The Effects of Anesthesia and Surgery on Count and Function of Neutrophils

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The effects of anesthesia and surgery on neutrophil count, chemotaxis and neutrophil alkaline phosphatase (NAP) score were investigated in 10 patients who had elective spine surgery. Plasma levels of adrenaline, noradrenaline and cortisol were measured and correlations between hormonal levels and neutrophil count and function were assessed.

Neutrophil count started increasing after the initiation of surgery, reached the highest level at 3 hours after surgery, and decreased gradually toward preanesthetic level on 3rd postoperative day. The increase in band cell: segment cell ratio is prominent, whereas lymphocytes decreased significantly. Neutrophil chemotaxis and spontaneous migration were increased significantly from the end of operation to 1st postoperative day. NAP score, assumed to reflect the neutrophil phagocytic activity, lowered transiently during anesthesia, then increased 1.6 times more than preanesthetic level on 1st postoperative day. It was indicated that the increased cortisol release rather than adrenaline due to body response to surgical stress might induce neutrophilia, and that the elective spine surgery might not be deleterious to the neutrophil function. (Key words: surgical stress, cortisol, catecholamine, neutrophil chemotaxis, neutrophil alkaline phosphatase)

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The role of the neutrophil in host defence against microbial infection is well established and recently attention has been focused on defective neutrophil function induced by surgery[1–4]. It is well known that the blood levels of ACTH, catecholamines and corticosteroids are elevated due to the endocrine response to the surgical stress[5]. Adrenaline is reported to induce predominant lymphocytosis accompanied by relative neutrophilia and then lead to slight lymphocytopenia[6]. Cortisol is stated that to produce marked neutrophilia with variable degree of lymphocytopenia[7]. El-Maallem et al.[1] showed that neutrophil functions change during neutrophilia, and that neutrophil count correlate inversely to leucocyte microbicidal activity. When neutrophil functions such as chemotaxis, phagocytosis and neutrophil alkaline phosphatase (NAP) activity were impaired, so incidence of opportunistic infections could be rised[4,8]. Concerning the effects of anesthesia and surgery on the neutrophil chemotactic and phagocytic functions, there are some arguments. Some reports have shown suppression on neutrophil function[9,10], while van Dijk et al.[2] found no change in phagocytosis after surgery. Mollit et al.[3] reported the enhanced neutrophil function following elective surgery in healthy children. The aim of this study was to clarify the relationship between hormonal alterations and neutrophil function due to anesthesia and surgical stress.

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Subjects and Methods

Seven male and 3 female patients, who

Table 1. Clinical characteristics of subjects

Subjects number	Age (yrs)	Sex	Diagnosis	Operation
1	53	M	OPLL of CS	Laminoplasty
2	47	F	Spondylolisthesis of LS	PSF
3	59	M	Spinal Fracture of LS	PSF with HI
4	50	F	Spondylolysis of LS	Laminectomy
5	59	M	Myelopathy of CS	Laminoplasty
6	47	M	Spinal Fracture of LS	PSF with HI
7	56	M	Canal Stenosis of LS	Laminectomy
8	74	M	Canal Stenosis of LS	Laminectomy
9	38	F	Canal Stenosis of LS	Laminectomy
10	34	M	CDH	ASF

Abbreviations
OPLL = Ossification of the Posterior Longitudinal Ligament; CS = Cervical Spine; LS = Lumbar Spine; CDH = Cervical Disc Herniation;
PSF = Posterior Spinal Fusion; HI = Harrington Instrumentation; ASF = Anterior Spinal Fusion

had elective spine surgery, were selected. Their ages ranged from 34 to 74 years (mean 53 ± 9.5 years). Patients characteristic are listed in table 1. They had no episode of endocrine, hepatic, renal or cardiovascular dysfunction, and were not receiving any specific medications.

