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Original article

Impact of peritoneal lavage temperature during laparotomy in a preterm peritonitis mouse model using cecal slurry

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ABSTRACT

Background: Peritoneal lavage (PL) during laparotomy is a treatment option for preterm bacterial peritonitis; however, its efficacy remains controversial. We investigated the effects of PL temperature during laparotomy on survival in a cecal slurry (CS)-induced preterm peritonitis mouse model.

Methods: Four-day-old pups that were intraperitoneally administered 1.8 mg/g CS solution underwent laparotomy through a 5-mm transverse incision 2 h after CS injection (sham group). An additional PL was established during laparotomy with 500 μl of 25°C, 35°C, and 45°C sterile saline, respectively (PL25, PL35, and PL45 groups). Postoperative 7-day survival, body temperature, and plasma and ascites cytokine concentrations were evaluated for each group.

Results: Postoperative 7-day survival rates in the sham, PL25, PL35, and PL45 groups were 52.9%, 56.3%, 33.3%, and 18.2% (p=0.097), respectively. Median BT changes between before and after surgery were −1.85°C, −2.30°C, −3.40°C, and −1.80°C for each group (p=0.0065). The median ascites MCP-1 and IL-6 concentrations (pg/ml) at postoperative 2 h were 32,432, 16,244, 6279, and 5100 (p=0.049) and 22,346, 11,537, 5519, and 4535 (p=0.076), and plasma MCP-1 and IL-6 concentrations (pg/ml) were 68,687, 16,327, 9277, and 1868 (p=0.084) and 112,290, 14,415, 11,403, and 4113 (p=0.123) for each group, respectively.

Conclusion: Postoperative 7-day survivals were slightly improved by PL with 25°C sterile saline, however decreased by increasing PL temperatures to 35°C and 45°C in a CS-induced preterm peritonitis mouse model. As PL temperature was increased, both plasma and ascites MCP-1 and IL-6 concentrations tended to be suppressed, suggesting to decrease postoperative survivals.

1. Introduction

Peritonitis in preterm infants is commonly associated with intestinal perforation caused by necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP), or meconium-related ileus (MRI) [1–3]. Although the survival of preterm infants, especially extremely low-birthweight infants, has increased over the last few decades owing to improvements in neonatal intensive care and surgical techniques, bacterial peritonitis complicated by bowel perforation remains a fatal condition [4]. A recent report has shown that the mortality rate of preterm bowel perforation is as high as 28.7% even with appropriate medical and surgical treatment [5], and it is an urgent issue worldwide to improve survival rate for preterm peritonitis.

Laparotomy (LAP) is a standard treatment option for preterm fatal bacterial peritonitis with intestinal perforation; however, the appropriate procedure remains controversial [5–7]. Additional peritoneal lavage (PL) is an effective option for reducing intra-abdominal bacterial contamination and protecting against progressive sepsis [8–10]. In the clinical setting, PL during LAP has been widely used and shown to improve survival and sepsis as a treatment for acute appendicitis and colon perforation in adult patients [8]. Moreover, in animal studies, a meta-analysis investigating the efficacy of PL in adult peritonitis animal models demonstrated that PL with normal saline improves survival rates [11]. However, its efficacy in treating bacterial peritonitis in preterm infants remains unknown.

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In 2007, Wynn et al. first established a neonatal peritonitis mouse model induced by cecal slurry (CS), which involved intraperitoneal administration of adult cecal contents suspended in dextrose, for 5–7 days postpartum (P5-7) in newborn mice [12]. In addition, several studies have used CS-induced P5-7 mice as the immunological equivalent of term human neonates [13–15]. In 2017, Fujioka et al. successfully created a mouse model of preterm peritonitis-induced polymicrobial sepsis by intraperitoneal injection of CS in 4-day-old (P4) mice pups [16]. Based on previous studies by Fujioka et al., P4 mice have been considered immunologically equivalent to preterm infants, and the pathogenesis of sepsis and peritonitis in preterm infants has been elucidated [16–20].

The impact of hypothermia should be considered when examining the effects of PL on survival in a preterm peritonitis mouse model because postoperative hypothermia in preterm infants is associated with increased mortality [21]. Regarding hypothermia in experimental adult peritonitis animal models, several reports have shown that survival rates improved to prevent peritonitis-induced hypothermia [22,23] and that warmed intraoperative PL prevented postoperative hypothermia [24]. However, no reports on PL and its temperature in a preterm peritonitis mouse model have been noted.

