7)	30 (53.6)
3	82 (17.8)	70 (15.2)	100 (21.7)	32 (15.8)	190 (18.8)	7 (12.5)
4	1 (0.2)	1 (0.2)	7 (1.5)	1 (0.5)	5 (0.5)	0 (0.0)
Emergency surgery, n (%)	95 (20.6)	106 (23.0)	181 (39.3)	23 (11.3)	283 (27.9)	44 (78.6)
Daily smoker, n (%)	137 (30.0)	128 (27.8)	150 (32.5)	49 (24.1)	311 (30.7)	17 (30.4)
Diabetes mellitus, n (%)	38 (8.2)	34 (7.4)	32 (6.9)	10 (4.9)	85 (8.4)	1 (1.8)
SENIC ^c , n (%)						
1	120 (26.0)	115 (25.0)	218 (47.3)	59 (29.1)	342 (33.7)	25 (44.6)
2	253 (54.9)	264 (57.4)	186 (40.3)	109 (53.7)	508 (50.1)	25 (44.6)
3	77 (16.7)	73 (15.9)	49 (10.6)	31 (15.3)	149 (14.7)	4 (7.1)
4	11 (2.4)	8 (1.7)	8 (1.7)	4 (2.0)	14 (1.4)	2 (3.6)
NNISS ^d , n (%)						
0	154 (33.4)	199 (43.3)	246 (53.4)	88 (43.3)	451 (44.5)	21 (37.5)
1	223 (48.4)	172 (37.4)	168 (36.4)	87 (42.9)	403 (39.8)	22 (39.3)
2	70 (15.2)	84 (18.3)	43 (9.3)	27 (13.3)	143 (14.1)	11 (19.6)
3	14 (3.0)	5 (1.1)	4 (0.9)	1 (0.5)	16 (1.6)	2 (3.6)
80% oxygen, n (%)	230 (49.9)	227 (49.3)	226 (49.0)	102 (50.2)	503 (49.7)	32 (57.1)
Surgical procedure, n (%)						
Colorectal	205 (44.5)	225 (48.9)	202 (43.8)	110 (54.2)	448 (44.2)	11 (19.6)
Gynaecological	104 (22.6)	89 (19.3)	74 (16.1)	59 (29.1)	206 (20.3)	0 (0.0)
Small-bowel	41 (8.9)	47 (10.2)	69 (15.0)	15 (7.4)	125 (12.3)	7 (12.5)
Appendectomy	43 (9.3)	46 (10.0)	35 (7.6)	1 (0.5)	93 (9.2)	24 (42.9)
Other ^e	68 (14.8)	53 (11.5)	81 (17.6)	18 (8.9)	141 (13.9)	14 (25.0)
Diagnosis, n (%)						
Cancer	253 (54.9)	247 (53.7)	211 (45.8)	134 (66.0)	511 (50.4)	8 (14.3)
Benign neoplasm	33 (7.2)	38 (8.3)	37 (8.0)	17 (8.4)	83 (8.2)	3 (5.4)
Appendicitis	39 (8.5)	48 (10.4)	34 (7.4)	2 (1.0)	87 (8.6)	25 (44.6)
Intestinal obstruction due to benign disease	24 (5.2)	26 (5.6)	74 (16.1)	8 (3.9)	100 (9.9)	7 (12.5)
Inflammatory bowel disease	20 (4.3)	30 (6.5)	29 (6.3)	8 (3.9)	67 (6.6)	2 (3.6)
Diverticulitis	27 (5.9)	16 (3.5)	14 (3.0)	9 (4.4)	38 (3.8)	2 (3.6)
Other ^f	65 (14.1)	55 (12.0)	62 (13.4)	25 (12.3)	127 (12.5)	9 (16.1)
Duration of surgery, median (5%-95%), min	158 (48-350)	145 (40-291)	97 (30-225)	140 (55-301)	130 (35-295)	89 (33-397)
Operation classification, n (%)						
Clean	114 (24.7)	97 (21.1)	107 (23.2)	48 (23.6)	252 (24.9)	8 (14.3)
Clean-contaminated	261 (56.6)	268 (58.3)	265 (57.5)	117 (57.6)	583 (57.6)	24 (42.9)
Contaminated	74 (16.1)	88 (19.1)	71 (15.4)	37 (18.2)	151 (14.9)	19 (33.9)
Dirty-infected	12 (2.6)	7 (1.5)	18 (3.9)	1 (0.5)	27 (2.7)	5 (8.9)
Surgical site infection, n (%)	87 (18.9)	91 (19.8)	94 (20.4)	40 (19.7)	192 (19.0)	14 (25.0)