The patients received no preanesthetic medication. Before the induction of anesthesia, radial artery was canulated for blood pressure monitoring and blood sampling. Anesthesia was induced with intravenous administration of thiopental (4 mg per kilogram) and pancuronium bromide (0.1 mg per kilogram) to facilitate endotracheal intubation. Anesthesia was maintained with enflurane (0.5–1.0%) and 60% N_2O in oxygen. Additional pancuronium was given whenever required. Patients were ventilated mechanically to keep Pa_{CO_2} 30–40 mmHg. Duration of surgery was 177 ± 17 min, and that of anesthesia was 238 ± 16 min. Hematocrit value was 42.0 ± 1.46% preoperatively, 37.5 ± 1.54% at the end of operation, and 32.9 ± 1.91% on 3rd postoperative day. During surgery 49 ± 34.8 ml of blood, and 1,675 ± 185.8 ml of fluid were given. The urine output was 253 ± 46.1 ml during surgery. All values were expressed as mean ± standard error of the means.

Blood samples were obtained before the induction of anesthesia, 1 min after endotracheal intubation, 40 min after intubation which corresponding just before skin incision, 2 hr after skin incision, at the completion of surgery, after extubation, 3 hr, 6 hr after surgery, and on 1st and 3rd postoperative day. The following measurements were done.

Adrenaline and noradrenaline in plasma were measured by high performance liquid chromatography (HPLC) with electrochemical detector (VMD 101, Yanapac L-4000W, Yanagimoto, Co.,), and 3,4-dihydroxybenzylamine (Sigma Chemical Co., St Louis, MO., USA) was used as the internal standard[11]. Plasma cortisol concentration was measured with radioimmunoassay kit obtained from Dainabot Radioisotope Inc. (Tokyo, Japan).

The total leucocyte count in blood was measured with automatic Coulter counter (CC-800, Toa Medical Electronics Co., Kobe, Japan). Differential cell counts were measured on a May-Giemsa (Merck Inc. Co., Germany) stained smear, by counting 100 cells under microscope with an oil-immersion lens at a magnification of 1000 ×.

Chemotaxis and spontaneous migration of neutrophils were evaluated under agarose as reported in previous study[12] with slight

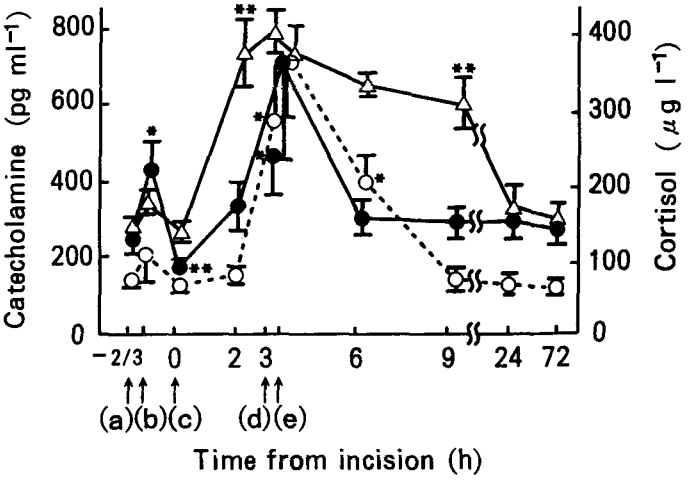

Fig. 1. The changes in plasma concentrations of noradrenaline (●—●), adrenaline (○--○) and cortisol (△—△) following anesthesia and surgery. (a), induction of anesthesia; (b), intubation; (c), incision; (d), end of surgery; (e), extubation. Values are expressed as mean ± SEM. $*P < 0.05$; $**P < 0.01$.

modifications. Neutrophils were separated from heparinized blood by density centrifugation with Ficoll 400 (Pharmacia Fine Chemicals AB, Sweden) - Conray (Daiichi seiyaku Co., Japan) solution (1.077 gram per cm^3). Five ml of agarose gel (1.2% agarose in Eagle's minimal essential medium (MEM) containing 10% heat-inactivated human serum) was poured into 60 mm tissue culture dish (Corning Glass Works Co., N.Y.). Six sets of three wells with a diameter of 3 mm and a distance of 3 mm were cut in a linear array. Ten μl of cell suspension containing 2.5×10^7 per μl neutrophils was placed in the central well of each set, zymosan (Sigma Chemical Co.) activated human serum and MEM as control were placed in outer wells. The dish was incubated for 2 hours at 37°C in a humidified atmosphere containing 5% CO_2 in air. The gel was removed after methanol - formalin fixation and Wright's stain was done. Migration distance was measured with Profile Projector (Model V-14, Nippon Kogaku Co., Japan). Chemotactic differential (CD) was calculated as chemotactic migration minus spontaneous migration. CD and spontaneous migration were presented as percentage for preanesthetic mean values.