This study aimed to investigate the effects of PL temperature during LAP on survival in a preterm peritonitis mouse model induced by an intraperitoneal injection of CS.

2. Materials and methods

2.1. Animals

Adult 6- to 8-week-old FVB/NJcl mice were obtained from CLEA Japan, Inc. (Tokyo, Japan) and housed under controlled temperature (21–23°C), humidity (30–70%), and lighting (12-h light/12-h dark) *ad libitum* with a standard rodent diet and water. All pups were bred with their mothers in the same environment throughout the study period. The pups were individually randomized within each litter to eliminate any litter bias effects. In addition, we used at least three different litters for survival experiments. This study was approved by the Institutional Animal Care and Use Committee (permission number: P190701).

2.2. Preparation of CS solution

As previously described, CS stock solution was prepared from cecum of adult mice and then stored in 1-ml aliquots at −80°C until subsequent experimental use [12,14,25]. Aliquots of the CS stock solution were thawed at room temperature to induce peritonitis.

2.3. Setting up CS concentration of 25% lethal dose (LD25)

P4 mice were administered various doses of CS intraperitoneally, followed by close monitoring of their health and survival for up to 7 days. The appropriate CS concentration was determined to be LD25 for seven days and used in subsequent experiments. In this study, the LD25 CS concentration was used based on the mortality rate of intestinal perforation in premature infants in a clinical setting [5].

2.4. LAP procedure for a preterm peritonitis mouse model

First, a preterm peritonitis mouse model was established by intraperitoneal injection of LD25 CS, and LAP was performed for 2 h after CS injection. The pups were fully anesthetized with isoflurane inhalation until the response to the stimulus disappeared and placed in the supine position on the operating table. A 5-mm transverse incision was made on the upper abdominal wall using a pair of scissors, and the abdomen was opened. The abdomen was left open for 1 min and then closed using two interrupted sutures with 6-0 PDS Plus (Ethicon Inc., Sommerville, NJ, USA, Fig. 1). After LAP, the pups were observed until spontaneous respiration and body movement fully recovered. The pups were then returned to the cage with their mother, and the postoperative course was observed.

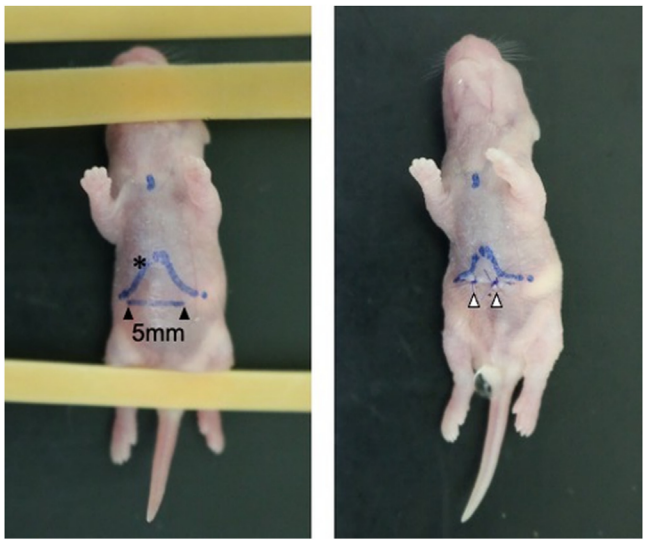

Fig. 1. LAP procedure. (*) Costal arch, (▲) transverse incision, (△) interrupted sutures. The head and lower limbs of the pups were fixed with rubber bands and placed in the supine position. A 5-mm transverse incision was made in the upper abdominal wall, and the abdomen was opened. The abdomen was closed using two interrupted sutures, LAP, laparotomy.

2.5. Additional PL during LAP for a preterm peritonitis mouse model

To assess the treatment effects of PL depending on the temperature during LAP for preterm peritonitis, additional PL at various temperatures was performed during LAP. PL was added during LAP for 1 min, with 500 μl: a sufficient volume for body size of 25°C, 35°C, and 45°C sterile saline, respectively (PL25, PL35, and PL45 groups). A temperature of 35°C corresponded to the mice average BT used in this experiment, and 25°C corresponded to ambient temperature. After PL, the wash solution was collected as much as possible by gentle wiping with gauze. The control group was set up with only LAP for 1 min without additional PL (sham group).

