J Anesth (1994) 8:64–71

Journal of
Anesthesia

Does intraoperative analgesia modify the immune response in surgical patients?

MAHITO YAMAGUCHI and RYO OGAWA

Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113 Japan

Abstract: The effect of epidural analgesia combined with inhalational anesthesia on the perioperative immune response was measured by using two-color analysis for the classification of functional lymphocyte subpopulations. Twenty-eight patients undergoing upper abdominal surgery were divided into four groups: group 1, isoflurane and with N_2O; group 2, sevoflurane with N_2O; group 3, epidural analgesia plus isoflurane with N_2O; and group 4, epidural analgesia and sevoflurane with N_2O. Peripheral lymphocyte subpopulations were measured before, during, and after the operation by using anti-CD4 and anti-CD8 monoclonal antibodies. Moreover, two-color analysis was performed using two kinds of monoclonal antibodies: anti-CD4 and anti-CD29W, and anti-CD4 and anti-CD45R. A decrease in $CD4^+$ cells and $CD4^+$ $CD29W^+$ cells (helper-inducer T lymphocytes) was observed after the operation in groups 1, 2, and 4. Additionally, stress hormones such as epinephrine (EP), norepinephrine (NE), and cortisol (CO) were measured. EP was increased during and after the operation in groups 1 and 2, and after the operation in group 4, but the level was maintained throughout the study in group 3. In conclusion, prevention of noxious stimuli originating from operative fields by epidural block could prevent the increase in EP and the reduction of helper-inducer T cells in patients undergoing upper abdominal surgery.

Key words: Epidural analgesia, Isoflurane, Sevoflurane, Lymphocyte subpopulation, Stress hormones

Introduction

There have been many studies showing that anesthesia and surgery depress immunological functions [1–3]. Depression of immune responses may decrease host defense ability, subsequently increasing the possibility of postoperative infection, and it affects the antitumor system, thus inducing proliferation of neoplasms [4–7].

Address correspondence to: M. Yamaguchi
Received for publication on November 24, 1992; accepted on June 13, 1993

Several investigators have pointed out that surgical injuries play more important roles than anesthesia in the mechanism of immunological depression [8–9]. A principal product of surgical injury is the pain originating from the operative field. If the pain could be blocked by local analgesia, the immune response could be improved. In the present study, the effects of epidural analgesia combined with inhalational anesthesia on the immune response were measured in patients with upper abdominal operations.

Materials and methods

Twenty-eight adult patients who underwent radical removal of gastric cancer were selected for the study. All patients were classified as ASA 1, without circulatory, respiratory, and/or metabolic diseases. They were informed of the details of the study and prior consent was obtained in writing. The patients were divided into 4 groups on the basis of anesthesia methods: group 1 was comprised of six patients given isoflurane and nitrous oxide, group 2 of six patients given sevoflurane and nitrous oxide, group 3 of eight patients given isoflurane/nitrous oxide combined with epidural analgesia, group 4 of eight patients given sevoflurane/nitrous oxide combined with epidural analgesia.

Anesthesia protocol

All patients received atropine sulfate, 0.5 mg, as premedication 1 h before induction of anesthesia, after having fasted overnight. They were brought to the operating room at 8 a.m. and catheters were introduced via the cubital vein and radial artery under local anesthesia. A cuff was attached to the opposite upper arm to measure arterial blood pressure. Three electrodes were attached to the chest to monitor a standard lead II electrocardiogram. Blood pressure was deter-