Score of alkaline phosphatase activity in neutrophil (NAP score) was measured as follows; Blood smear was prepared on cover slide, air-dried and fixed for 30 seconds in formalin:methanol (1:9). The fixed cells were stained with the method described by Kaplow[13] with slight modification, using naphthol AS-MX phosphate and Fast Blue RR salt (Muto Chemical Co., Japan). The counterstain was performed with 1% safranin-O (Muto Chemical Co., Japan). Each cell of 100 neutrophils was rated from 0 to 4 according to number of blue granules in the cytoplasm. NAP scores, which were the summation of the rate of each cell decided above, were assumed to reflect the phagocytic activity of neutrophils. The possible ranges of this score were from 0 to 400.

Statistical analysis

Results were presented as means ± standard errors of the means (SEM). The probabilities for differences of data from corresponding preanesthetic values were tested by Student's t-test and differences were considered significant if $P \leqq 0.05$. Regression analyses of data were performed on data from preanesthesia to 6 hr after surgery and correlation coefficients (r) were calculated.

Results

The preanesthetic plasma concentrations of adrenaline, noradrenaline and cortisol were 148 ± 27, 250 ± 41 and 142 ± 26 pg per ml, respectively. As shown in figure 1 after intubation, plasma concentration of noradrenaline was increased significantly, while adrenaline and cortisol increased slightly,

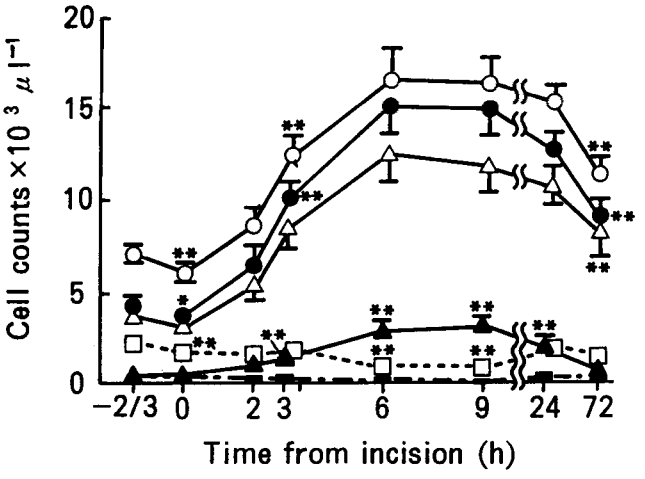

Fig. 2. Serial changes in whole blood leucocyte count (○—○), neutrophil count (●—●), segment cell count (△—△), band cell count (▲—▲), lymphocyte count (□---□) and monocyte count (■---■) in peripheral blood following anesthesia and surgery. Explanation for abscissa is as in figure 1. Values are expressed as mean ± SEM. *p <0.05; **p <0.01.

then became lower than the preanesthetic level before the skin incision. After the initiation of surgery, the plasma concentrations of these three hormones started increasing. The cortisol concentrations showed the steepest increase and reached the highest level (402 ± 75 pg per ml) at the end of surgery. They remained in rather higher level until 6 hr after surgery, and returned to the preanesthetic state on 1st postoperative day. The concentrations of adrenaline and noradrenaline increased significantly at the end of surgery, reached the peak level after extubation, and declined near preanesthetic level 3 to 6 hr after surgery.

The preanesthetic leucocytes count were as follows; total count of leucocyte 6,990± 564 (count per μl); total count of neutrophils 4,274 ± 466; segment cells 3,811 ± 329; band cells 463 ± 189; lymphocytes 2,115± 230 and monocytes 411 ± 53, respectively. Kinetics of leucocytes were shown in figure 2. During anesthesia total count of leucocytes, neutrophils and lymphocytes decreased to 84% ($P < 0.01$), 88% ($P < 0.05$) and 74% ($P < 0.01$) of preanesthetic level, respectively. After the initiation of surgery, these cells except lymphocytes increased progressively, reached the highest level 3 hr after surgery, and gradually decreased thereafter. However, even on 3rd postoperative day they remained significantly higher than preanesthetic state. It was apparently shown that the changes in total leucocyte count were