2.6. Evaluation of postoperative 7-day survival and body weight (BW) change

To evaluate the postoperative survival depending on the additional PL at various temperatures during LAP, pups were observed until 7 days after the operation. When they showed the following signs of impending death throughout the experiment: pale coloring, scattering, or absence of milk in the stomach, they were euthanized. In addition, BWs before and 24 h after surgery were measured, and the percentage of BW gain during postoperative 24 h (%24-h BWG) was evaluated in each group.

2.7. Perioperative body temperature (BT) change

To assess the effects of postoperative hypothermia associated with LAP and PL, BTs were measured before and immediately after surgery, and perioperative BT changes were calculated. BT was measured at the level of the xiphoid process using a noncontact infrared thermometer (CUSTUM Corporation, Tokyo, Japan) as previously described [22].

2.8. Measurement of the postoperative ascites and plasma cytokines

Ascites and blood were collected 2 h after LAP and PL in each group, and the pro- and anti-inflammatory cytokines were measured to assess postoperative local in the abdominal cavity and systemic inflammation. The pups were deeply anesthetized by isoflurane inhalation, and

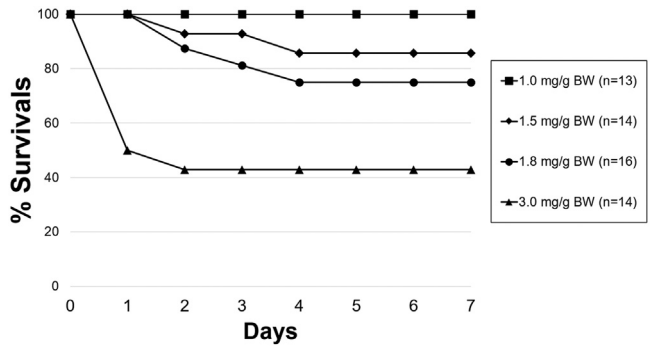

Fig. 2. Survival curves with various CS concentrations. Survival curves of P4 pups administered different doses of CS intraperitoneally: 1.0 (n=13), 1.5 (n=14), 1.8 (n=16), and 3.0 (n=14) mg/g BW, BW, body weight; LD25, lethal dose 25 %; P4, day 4 postpartum.

BW × 40 (μl) of sterile phosphate-buffered saline (PBS) was injected into the abdominal cavity with a 28G needle microsyringe puncture and collected as much as possible to be used as ascites. Blood was collected by cardiac puncture from the superior thoracic aperture through the mediastinum using a microsyringe with a 28G needle that was heparinized with 1,000 U/ml heparin. After ascites and blood collection, the pups were immediately sacrificed. The collected blood was stored on ice and immediately centrifuged at 4°C, 1,200 g for 15 min using a Sorvall Legend Micro 21R microcentrifuge (Thermo Fisher Scientific, Waltham, MA, USA), and the supernatant plasma was collected after centrifugation. The ascites and plasma were stored at −80°C until use.

The concentrations of ascites and plasma interleukin-6 (IL-6), monocyte chemotactic protein 1 (MCP-1), interleukin-10 (IL-10), tumor necrosis factor (TNF), interleukin-12p70 (IL-12p70), and interferon-γ (IFN-γ) were measured using a BD Cytometric Bead Array Mouse Inflammation Kit (BD Biosciences, San Jose, CA, USA) by a flow cytometry, according to the manufacturer's recommended protocol. Flow cytometry analysis was performed using the LSRFortessa X-20 (BD Biosciences, San Jose, CA, USA) and FCAP Array software (BD Biosciences, San Jose, CA, USA).

2.9. Statistical analyses

All statistical analyses were performed using JMP® 15 (SAS Institute Inc., Cary, NC, USA). Survival data were assessed using Kaplan–Meier plots with the log-rank test. Data on %24-h BWGs, perioperative BT change, and plasma and ascites cytokines were expressed as median values. These data were compared using the Kruskal–Wallis test, followed by a post-hoc Bonferroni test to compare all groups. Statistical significance was set at p value < 0.05.

