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Differences in the Leukocyte Response to Incision During Upper Abdominal Surgery with Epidural Versus General Anesthesia

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Abstract

Epidural anesthesia attenuates surgical stress responses, such as the immune reaction and the pituitary hormone response. In the present study, we investigated the leukocyte response to initial surgical stimulation during upper abdominal surgery. Twenty adult patients (American Society of Anesthesiologists physical status I～II) undergoing elective upper abdominal surgery were randomly assigned to an epidural anesthesia group or a general anesthesia group. An epidural catheter for postoperative pain relief was inserted into all patients before induction. In the epidural anesthesia group, patients obtained preemptive analgesia from Th4 to Th12 with 2% mepivacaine, whereas general anesthesia was maintained with 2 L of oxygen, 4 L of nitrous oxide, and 1% to 3% isoflurane. Changes in the leukocyte count and leukocyte subset distribution were determined before induction (baseline), immediately after induction, 5 minutes after induction, 5 minutes after skin incision, and 5 minutes after peritoneal incision. The changes were significantly different between the groups throughout the observation period ($p<0.0001$). The general anesthesia group demonstrated an increase in the leukocyte count compared with the baseline data 5 minutes after skin incision and 5 minutes after peritoneal incision ($p<0.01$). Moreover, these counts were significantly higher in the general anesthesia group than in the epidural anesthesia group ($p<0.05$). The subset distributions were also significantly different between the groups throughout the observation period ($p<0.0001$). In the general anesthesia group, neutrophils decreased and lymphocytes increased significantly compared with baseline ($p<0.05$). Moreover, lymphocyte distribution was significantly higher in the general anesthesia group than in the epidural anesthesia group 5 minutes after peritoneal incision. Thus, anesthesia modifies the early response of leukocytes to surgical stress. The link between the early leukocyte response to surgery and postoperative outcome is the next subject of investigation.

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Key words: preemptive epidural analgesia, general anesthesia, leukocyte, surgical stress, upper abdominal surgery

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Introduction

Patients undergoing major abdominal surgery are subjected to early surgical stress triggered by incisions of the skin and peritoneum[1]. Such stress induces endocrine and immune responses, which may affect operative outcomes. Skin and peritoneal incisions increase levels of pituitary hormones, such as adrenocorticotropic hormone and arginine vasopressin[1], and increase the response of $CD4^+$ and $CD8^+$ cells[2]. Therefore, it is reasonable to perform proper perioperative care, including anesthesia, in an attempt to reduce the very early unfavorable events of abdominal surgery.

Epidural anesthesia is one therapeutic option. Although they have not been proven in abdominal surgery[3], beneficial effects of epidural anesthesia over general anesthesia on perioperative outcome have been demonstrated in major orthopedic surgery[4]: a significant decrease in mortality, deep venous thrombosis, pulmonary embolism, myocardial infarction, pneumonia, respiratory depression, and transfusion requirement. Moreover, recent studies have shown that, in major abdominal surgery, epidural anesthesia has advantageous effects on tissue metabolism[5], the endocrine response[1,6,7], and the immune response[8]. However, most of these studies examined only postoperative events, with few focusing on the start of surgery[1,7].

The purpose of the present study was to investigate whether epidural anesthesia attenuates early surgical stress in abdominal surgery when compared with general anesthesia. To this end, we used leukocyte counts and subset distributions, simple indicators of systemic inflammation and stress in critically ill patients[9], to monitor responses to the initial stress immediately after skin and peritoneal incisions.

Patients and Methods

This study was approved by Kitamurayama Hospital, Yamagata, Japan, and informed consent was obtained from all patients. Twenty adult patients (American Society of Anesthesiologists physical status I～II) undergoing elective upper abdominal surgery were randomly assigned to one of two groups: an epidural anesthesia group (n=10) or a general anesthesia group (n=10). Patients with preoperative signs of infection (leukocyte count > 10,000/mm^3, body temperature > 38℃, and C-reactive protein > 2 mg/d*l*) and preexisting renal, hepatic, or heart disease were excluded.

After intramuscular premedication with 0.5 mg atropine and 0.06 mg/kg midazolam, an epidural catheter was inserted into each patient at the Th8-9 or Th9-10 interspace. The tip was advanced 4 to 5 cm into the epidural space. A 22-G Teflon catheter was placed in the left radial artery under local anesthesia with 1% lidocaine and used for collecting blood samples. Infusion was started with 500 m*l* of physiological saline with 6% hydroxyethyl starch (Salinhes; Kyorin Pharmaceutical Co., Ltd., Tokyo, Japan) followed by sufficient infusion of acetated Ringer's solution (Veen F; Nikken Chemicals Co., Ltd., Tokyo, Japan) to maintain blood pressure. Anesthesia was induced with 5 mg of thiamylal and 0.1 to 0.15 mg/kg of vecuronium, after which tracheal intubation was performed.