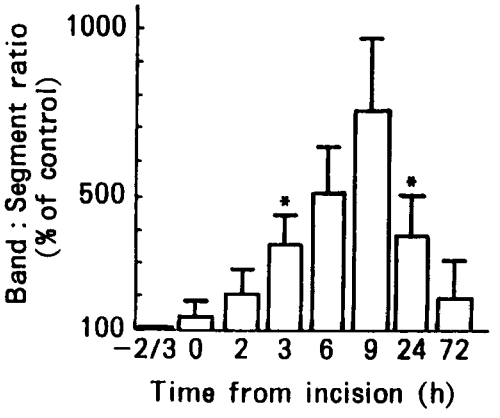

Fig. 3. Changes in band cell:segment cell ratio following anesthesia and surgery. Each column expresses as mean ± SEM of percentage of the preanesthetic value. Explanation for abscissa is as in figure 1. *$P < 0.05$; **$P < 0.01$.

closely related to those of neutrophils ($r = 0.956$, $P < 0.01$).

Before anesthesia the band cell : segment cell ratio was 0.121 ± 0.037. The band cells increased significantly during and after surgery, and band cell : segment cell ratio was increased considerably. It reached the highest level (8 times of preanesthetic level) 6 hr after surgery (fig. 3).

After the induction of anesthesia, count of lymphocytes was decreased progressively, and the lowest level (36% of the preanesthetic level) was found 6 hr after surgery. No significant change was seen in monocytes

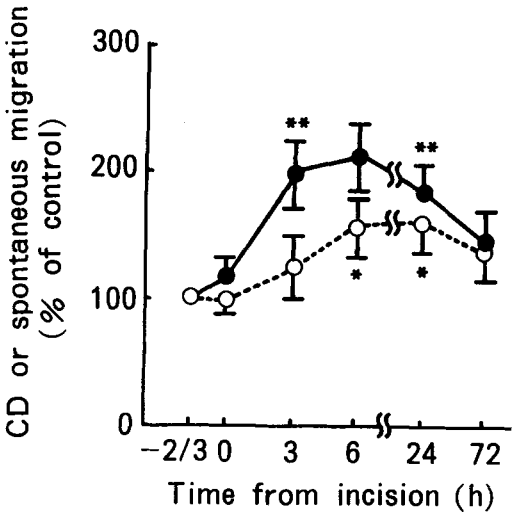

Fig. 4. Influence of anesthesia and surgery on neutrophil functions as chemotactic differential (CD) (●—●) and spontaneous migration (○--○). Results are shown as percentages (mean ± SEM) of preanesthetic values which are 0.47 ± 0.06 mm for CD and 0.34 ± 0.05 mm for spontaneous migration. Explanation for abscissa is as in figure 1. $*P < 0.05$; $**P < 0.01$.