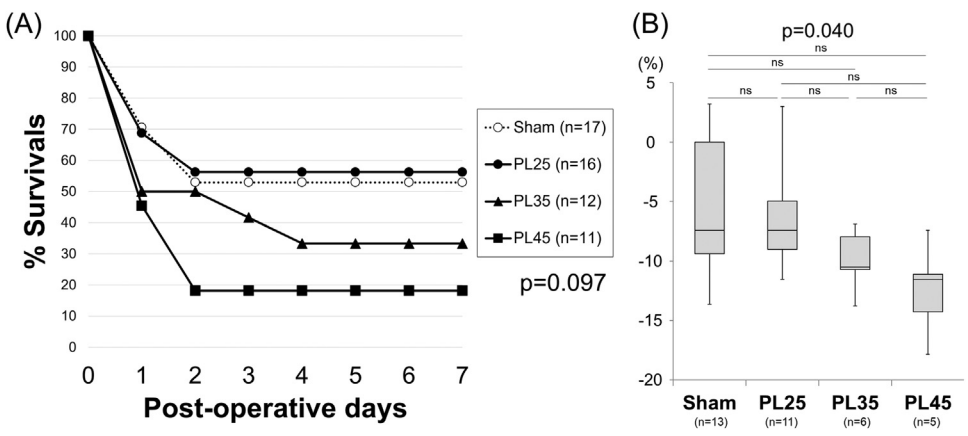

Fig. 3. Postoperative survival curves and %24-h BWG. (A) Postoperative survival curves for 7 days in the sham (n=17), PL25 (n=16), PL35 (n=12), and PL45 (n=11) groups, (B) %24-h BWG in the sham (n=13), PL25 (n=11), PL35 (n=6), and PL45 (n=5) groups, BWG, body weight gain; ns, not significant; %24 h, percent 24 h; PL, peritoneal lavage.

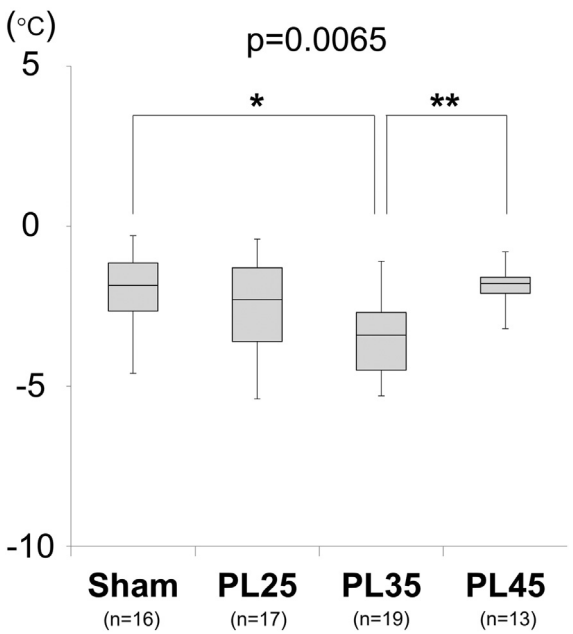

Fig. 4. Perioperative BT change. BT changes before and after LAP in the sham (n=16), PL25 (n=17), PL35 (n=19), and PL45 (n=13) groups, BT, body temperature. *p<0.05, **p<0.01.

3. Results

3.1. Determination of CS injection volume for LD25

The appropriate CS concentration was set up to correspond to a 25% mortality rate at 7 days after CS intraperitoneal injection. The survival rates of P4 pups administered 1.0 (n=13), 1.5 (n=14), 1.8 (n=16), and 3.0 (n=14) mg/g BW CS intraperitoneally were 100.0%, 85.7%, 75.0%, and 42.9%, which demonstrated a dose-dependent rise in mortality with increasing intraperitoneal injected CS dose (Fig. 2). The LD25 of the CS concentration was interpolated to be 1.8 mg/g BW.