Legends: ASA: American Society of Anesthesiologists; SENIC: Study of the Efficacy of Nosocomial Infection Control; NNISS: National Nosocomial Infection Surveillance System. ^a - Body temperature measured at the end of surgery. ^b - Calculated as weight in kilograms divided by squared height in meters. ^c - In the SENIC scoring system, 1 point is given for each of (1) presence of three or more diagnoses; (2) surgery lasting longer than 2 hours; (3) operation classified as contaminated or dirty-infected; (4) abdominal surgery.[27] ^d - In the NNISS scoring system, 1 point is given for (1) ASA score of 3, 4 or 5; (2) operation classified as contaminated or dirty-infected; (3) operation lasting longer than expected for the operative procedure being performed.[28] ^e Includes cholecystectomy, repair of hernia, gastric and hepatobiliary resections, nephrectomy and splenectomy. ^f - Includes perforated peptic ulcer and cholecystolithiasis.

and 1,272 patients were available for analysis of the association between FII or BT and SSI, respectively. SSI occurred in 272 of 1,382 (19.7%) patients (*Table 1*).

Some characteristics had a skewed distribution according to FFI and BT. Larger amounts of infused fluid per body weight were associated with high age, female gender, low body mass index, high ASA physical score, emergency surgery, low SENIC-score (27), low NNISS-score (28), small-bowel procedure, intestinal obstruction due to benign disease, and short duration of surgery.

Hyperthermia was more common in young male patients with a high body mass index, in emergency surgery, and in patients with dirty-infected surgical wounds. Patients undergoing prolonged surgical procedures were more prone to hypothermia.

Univariable Analyses

No significant association was found between FII and the incidence of SSI (*Table 2*). There was a significantly increased risk of SSI (OR = 3.15; $P = 0.01$) in patients having both emergency surgery and hypothermia (*Table 2*). A significant interaction ($P = 0.01$) was found

between the variables hypothermia and emergency surgery, indicating that the effect of hypothermia depended on whether the patient underwent surgery in an elective or emergency situation.

Multivariable Analyses

There was no significant association between SSI and FII when FII was included as a continuous variable (OR=1.03; $P=0.09$; OR given as a function of 1 mL/kg/h increase of FII). SSI occurred in 18.9% of the patients in the lower tertile FII group (OR=0.86; $P=0.41$) and in 20.4% in the upper tertile FII group (OR = 1.49; $P = 0.05$) compared with 19.8% in the reference group (*Table 3*). No statistically significant interaction ($P = 0.23$) was found between the allocation and FFI.

There was no significant association between SSI and BT when BT was included as a continuous variable (OR=0.89; $P=0.28$, OR given as a function of 0.1°C increase of BT) or a categorical variable. SSI occurred in 19.7% of the patients with hypothermia (OR=1.28; $P=0.25$) and in 25.0% with hyperthermia (OR=1.26; $P=0.52$) compared with 19.0% in the reference group (*Table 3*).