mined every 2.5 min by the oscillometeric technique via an automatic sphygmomanometer (Type BX-2, Nippon Kolin, Tokyo, Japan). Electrocardiograms were displayed on a polygrapy (Life Scope-6, Nihon Kohden Kogyo, Tokyo, Japan). Five hundred milliliters of isooncotic dextran solution (Saviosol, Midorijuji Pharmaceutical, Osaka, Japan) were infused at the rate of 5–10 $ml \cdot kg^{-1} \cdot h^{-1}$ followed by Ringer's lactate solution at the rate of 5–10 $ml \cdot kg^{-1} \cdot h^{-1}$ during the study. After preparation for monitoring, all patients were positioned in the right lateral position and the skin of the back was sterilized and draped. Lidocaine 1% was injected intradermally and subcutaneously at T8–9 or T9–10. The epidural space was identified with a 17 gauge Tuohy needle inserted cephalad by the paramedian approach. Entry of the needle point into the epidural space was confirmed by the loss of resistance technique with a saline-filled syringe. An 18 gauge epidural catheter (Abbott Ireland, Sligo, Ireland) was inserted through the needle and 4–5 cm of the catheter was placed into the epidural space. Two milliliters of 2% plain mepivacaine were injected as a test dose into the epidural catheter with the patient in the supine position in groups 3 and 4. The same concentration of plain mepivacaine (10–15 ml) was given after 2 min of observation. The spread of analgesia was determined by noting the loss of sharpness of a pinprick after 15 min. The patients showing an analgesia level over T4 were given two-thirds of the initial dose at 50- to 60-min intervals throughout the operation. In groups 1 and 2, saline 10–15 ml was injected into the epidural space as a control. General anesthesia was induced by injecting thiamylal sodium 5 $mg \cdot kg^{-1}$ iv, and muscle relaxation was obtained by giving vecuronium bromide 0.15 $mg \cdot kg^{-1}$ iv. After placement of an endotracheal tube into the trachea, anesthesia was maintained with 1–2 MACs of isoflurane or sevoflurane carried by a gas mixture of 66% N_2O and 33% oxygen. The MACs of isoflurane sevoflurane with 66% N_2O were determined as 0.50% and 0.66% respectively, according to instructions issued by the manufacturers. The concentration of inhaled anesthetic was checked by means of a gas analyzer (Anesthetic Gas Monitor Type-1304, Bruel-Kjœr, Naerum, Denmark).

Observation and maintenance of circulation

Systolic and diastolic blood pressures were obtained every 2.5 min, and the mean blood pressure (MAP) was calculated mechanically. Heart rates (HR) were also recorded every 2.5 min. When MAP declined to under 50 mmHg, ephedrine hydrochloride 5–10 mg was injected iv repeatedly to maintain blood pressure. The patients who received vasopressors were excluded from the study.

Assay of stress hormones

Plasma cortisol (CO) and catecholamines, epinephrine (EP) and norepinephrine (NE), were determined as indicators of responses to surgical injury. Blood samples were taken from the arterial catheter before induction of anesthesia, 1 h after the beginning of the operation and 1 h after recovery from the operation. Blood for catecholamine analysis was collected in heparinized glass tubes, while the blood samples for assaying the hormones were collected in EDTA-treated tubes. These samples were immediately placed on ice and the plasma was separated with refrigerated centrifuge. All samples were stored at −40°C until the assays were performed. EP and NE concentrations were determined by high-performance liquid chromatography (HPLC). CO concentration was determined by a radioimmunoassay technique.

Subpopulations of T lymphocytes

Subpopulations of T lymphocytes were analyzed as a quantitative determination of the immune response. In the first step, the proportion of inducer/helper T lymphocytes ($CD4^+$ cells) and suppressor/cytotoxic T lymphocytes ($CD8^+$ cells) were determined by single-color analysis. The former is known to stimulate and the latter to suppress the immune response. Arterial blood was drawn into the heparinized syringe before induction of anesthesia, 1 h after the beginning of the operation and 1 h after recovery from anesthesia. Monoclonal antibodies against cell membrane antigens, anti-CD4 and anti-CD8 (OKT4-FITC and OKT8-FITC, Ortho Diagnostic Systems, Raritan, NJ), were added to the blood, which was then incubated to mark cell membrane. After the lymphocytes were separated by washing and centrifugation, subpopulations were determined by flow cytometry (FCM-1D, Jasco, Tokyo, Japan).