3.2. Postoperative 7-day survivals and BW assessment

Postoperative 7-day-survivals in the sham (n=17), PL25 (n=16), PL35 (n=12), and PL45 (n=11) groups were 52.9 %, 56.3%, 33.3%, and 18.2%, respectively (p=0.097, Fig. 3A). P4 pup BW typically increased by 20% to 30 % for 24 h; however, the %24-h BWG in the sham (n=13), PL25 (n=11), PL35 (n=6), and PL45 (n=5) groups were −7.4%, −7.4%, −10.5%, and −11.5% (p=0.040, Fig. 3B), but no significant differences were noted between any two groups.

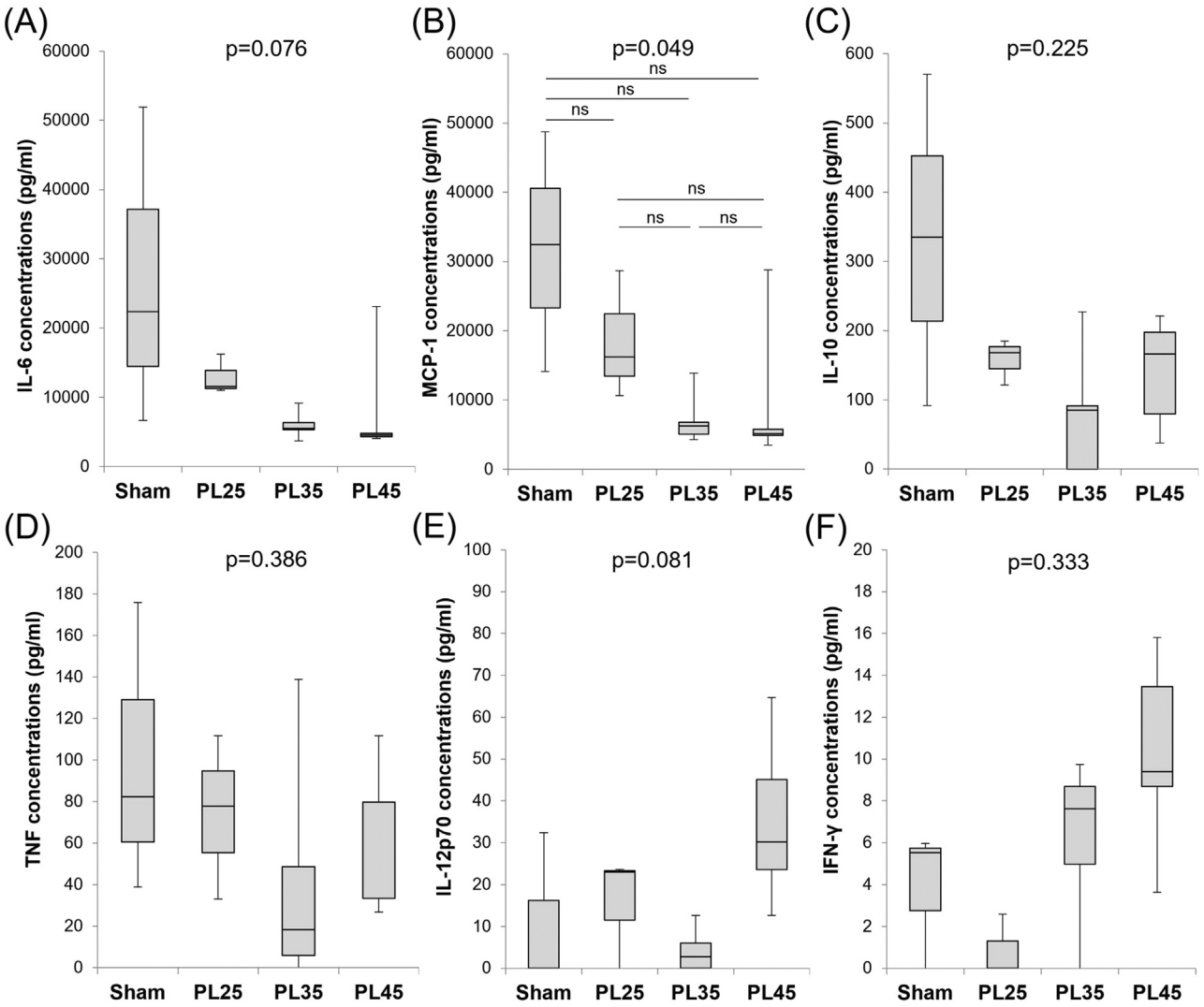

Fig. 5. Postoperative ascites cytokine concentrations at 2 h after LAP and PL (n=3-5). Median ascites: (A) IL-6, (B) MCP-1, (C) IL-10, (D) TNF, (E) IL-12p70, and (F) IFN-γ concentrations (pg/ml) IFN-γ, interferon-γ; IL-6, interleukin-6; IL-10, interleukin-10; IL-12p70, interleukin-12p70; LAP, laparotomy; MCP-1, monocyte chemotactic protein 1; ns, not significant; PL, peritoneal lavage; TNF, tumor necrosis factor.

3.3. Perioperative BT change

BT changes from before to after LAP and PL in the sham (n=16), PL25 (n=17), PL35 (n=19), and PL45 (n=13) groups were −1.85°C, −2.30°C, −3.40°C, and −1.80°C, respectively (p=0.0065, Fig. 4). The perioperative BT changes in the PL35 group were significantly lower than those in the LAP and PL45 groups (p=0.043 and p=0.0080, respectively).

3.4. Postoperative ascites and plasma cytokine levels 2 h after LAP

The median ascites IL-6, MCP-1, IL-10, TNF, IL-12p70, and IFN-γ concentrations (pg/ml) at 2 h after LAP and PL in a CS-injected peritonitis mouse were 22,346, 11,537, 5519, and 4535 (p=0.076); 32,432, 16,244, 6279, and 5100 (p=0.049); 335, 168, 85, and 166 (p=0.486); 82, 78, 18, and 80 (p=0.386); 0, 23, 3, and 30 (p=0.081); and 6, 3, 8, and 