Table 2. Intraoperative fluid therapy and body temperature as risk factors for surgical site infection. Univariable analyses

Variable	Type of surgery	n	SSI (%)	Univariable OR (95% CI)	P
Fluid Infusion Index, continuous variable	Elective	1000	196 (19.6)	0.99 (0.95-1.02)	0.48
	Emergency	382	76 (19.9)	1.00 (0.97-1.04)	0.96
Fluid Infusion Index, categorical variable, (mL/kg/h)					
< 2.71	Elective	366	69 (18.9)	0.89 (0.62-1.29)	0.55
2.71 – 5.64	Elective	354	73 (20.6)	1	
> 5.64	Elective	280	54 (19.3)	0.92 (0.62-1.36)	0.68
< 2.71	Emergency	95	18 (18.9)	1.14 (0.56-2.35)	0.72
2.71 – 5.64	Emergency	106	18 (17.0)	1	
> 5.64	Emergency	181	40 (22.1)	1.39 (0.75-2.57)	0.30
Body temperature, continuous variable					
	Elective	922	179 (19.4)	1.18 (0.92-1.52)	0.20
	Emergency	350	67 (19.1)	0.87 (0.63-1.20)	0.38
Body temperature, categorical variable, (°C)					
≤ 35.4	Elective	180	31 (17.2)	0.85 (0.55-1.30)	0.45
35.5 – 37.5	Elective	730	144 (19.7)	1	
≥ 37.6	Elective	12	4 (33.3)	2.04 (0.60-6.85)	0.25
≤ 35.4	Emergency	23	9 (39.1)	3.15 (1.29-7.69)	0.01
35.5 – 37.5	Emergency	283	48 (17.0)	1	
≥ 37.6	Emergency	44	10 (22.7)	1.44 (0.67-3.11)	0.35

Legends: OR = odds ratio, CI = confidence interval

Table 3. Intraoperative fluid therapy and body temperature as risk factors for surgical site infection. Multivariable analyses

Variable	n	SSI (%)	Adjusted OR (95% CI) ^a	P
Fluid Infusion Index, continuous variable	1382	272 (19.7)	1.03 (1.00-1.06)	0.09
Fluid Infusion Index, categorical variable, mL/kg/h				
< 2.71	461	87 (18.9)	0.86 (0.60-1.23)	0.41
2.71 – 5.64	460	91 (19.8)	1	
> 5.64	461	94 (20.4)	1.49 (1.00-2.05)	0.05
Body temperature, continuous variable	1272	246 (19.3)	0.89 (0.71-1.10)	0.28
Body temperature, categorical variable, °C				
≤ 35.4	203	40 (19.7)	1.28 (0.84-1.93)	0.25
35.5 – 37.5	1013	192 (19.0)	1	
≥ 37.6	56	14 (25.0)	1.26 (0.63-2.50)	0.52

Legends: OR = odds ratio, CI = confidence interval

Discussion

The main finding was a trend towards an increased risk of SSI in patients who received a greater volume of intravenous fluid. No association was found between BT at the end of surgery and SSI. Thus, the study does not support the hypothesis that a restrictive intravenous fluid regimen and hypothermia could explain the absence of a reduction of SSI in patients assigned to 80% in the PROXI trial. An increased incidence of SSI was, however, found among the minority of hypothermic patients who underwent emergency surgery.

The effect of different fluid regimens on the incidence of complications, including SSI, after abdominal surgery has been assessed in several randomized trials (11, 14-18). A restrictive fluid volume regimen was associated with a significantly lower risk of postoperative complications in three trials (11, 16, 18). Although these trials did not assess the incidence of SSI in specific analyses, they all reported a lower incidence of SSI among patients randomized to the restricted fluid volume regimen. On the other hand, no difference in the incidence of SSI was found in three other trials (14, 15, 17). The total amount of intravenous fluid that was administered during and after surgery to patients assigned to the restricted fluid regimen varied considerably among the trials as did the definitions of the terms “intraoperative” and “postoperative” making impossible a

proper comparison of the fluid administration (11, 14-18). As opposed to the PROXI trial, the other trials included a smaller number and selected patients reducing the external validity of their findings.