In the epidural anesthesia group, a test dose of 2 mL of 1% lidocaine was given via the epidural catheter to confirm that no intrathecal block occurred before induction. Five minutes later, 12 m*l* of 2% mepivacaine was used to induce analgesia. All patients in this group had analgesia from at least Th4 to Th12 within 15 minutes after mepivacaine administration. After tracheal intubation, all patients were ventilated with 66% nitrous oxide in oxygen. A further 6 to 8 m*l* of 2% mepivacaine was added 40 to 45 minutes after administration of the first 12 m*l*. In the general anesthesia group, anesthesia was maintained with 66% nitrous oxide and 1% to 3% isoflurane in oxygen. All patients in both groups were given an adequate amount of morphine and 0.25% bupivacaine via the epidural catheter for postoperative pain relief. The same surgical team performed all operations to minimize differences in surgical technique.

Blood samples were collected from the radial artery catheter before induction (baseline), immediately after induction (time 1), 5 minutes after

Table 1 Demographic data of patients

	General anethesia	Epidural anesthesia
Number of patients	10	10
Sex (male/female)	4/6	8/2
Age (years)	62 ± 10	67 ± 10
Body weight (kg)	56 ± 13	59 ± 9
performed surgery	gastrectomy (6) cholecystectomy (4)	gastrectomy (7) cholecystectomy (3)

Data are shown as means ± SD

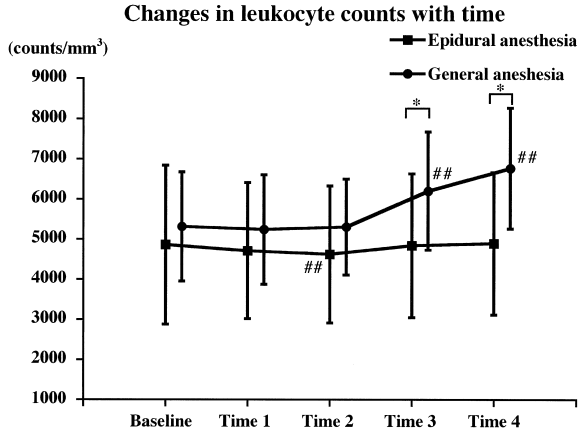

Fig. 1 Leukocyte count before induction (baseline), immediately after induction (time 1), 5 minutes after induction (time 2), 5 minutes after skin incision (time 3), and 5 minutes after peritoneal incision (time 4). Two-way repeated measures ANOVA was performed to determine significant differences ($p<0.0001$). $^{*}p<0.05$ significant difference between groups, $^{\#\#}p<0.01$ significant difference with baseline.

induction (time 2), 5 minutes after skin incision (time 3), and 5 minutes after peritoneal incision (time 4). Leukocyte counts were determined with an analyzer (Sysmex SE-9000: Sysmex Corp., Hyogo, Japan), and subset distributions were determined manually under a microscope.

Statistical Analysis

The Chi-square test was used to estimate differences in demographic data. Two-way repeated-measures analysis of variance (ANOVA) was used to estimate absolute changes in leukocyte counts and subset distributions in both groups. If a significant difference was observed, one-way repeated-measures ANOVA was performed for the same purpose. Post-hoc analysis was conducted using Fisher's protected least significant difference (PLSD) test when a significant difference was noted. The Mann-Whitney U-test was performed for comparisons between groups. The significance level was set at $P<0.05$.

Results

Demographic data of all patients are shown in **Table 1**; there were no significant differences in sex, age, body weight, and performed surgery between the groups.

The changes in leukocyte counts were significantly different between the groups throughout the observation period ($p<0.0001$). The general anesthesia group demonstrated an increase in leukocytes at skin incision (time 3) and at peritoneal incision (time 4) compared with the baseline data ($p<0.01$). Moreover, these counts were significantly higher in the general anesthesia group than in the epidural anesthesia group at these time points ($p<0.05$). In the epidural anesthesia group, the leukocyte counts 5 minutes after induction (time 2) were significantly lower than those at baseline ($p<0.01$) (**Fig. 1**).

Leukocyte subset distributions were also significantly different between the groups throughout the observation period ($p<0.0001$) (**Fig. 2**). In the general anesthesia group, neutrophil counts decreased and lymphocyte counts increased significantly compared with those at baseline ($p<0.05$) (**Fig. 3, 4**). Moreover, the lymphocyte subset was significantly higher in the general anesthesia group than in the epidural anesthesia group at peritoneal incision (time 4, $p<0.05$, **Fig. 4**).