9 (p=0.333) for the sham, PL25, PL35, and PL45 groups, respectively (n=3-5, Fig. 5). Post hoc analysis showed no statistical differences in MCP-1 concentrations among the groups. Conversely, median plasma IL-6, MCP-1, IL-10, TNF, IL-12p70, and IFN-γ concentrations (pg/ml) at 2 h after LAP and PL were 112,290, 14,415, 11,403, and 4113 (p=0.123); 68,687, 16,327, 9277, and 1868 (p=0.084); 740, 520, 811, and 569 (p=0.724); 513, 479, 656, and 402 (p=0.172); 0, 28, 32, and 19 (p=0.298) and 6, 7, 12, and 9 (p=0.329) for each group (n=3–7, Fig. 6).

4. Discussion

In this study, we evaluated the effects of PL treatment during LAP using a previously constructed and reproducible preterm peritonitis mouse model induced by CS. Our findings showed that postoperative 7-day survival was slightly improved from 52.9% to 56.3% by additional PL with 25°C sterile saline during LAP and, moreover, worsen with the warmer PL temperatures (33.3% at 35°C and 18.2% at 45°C) in this mouse model. The mechanism of the increase in mortality as the PL temperature increased in this study suggested postoperative hypothermia and the suppression of both ascites and plasma MCP-1 and IL-6.

An adult CS-induced peritonitis mouse model is known to induce hypothermia and to increase mortality [22]. Our preterm peritonitis mouse models also showed a median 2.3°C decrease in BT 2 h after CS administration compared with sham models (data not shown). LAP under peritonitis conditions resulted in further decrease in postoperative BT, and the additional PL at 35°C significantly enhanced the decrease in BT. LAP itself is widely known to cause hypothermia because surgical field is exposed to the atmosphere with heat loss by evaporation and radiation