In the second step, T lymphocytes of system stimulating the immune response ($CD4^+$ cells) were separated into helper-inducer T cells ($CD4^+/CD29W^+$ cells) and suppressor-inducer T cells ($CD4^+/CD45R^+$ cells) using two-color analysis. The combination of monoclonal antibodies against cell membrane antigens, anti-CD4 (CD4-FITC, Becton-Dickinson, Franklin Lakes, N.J.) and anti-CD45R (2H4-RD1, Coulter, Miami, Fla.) anti-CD4 and anti-CD29W (4B4-RD1, Coulter) was added to the withdrawn blood to mark the cells. The subpopulations were analyzed by flow cytometry. The results were expressed as the proportion of the number of cells in each subpopulations to the total number of peripheral lymphocytes.

Statistical analysis

Continuous variables were presented as means with standard deviations (SDs) when distributions were normal. Differences in three or more groups were tested by one-way analysis of variance, and Student's *t*-test was used to test the difference between two groups when the null hypothesis of equality among groups was rejected. In the case of variables expressed as a percentage, the difference was assessed by the chi-square test. A *P*-value less than 0.05 was used to reject the hypothesis.

Results

Age, body weight, body height, duration of anesthesia, duration of the operation, bleeding volume, total amount of fluid infused during anesthesia, and urine output during anesthesia in the four groups are shown in Table 1. There were no differences among the four groups. The total amounts of inhalational anesthetics administered were 10.52 ± 2.34 MAC·h in group 1, 7.75 ± 1.12 MAC·h in group 2, 8, 84 ± 1.72 MAC·h in group 3, and 7.94 ± 1.93 MAC·h in group 4. There was no difference among the four groups.

MAP and HR are shown in Table 2. MAP was significantly lower in groups 3 and 4 during the operation than in the preanesthetic controls and matched groups without epidural block.

The changes in stress hormone concentration are shown in Table 3. Plasma EP concentration increased significantly in groups 1 and 2 during the operation, followed by a marked elevation 1 h after recovery from anesthesia. No changes were observed in groups 3 and 4 (with epidural analgesia) during the operation. A slight increase was obtained in group 4 at 1 h after recovery from anesthesia (Fig. 1a). Plasma NE was significantly increased in groups 1 and 2 during the operation and after recovery from anesthesia. Significant increases were observed in groups 3 and 4 after recovery from anesthesia. There were no differences in NE levels among the four groups after recovery from anesthesia (Fig. 1b). The plasma cortisol level increased signifi-

Table 1. Patient characteristics of the four groups and variables in anesthesia

Group no. (*n*)	1 (6)	2 (6)	3 (8)	4 (8)
Anesthetic	I + N	S + N	I + N + E	S + N + E
Age (years)	51.4 ± 5.31	55.4 ± 3.26	56.0 ± 9.10	51.8 ± 3.97
Weight (kg)	58.0 ± 3.03	51.6 ± 7.79	58.6 ± 11.68	53.0 ± 6.60
Height (cm)	164.8 ± 5.27	161.4 ± 7.78	161.0 ± 12.57	160.8 ± 5.50
Anesthesia time (min)	285 ± 30.0	246 ± 25.6	267 ± 39.6	263 ± 40.2
Operation time (min)	196 ± 27.9	184 ± 19.8	192 ± 38.8	203 ± 41.3
Blood loss during operation (g)	706 ± 288.4	636 ± 233.5	676 006 300.5	724 ± 260.1
Infused volume during anesth. (ml)	2654 ± 816.0	2456 ± 357.0	2950 ± 699.0	3052 ± 540.0
Urine volume during anesthesia. (ml)	260 ± 87.5	226 ± 93.2	143 ± 104.0	346 ± 253.0

Values are mean ± SD.
I, isoflurane; S, sevoflurane; N, nitrous oxide; E, epidural anesthesia.