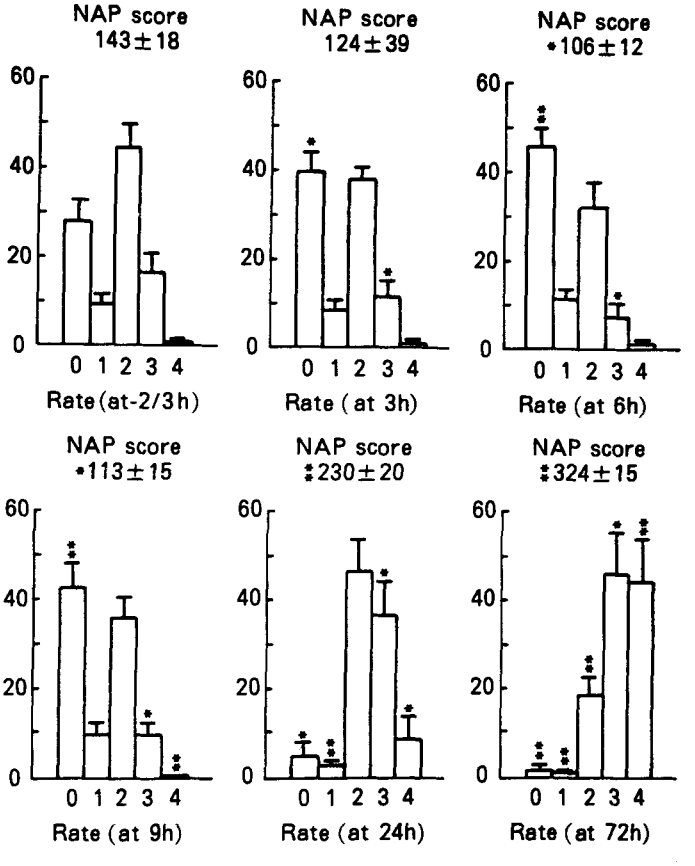

Fig. 5. Changes in NAP score (mean ± SEM) of neutrophils in peripheral blood following anesthesia and surgery. Histograms show changes in neutrophil counts (% of total neutrophils) with various rates (0 to 4+) of NAP activity. The time schedule is same as in figure 1. $*P < 0.05$; $**P < 0.01$.

count.

The chemotactic differential (CD) an index of neutrophil phagocytic activity increased significantly after surgery (fig. 4). The correlation coefficients were 0.658, $P < 0.01$ between CD and neutrophil count; r = 0.627, $P < 0.01$ between CD and segment cell count; and r = 0.518, $P < 0.01$ between CD and band cell count. The spontaneous migration of neutrophils elevated af-

Table 2. Correlation coefficients

	Cortisol	Noradrenaline	Adrenaline	Band cell	Segment cell
Counts of					
Band cell	0.397**	0.009	0.111		0.493**
Segment cell	0.563**	0.364**	0.371**	0.493**	
Neutrophil	0.560**	0.335*	0.329*	0.588**	0.991**
Lymphocyte	−0.188	−0.137	0.130	−0.303*	−0.377*
NAP score	−0.528**	−0.432**	−0.305*	−0.424**	−0.628**
CD	0.643**	0.249	0.539**	0.518**	0.627**
S.Migration¶	0.221	0.082	0.117	0.567**	0.271

*$P \leqq 0.05$, **$P \leqq 0.01$, ¶ Spontaneous Migration

ter surgery, and it was correlated with band cell count ($r = 0.567$, $P < 0.01$), but not with segment cell count.

As shown in figure 5 a significant decrease in NAP score was seen 3 hr and 6 hr after surgery, while neutrophilia was persistent. NAP score increased significantly on 1st and 3rd postoperative day. It indicates that neutrophilia induced by surgical stress is mainly due to the increase in neutrophils with lower NAP activity, and that neutrophils with higher NAP activity become predominant as neutrophilia subsides after surgery.

In table 2, the correlaltion coefficients between plasma concentrations of three hormones and count of different type of leucocytes or function of neutrophils were presented. Apparently neutrophil count was well correlated with each of three hormones, and best correlation was seen between neutrophil count and cortisol concentration.

The count of segment cells correlated well with each of three hormones, however, count of band cells correlated only with cortisol concentrations. NAP score reversely correlated with the plasma concentrations of each of the three hormones, and best correlation was found between NAP score and cortisol. These results indicate the intimate relevance of plasma cortisol level to neutrophilia and alteration in neutrophil function.

Discussion

In this study there were slight increases in plasma concentrations of adrenaline and cortisol after endotracheal intubation, which decreased to below preanesthetic level thereafter. So it was considered that the anesthetic procedures induced a slight activation to endocrine systems[5], and that anesthesia per se depressed the endocrine response[14].

After the initiation of surgery, substantial elevations in the plasma concentrations of cortisol, adrenaline and noradrenaline were observed. From previous studies, the increased release of adrenaline[6,15] or cortisol[7] was assumed to produce neutrophilia. It was also accepted that adrenaline could induce only redistribution of neutrophils from marginal granulocyte pool to the circulating granulocyte pool without change in band cell : segment cell ratio[16]. Samuels[6] has reported that predominant lymphocytosis occurred within the first 30 min after intramuscular injection of 1 mg adrenaline, and that some degree of neutrophilia occurred thereafter. The neutrophilia induced by corticosteroid administration was characteristically accompanied by elevated band cell : segment cell ratio[16]. Thus neutrophilia induced by corticosteroid was assumed to reflect the accelerated neutrophil release from bone marrow[7,15].

The leucocytosis observed after the initiation of surgery was predominantly due to the increase in neutrophil count. In addition a significant rise in band cell : segment cell ratio comparable to neutrophilia, and significant decrease in lymphocytes were also found. So it is indicated that this neutrophilia may be induced mainly due to the enhanced secretion of cortisol.