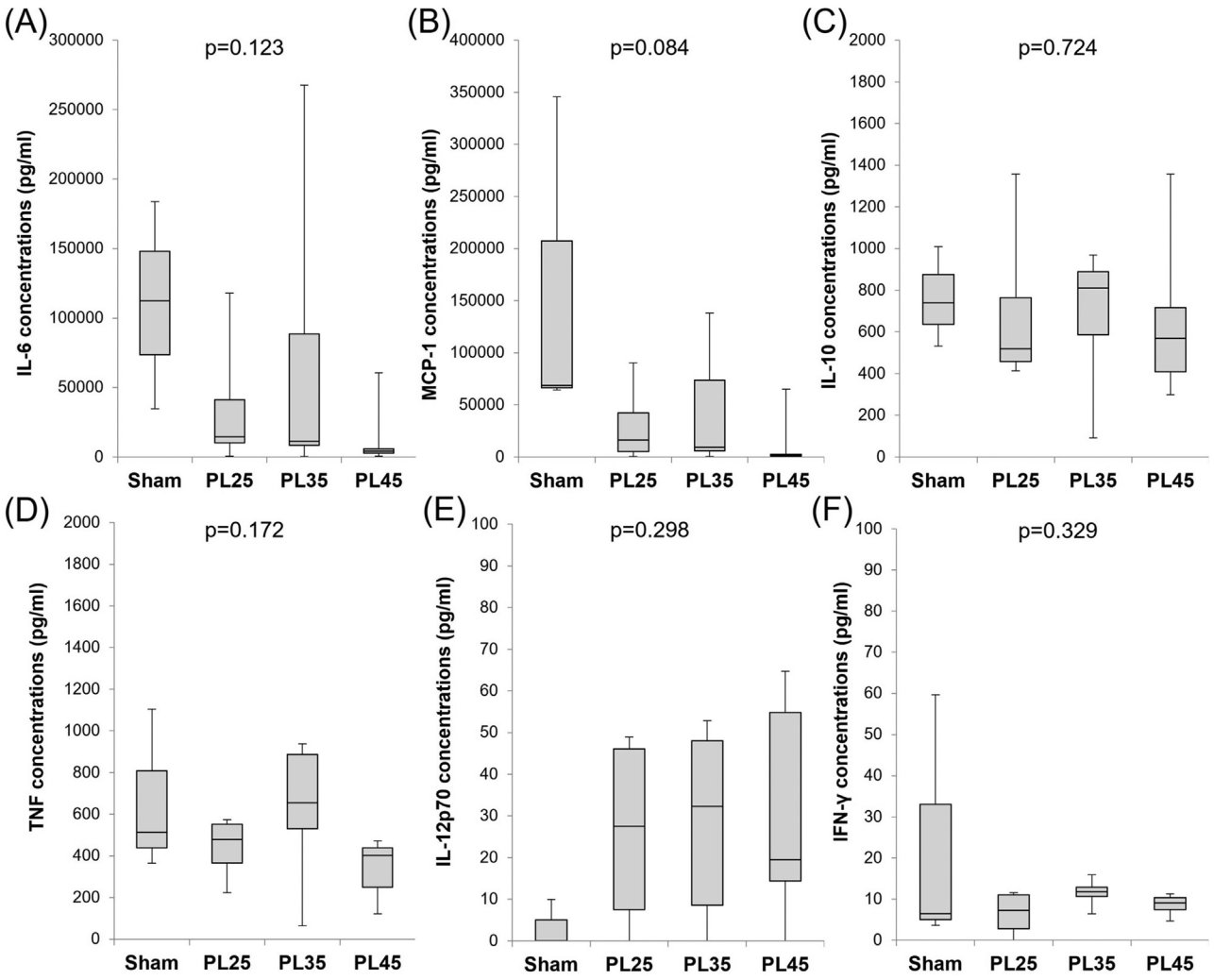

Fig. 6. Postoperative plasma cytokine concentrations at 2 h after LAP and PL (n=3-7). Median plasma (A) IL-6, (B) MCP-1, (C) IL-10, (D) TNF, (E) IL-12p70, and (F) IFN-γ concentrations (pg/ml) IFN-γ, interferon-γ; IL-6, interleukin-6; IL-10, interleukin-10; IL-12p70, interleukin-12p70; LAP, laparotomy; MCP-1, monocyte chemotactic protein 1; PL, peritoneal lavage; TNF, tumor necrosis factor.

[24]. In addition, it is known that fluids at higher temperatures in the surgical field stimulate parasympathetic nerves and induce vasodilation, then increase blood flow and heat loss from the abdomen to the atmosphere; therefore it was hypothesized that additional PL at 35°C, equivalent to normal P4 mouse BT, but higher than CS-induced hypothermia mouse BT, would increase heat loss due to vasodilation and to exacerbate postoperative hypothermia in our mouse model. Postoperative hypothermia in the PL35 group was suggested to be one of the reasons for the increased mortality compared to the Sham and PL25 groups.