Table 2. Time course of the changes in mean arterial pressure and heart rate

		Pre-anesthetic	During anesthetic	Post-anesthetic
Group 1	MAP (mmHg)	97 ± 8.4	93 ± 5.7	91 ± 6.5
(*n* = 6)	HR (bpm)	74 ± 12.2	77 ± 13.8	77 ± 16.1
Group 2	MAP (mmHg)	101 ± 8.9	93 ± 5.7	92 ± 5.7
(*n* = 5)	HR (bpm)	73 ± 11.8	78 ± 9.3	76 ± 14.1
Group 3	MAP (mmHg)	97 ± 13.5	75 ± 13.5*,#	87 ± 2.7
(*n* = 8)	HR (bpm)	76 ± 10.8	78 ± 5.8	80 ± 14.1
Group 4	MAP (mmHg)	93 ± 4.5	76 ± 10.8*,#	94 ± 17.5
(*n* = 8)	HR (bpm)	81 ± 18.0	73 ± 10.1	73 ± 13.3

Values are mean ± SD.
MAP, mean arterial pressure; HR, heart rate.
* $P < 0.05$ *vs* control.
# $P < 0.05$ *vs* groups 1 and 2.

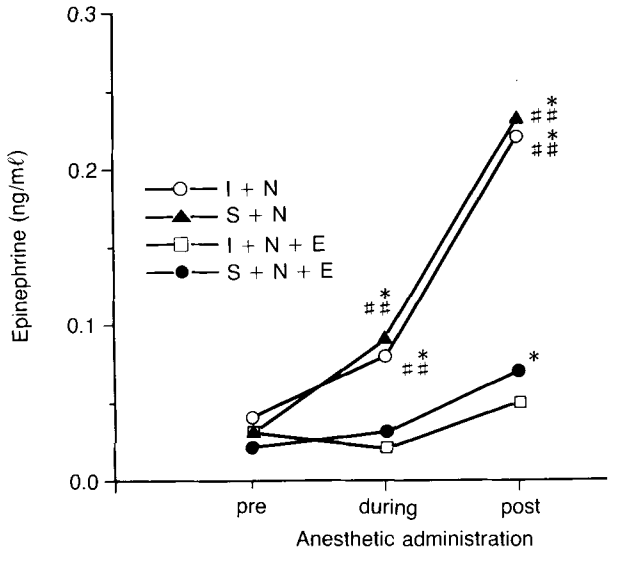
Table 3. Time course of the changes in stress hormone concentrations

Group no.		Pre-anesthetic	During anesthetic	Post-anesthetic
EP (ng/ml)	1	0.04 ± 0.020	0.08 ± 0.048*,#	0.22 ± 0.188*,#
	2	0.03 ± 0.017	0.09 ± 0.032*,#	0.23 ± 0.130*,#
	3	0.03 ± 0.011	0.02 ± 0.011	0.05 ± 0.037
	4	0.02 ± 0.014	0.03 ± 0.020	0.07 ± 0.024*
NE (ng/ml)	1	0.14 ± 0.049	0.31 ± 0.230*,#	0.56 ± 0.302*
	2	0.13 ± 0.063	0.39 ± 0.205*,#	0.70 ± 0.428*
	3	0.12 ± 0.044	0.11 ± 0.063	0.54 ± 0.318*
	4	0.13 ± 0.070	0.11 ± 0.056	0.57 ± 0.344*
CO (μg/dl)	1	10.1 ± 7.18	18.7 ± 4.02*	25.6 ± 2.75*
	2	11.2 ± 4.49	22.7 ± 5.55*	28.0 ± 4.16*
	3	9.6 ± 3.33	21.2 ± 2.76*	25.1 ± 2.28*
	4	15.3 ± 4.55	24.1 ± 1.44*	34.1 ± 5.69*