It is generally considered that the systemic resistance against the infection may

be reduced during lymphocytopenia. Though the mechanisms, through which lymphocytopenia is induced, is not clarified, it is suggested that lymphocytopenia may be resulted from a cortisol-induced redistribution of lymphocytes out of the circulation to the other compartments such as bone marrow and reticuloendothelial system[3,7]. In this study no significant correlation was found between lymphocyte count and plasma concentrations of cortisol or catecholamines. Monocytopenia, which was reported to be induced by corticosteroids[7], was not observed at significant level.

In several reports[9,17] the inhibition of chemotaxis by surgery performed under enflurane anesthesia has been observed. In this study the enhanced chemotactic activity due to surgery has been found. There was a close relation between chemotaxis and spontaneous migration ($r = 0.95$). The enhanced activity of chemotxis was presumably attributable to the increase in band cell and segment cell as shown by correlation between them ($r = 0.518$, $r = 0.627$; $P < 0.01$).

There are some arguments about the effects of surgery performed under anesthesia on neutrophil chemotaxis. It might be due to the technical problem for the measurements of chemotaxis. Currently filter method is widely used, in which filters with $3\mu m$[9] and $5\mu m$[17] pore size were selected. In our experience it seems to be difficult for young band cells to pass through such a small pores, because of their low deformability[18,19]. Therefore, chemotactic activity determined by filter method became lower compared with agarose method[19], especially band cell count elevated[20].

Several biologically active substances are stated to be released due to surgical stress[5,21], and these have some modulating effects on neutrophil chemotaxis. Concerning the effects of adrenaline on chemotaxis, there are some controversies. Cyclic AMP (c-AMP), intracellular second messenger substance for adrenaline, was reported to inhibit chemotactic migration[22,23], however, some authors have reported the enhancing action[24,25] of c-AMP to chemotaxis. It is considered that chemotaxin C_{5a} requires the presence of a cochemotaxin such as ATP and c-AMP for its effectiveness[26]. From this point of view, increase in c-AMP, glucocorticoids[27,28] and beta-endorphin[29] presumably induced by surgery under N_2O-O_2-enflurane anesthesia[21] could lead to the enhanced chemotaxis.

It is stated that the NAP activity links to the phagocytic capacity of cells through production of lactic acid via glycogenolysis[30]. NAP positive polymorphonuclear leucocytes were suggested to possess greater phagocytic activity than NAP negative ones[31]. In this study the kinetics of NAP score were examined to evaluate the phagocytic activity of neutrophils. A significant decrease in NAP score was observed when neutrophilia with high band cell : segment cell ratio was present. According to previous reports[15,32], neutrophilia with high NAP score was induced by the injection of adrenaline, on the other hand, neutrophilia with low NAP score was induced by higher plasma cortisol concentrations. Probably young neutrophils which show low NAP activity are released from the bone marrow into blood stream by cortisol. As the plasma concentrations of cortisol returned to near preanesthetic level, release of young neutrophils seems to subside, and matured neutrophils[33], which showed high NAP activity become predominant on 3rd postoperative day, then preanesthetic situation was regained on 6th postoperative day[1]. Consequently it is indicated that the phagocytic activity of neutrophils can not be restored as long as the cortisol concentrations remain high.

El-Maallem et al.[1] have reported that the NAP activity did not directly correlate with changes in microbicidal activity, but might simply reflect increased count of younger neutrophils in peripheral blood. Actually this depression of NAP activity was of shorter duration, and the rise in the number of circulating neutrophils might compensate the decrease in the NAP activity of each neutrophil.

The operative outcome of the all patients except one female patient, who was

reoperated for the wound infection 2 weeks after the first operation, were satisfactory. In this female patient there was no specific differences in chemotaxis and NAP activity compared with those of other patients.

In conclusion, the release of cortisol as a result of body response to surgical stress may increase the neutrophils count mostly younger neutrophils, which usually show the low NAP activity. The depression of NAP activity by surgery was transient, and it returned to preanesthetic level on 1st postoperative day. There was a significant increase in neutrophil chemotaxis during intra- and post-operative period. It is considered that the elective spine surgery may not be deleterious to the function of neutrophils.

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