Conversely, survival in the PL45 group was lower less than 20%, even though hypothermia was prevented by PL at a higher temperature than normal BT. Although no reports have been published on BT change with hyperthermic PL for preterm peritonitis, Barnes et al. demonstrated as well as our results that PL at 40°C during ileostomy in cats and small dogs less than 10kg prevented hypothermia compared to PL at 34°C [24]. While the benefits of preventing postoperative hypothermia, they conversely postulated that hyperthermic PL could lead to vasodilation and resultant hypotension [24], and Sanda et al. reported that hyperthermic intraoperative PL in an adult rabbit peritonitis model worsened the prognosis owing to abdominal compartment syndrome [26]. Furthermore, Kappas et al. revealed that intraoperative hyperthermic PL at 45–60°C normal saline damaged the serosa and promoted intra-abdominal adhesions in an adult peritonitis rat model [27]. Thus, hyperthermic PL postulated to lead to increased mortality due to various adverse factors, despite prevention of hypothermia, in our preterm peritonitis mouse model.

Then pro- and anti-inflammatory cytokines in the ascites and plasma 2 h after LAP and PL were evaluated to clarify the association between hypothermia and increased mortality. Our results showed that the local ascites MCP-1 and IL-6 levels tended to be suppressed as the PL temperature increased. PL itself might cause washout of immune responsible cells, such as neutrophils or macrophages in the abdominal cavity, which results in the suppression of pro-inflammatory cytokine release. In addition, the plasma MCP-1 and IL-6 levels revealed concomitant trends with those in the ascites fluid. It was speculated that the suppression of local IL-6 and MCP-1 levels in the abdominal cavity contributed to the systemic suppression of these cytokines, which was also associated with decreased survival. It also correlated with BW loss at 24 h postoperatively, reflecting systemic inflammation.

The association between pro-inflammatory cytokines and hypothermia under peritonitis conditions remains controversial in previous studies in adult animal models [23,28–30]. In our data from a preterm peritonitis mouse model, hypothermia by LAP and PL tended to decrease ascites and plasma MCP-1 and IL-6 levels in a temperature-dependent manner. Interestingly, Carpenter et al. showed that hypothermia inhibits the activity and phagocytosis of neutrophils in the abdominal cavity [23]. In preterm infants, the immune system, including phagocytosis,

is immature [31]; thus, we speculated that the inhibition of phagocytic activity by hypothermia, in addition to phagocytic cell loss by PL, might be related to temperature-dependent MCP-1 and IL-6 suppression. Further research is needed to characterize temperature-related immune responses in preterm peritonitis mouse models.

This study had some limitations. First, we did not evaluate organ damage associated with the suppression of systemic pro-inflammatory cytokines, although we confirmed that BW reduction, a measure of circulatory dynamics, contributed to increased mortality. Second, clinical intestinal perforation is typically fatal owing to persistent bacterial peritonitis; however, in this mouse model, CS was administered intraperitoneally only once. Therefore, this mouse model is difficult to evaluate only in the acute phase immediately after CS administration, as it can self-heal over a long period of time. Finally, the mortality rate with CS administration alone was 25%, however it increased to approximately 50% in addition to LAP. This result revealed that the impact of the surgical stress by LAP might not be negligible, and further research is needed to evaluate the surgical stress for preterm peritonitis.

This was the first study to build the survivable LAP technique for small and fragile P4 mice to evaluate surgical treatment for preterm peritonitis. Future studies should investigate the pathogenesis of peritonitis and develop a novel surgical treatment in our mouse model with an immature immune system.

In conclusion, postoperative 7-day survivals were slightly improved by PL with 25°C sterile saline, however decreased by increasing PL temperatures to 35°C and 45°C in a preterm peritonitis mouse model induced by CS. As PL temperature was increased, both plasma and ascites MCP-1 and IL-6 concentrations tended to be suppressed, suggesting to decrease postoperative survivals.

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Author contributions

S.Y. and Y.O. contributed to the conception and design of the study; S.Y., Y.S., H.M., and M.S. performed the experiments; S.Y. performed statistical analyses and drafted the manuscript; Y.O., M.S., S. I., K.F., S.I., Y.K., A.W., K.U., Y.T., and Y.B. reviewed the manuscript and supervised the entire study process. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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