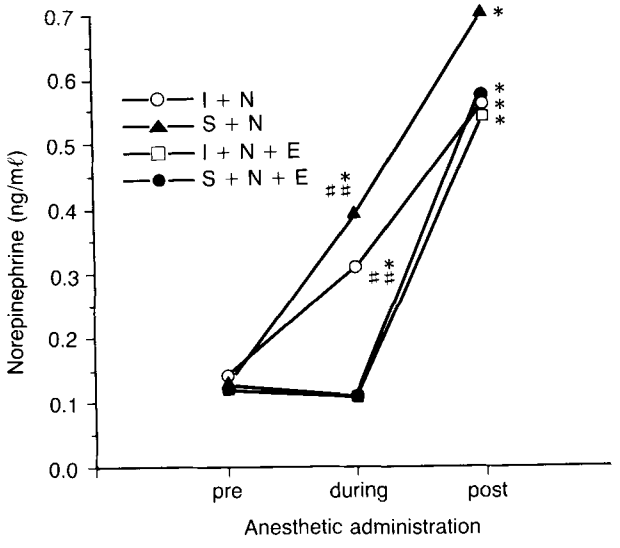
Values are mean ± SD.
EP, epinephrine; NE, norepinephrine; CO, cortisol.
* $P < 0.05$ *vs* control.
# $P < 0.05$ *vs* group 3 and 4.

cantly during the operation in all four groups, followed by a further elevation 1 h after recovery from anesthesia. There was no difference among the four groups during the operation and 1 h after recovery from anesthesia (Fig. 1c).

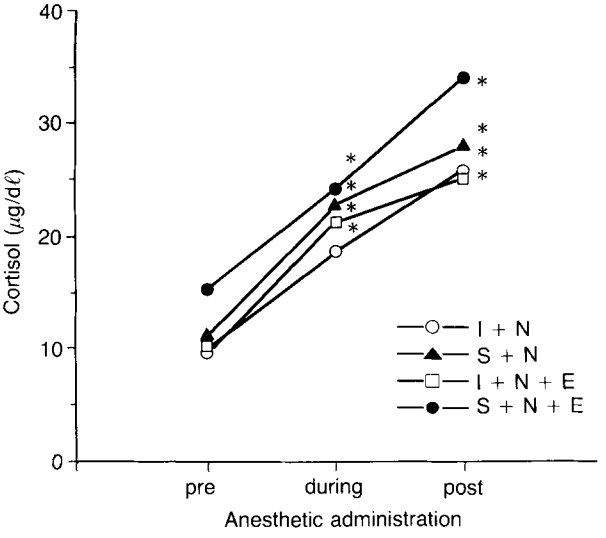
Distribution of the subpopulations of T lymphocytes is shown in Table 4. The proportion of inducer/helper T lymphocytes ($CD4^+$ cells) decreased significantly in groups 1, 2 and 4 after recovery from anesthesia. However, there was no difference in $CD4^+/CD8^+$ rate among the four groups. The decrease in $CD4^+$ lymphocytes was reflected in a decrease in helper-inducer T lymphocytes ($CD4^+/CD29W^+$ cells) in groups 1, 2, and 4 after recovery from anesthesia. There was no difference in the proportion of suppressor-inducer T lymphocytes ($CD4^+/CD45R^+$ cells) among the four groups (Fig. 2a–e).



a



b



c

Fig. 1. a. Time course of the changes in plasma epinephrine concentration. *I*, isoflurane; *S*, sevoflurane; *N*, nitrous oxide; *E*, epidermal anesthetic. **b** Time course of the changes in plasma norepinephrine concentration. **c** Time course of the changes in plasma cortisol concentration. *$P < 0.05$ *vs* control; #$P < 0.05$ *vs* groups 3 and 4.