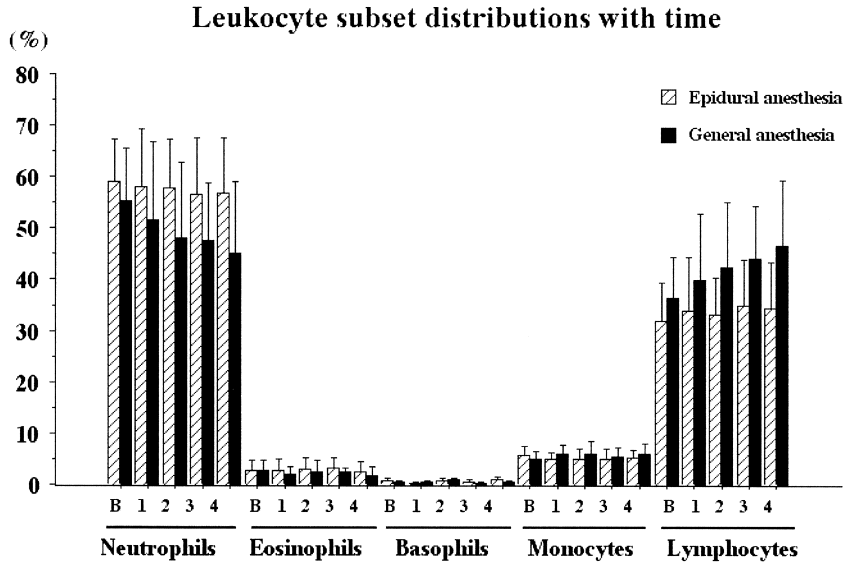

Fig. 2 Distribution of the leukocyte subsets before induction (baseline), immediately after induction (time 1), 5 minutes after induction (time 2), 5 minutes after skin incision (time 3), and 5 minutes after peritoneal incision (time 4). Two-way repeated-measures ANOVA was performed to determine significant differences ($p<0.0001$).

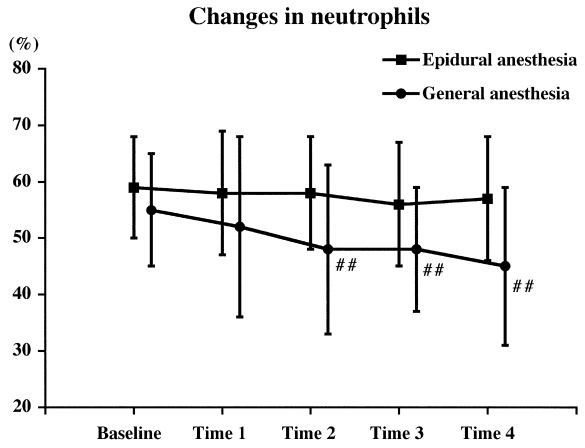

Fig. 3 Neutrophil count before induction (baseline), immediately after induction (time 1), 5 minutes after induction (time 2), 5 minutes after skin incision (time 3), and 5 minutes after peritoneal incision (time 4). $^{\#\#}p<0.01$ significant difference compared with baseline.

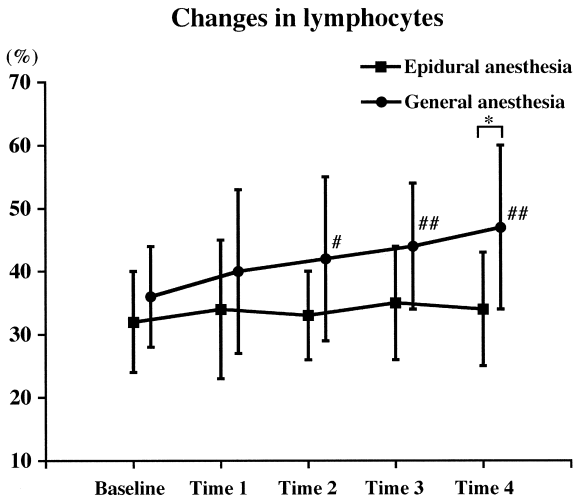

Fig. 4 Lymphocyte count before induction (baseline), immediately after induction (time 1), 5 minutes after induction (time 2), 5 minutes after skin incision (time 3), and 5 minutes after peritoneal incision (time 4). $^{*}p<0.05$ significant difference between groups, $^{\#}p<0.05$, $^{\#\#}p<0.01$ significant difference compared with baseline.

Discussion

We have demonstrated that the leukocyte response to early stimulation during upper abdominal surgery differs between epidural anesthesia and general anesthesia. Leukocyte counts in the general anesthesia group increased compared with baseline 5 minutes after skin and peritoneal incisions. Furthermore, the manner in which leukocyte subsets changed differed between the groups. Interestingly, a rapid response was not seen in the epidural anesthesia group. These findings suggest that the leukocyte response occurs

immediately after skin incision and can be modified by anesthesia.