It is widely agreed that perioperative warming reduces the incidence of SSI (19-21). Patients in the PROXI trial were all managed to avoid hypothermia aiming at a BT of 36 to 37°C (13, 22). Despite these efforts, 203 patients (16%) had a BT of ≤ 35.4°C at the end of surgery (mean 35.1°C). Although the mean BT of the patients with hypothermia in the PROXI trial corresponded to the temperatures recorded in trials that found an increased incidence of SSI among these patients, we were not able to detect the same association (19, 20). One explanation could be the lack of randomization to different temperature preserving regimens in our study as well as the possible occurrence of competing (unknown) risk factors for SSI in patients with normal or high BT. Hyperthermic patients had, for example, a much higher frequency of contaminated and dirty-infected procedures.

Comparing the present findings with the first trial favouring 80% oxygen, the overall median BT at the end of surgery was almost identical in the two groups of patients randomized to 80% oxygen (36.1°C vs. 35.9°C) (8, 9). Thus, local vasoconstriction due to hypothermia is an unlikely explanation as to why the PROXI trial did not report an effect of

80% oxygen on the incidence of SSI, as formerly suggested (10).

Hypothermia was associated with a significantly increased risk of SSI specifically in patients subjected to emergency surgery. The association between hypothermia during emergency surgery and SSI has been investigated in 524 trauma patients. Patients with SSI had a significantly lower mean intraoperative BT. Consistent with the present study, an intraoperative BT of 35°C was the most important predictor for SSI development (23). Hypothermia activates the sympathetic nervous system leading to peripheral vasoconstriction, reduced supply of oxygen to the wound, low partial pressure of oxygen and inhibition of the crucial oxidative bactericidal effect of neutrophils (4-6, 24). Moreover, hypothermia impairs innate immune functions (25). Patients undergoing emergency abdominal surgery may have sepsis and hypovolaemia. In addition, cardiovascular or respiratory dysfunction is more prevalent in these patients. Pain may also lead to peripheral vasoconstriction (26). Accordingly, patients undergoing emergency surgery should be considered particularly sensitive to hypothermia.

The strength of this study is the large number of patients included in the analyses, allowing multivariable analyses of several risk factors and the completeness of the 14-day follow-up with regard to the rate of SSI as the primary outcome. We believe that the FFI provided a useful measure of the fluid therapy in individual patients, taking body weight and duration of surgery into consideration. The PROXI trial included a variety of patients undergoing elective or emergency laparotomy due to gastrointestinal or gynaecological disease at various centres, suggesting substantial external validity of the results.

The present study has some limitations. The volume of fluid administration and actual BT depended on compliance with the protocol rather than random allocation. Accordingly, confounding by indication must be considered in the interpretation of the results, e.g. a larger amount of fluid may have been given to patients who were sicker. No objective meas-

ures of volume status, such as central venous pressure, blood lactate levels, or central venous oxygen saturation were recorded intraoperatively, although they may have been used to guide fluid therapy. Furthermore, the calculated FFI must be considered as an estimate of the volume of fluid given to each patient. BT at the end of surgery was not recorded in all cases and the mean temperature during surgery was not registered.

Conclusions

In conclusion the main finding was a trend towards an increased risk of SSI in patients who received a greater volume of intravenous fluid. Accordingly no association was found between BT at the end of surgery and SSI. Thus, a restrictive intravenous fluid regimen and hypothermia were unlikely explanations of the lack of benefit from allocation to 80% oxygen, as reported in the PROXI trial. The present study is consistent with findings in other studies demonstrating an increased incidence of SSI among patients with high volume of infused fluid during surgery. A BT $\leq 35.4^{\circ}\text{C}$ after emergency surgery was associated with an increased risk of SSI.

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Conflicts of Interest

None declared.

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