The influence of anesthesia on leukocyte function has been examined[2,10–14] and was observed at 6 and 9 hours after skin incision. Volatile anesthetics (halothane, isoflurane, and sevoflurane) prevent human neutrophil adhesion to endothelial cells *in vitro* by reducing neutrophil activity[13]. Lidocaine, a local anesthetic, also inhibits human neutrophil function by suppressing inflammatory cytokines *in vitro*[11]. Both volatile and local anesthetics inhibit neutrophil function 6 to 9 hours after skin incision.

In this study, we used mepivacaine as a local anesthetic in the epidural anesthesia group and isoflurane as a volatile anesthetic in the general anesthesia group and found that the effects on neutrophil counts differed between the groups. That is, the neutrophil subset decreased in the general anesthesia group. If this decrease resulted from neutrophil adhesion to endothelial cells, general anesthesia might maintain neutrophil function; however, the study design dose not allow us to determine whether this effect was the result of suppressed neutrophil activity. The difference in sampling time compared with earlier studies could be another reason for the different responses between the groups. Moreover, the surgical stress examined here, skin and peritoneal incisions, might also have had effects different from those in earlier studies.

Fentanyl and Hypnorm® (the veterinary equivalent of the human anesthetic thalamonal) increase leukocyte rolling in rat skin, but pentobarbital does not[12]. Thus, pentobarbital was considered preferable for anesthesia induction in this study; we used thiamylal, which is pharmacologically identical to pentobarbital. On the other hand, vecuronium has been shown to cause a decrease in total lymphocytes after surgery[15]. Consequently, it is possible that vecuronium affected our results, but we do not believe it induced the differences between the groups.

In the present study, we focused on the response immediately after skin incision. To the best of our knowledge, this is the first study to investigate leukocyte function at this time. Leukocyte subsets, on the other hand, have been assessed after surgery in earlier studies. For example Volk et al. compared the effects of postoperative epidural analgesia (continuous infusion of 0.125% ropivacaine and 1.0 μg/m*l* sufentanil at a rate of 12 m*l*/h) on leukocytes and immune function during major spine surgery with the effects of intravenous analgesia using morphine[16]. Immediately after surgery, neutrophils and monocytes were shown to increase and lymphocytes were shown to decrease significantly, but there were no significant differences between epidural and intravenous analgesia. In abdominal hysterectomy, epidural anesthesia prevented postoperative lymphopenia and granulocytosis induced by general anesthesia[10]. In contrast, Akural et al. have shown that both leukocytes and neutrophils increase under preemptive epidural analgesia with sufentanil and general anesthesia (propofol with isoflurane) during abdominal hysterectomy, whereas lymphocytes increased under general anesthesia only 4 hours after surgery[17]. Consequently, there is no consensus on postoperative changes in counts and leukocyte subset distributions. Here, we found changes immediately after skin incision. These differences suggest that there is perioperative dynamic change in the leukocyte response at the beginning of surgery that could be modified by anesthesia.

Volk et al. have shown that postoperative epidural analgesia, but not intravenous analgesia, increases B cells and the postoperative CD4/CD8 ratio and decreases natural killer cells[16]. Although these cells originate from lymphocytes, there was no significant difference in the number of leukocytes with either epidural or intravenous analgesia throughout their observation. They therefore concluded that postoperative epidural analgesia is important for modulating the systemic immune reaction, but they could not determine why. General anesthesia with isoflurane has also been shown to induce significant reductions in the number and function of $CD4^+$ cells during hysterectomy, whereas epidural anesthesia with bupivacaine significantly impairs $CD8^+$ cell function (observation period: 10 minutes and 48 hours after the start of surgery)[2]. Anesthesia has also been shown to affect natural killer cell activity,

but there is no difference between general and epidural anesthesia during hysterectomy[17] and upper abdominal surgery (no observation during surgery)[18]. Although comparison with our results would be interesting, we could not evaluate the effects of epidural analgesia on these immune functions with our study design. Changes in these immune functions during surgery, especially immediately after skin incision, and the effect of anesthesia on these changes should therefore be investigated in the future.

In this study, we demonstrated that anesthesia attenuates the response of leukocytes to surgical stimulation, i.e., skin and peritoneal incisions. Neutrophils continued to decrease after skin incision, while lymphocytes continued to increase in the general anesthesia group. This finding indicates that neutrophils were consumed at the site of incision while lymphocytes were stimulated to initiate immune functions, suggesting that a stress response, or immune reaction, is evoked by skin incision or peritoneal incision or both. This change in leukocyte subsets did not occur in the epidural anesthesia group. Despite these findings, we could not determine whether, in upper abdominal surgery, epidural anesthesia is superior to general anesthesia in terms of operative outcome. Further studies addressing the causal relation between the early leukocyte response to surgery and postoperative outcome are therefore necessary.

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