Table 4. Time course of the changes in lymphocyte subpopulations

Group no.		Pre-anesthetic	During anesthetic	Post-anesthetic
$CD4^+$ (%)	1	42.2 ± 8.38	36.4 ± 6.90	35.0 ± 7.68*
	2	42.3 ± 7.29	36.0 ± 6.85	33.7 ± 6.85*
	3	42.8 ± 8.70	44.6 ± 7.52	38.0 ± 11.43
	4	40.0 ± 6.17	39.6 ± 5.12	27.8 ± 8.78*
$CD8^+$ (%)	1	19.1 ± 4.10	21.1 ± 3.89	17.2 ± 4.34
	2	24.0 ± 7.86	24.4 ± 6.94	19.9 ± 6.78
	3	23.1 ± 5.03	24.5 ± 4.70	20.0 ± 4.94
	4	26.6 ± 5.32	28.2 ± 4.46	27.8 ± 6.18
$CD4^+/CD8^+$ rate	1	2.44 ± 1.146	1.82 ± 0.576	2.23 ± 0.917
	2	2.05 ± 1.072	1.59 ± 0.508	2.03 ± 1.222
	3	2.07 ± 0.724	1.96 ± 0.535	2.05 ± 0.750
	4	1.46 ± 0.558	1.48 ± 0.488	1.12 ± 0.725
$CD4^+/CD29W^+$ (%)	1	26.6 ± 6.70	24.1 ± 5.40	19.9 ± 4.35*
	2	27.1 ± 5.25	23.1 ± 7.30	18.6 ± 5.36*
	3	24.1 ± 6.62	25.9 ± 7.84	20.3 ± 5.48
	4	26.0 ± 4.95	25.6 ± 4.73	17.3 ± 5.76*
$CD4^+/CD45R^+$ (%)	1	12.3 ± 3.46	11.0 ± 2.70	13.3 ± 5.43
	2	15.3 ± 5.54	11.2 ± 3.73	14.8 ± 4.49
	3	15.1 ± 2.77	14.9 ± 2.46	14.9 ± 2.78
	4	13.5 ± 3.05	15.9 ± 5.40	9.7 ± 3.55

* $P < 0.05$ *vs* control.

Discussion

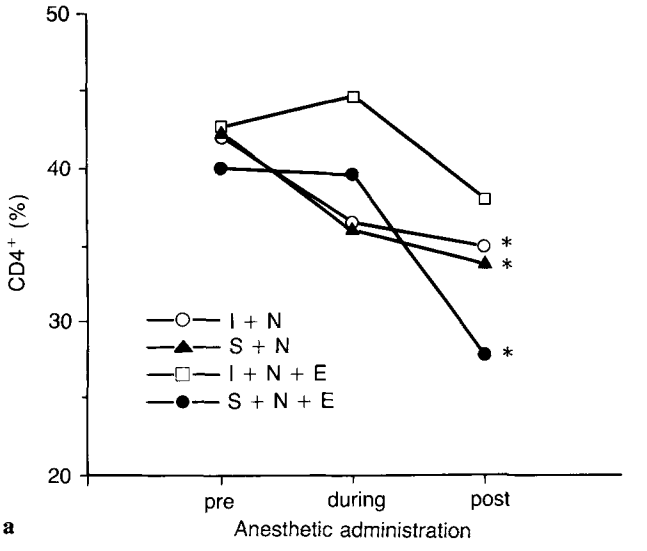
Modern surgical treatments require prolonged anesthesia and have profound effects on the patients. Anesthetics and operative injury have been reported to depress the immunological functions and to increase the possibility of bacterial infection and tumor proliferation in the perioperative period [4–7].

T lymphocytes are critical in the development of cell-mediated immune reactions. Functional classification of T cells become possible by introducing monoclonal antibodies such as the OKT and Leu series. The subpopulations of T cells are divided into inducer/helper T cells ($CD4^+$ cells) and suppressor/cytotoxic T cells ($CD8^+$ cells). The former includes lymphocytes which stimulate an immune reaction and the latter contains lymphocytes which inhibit immune responses and are cytotoxic[10–12].

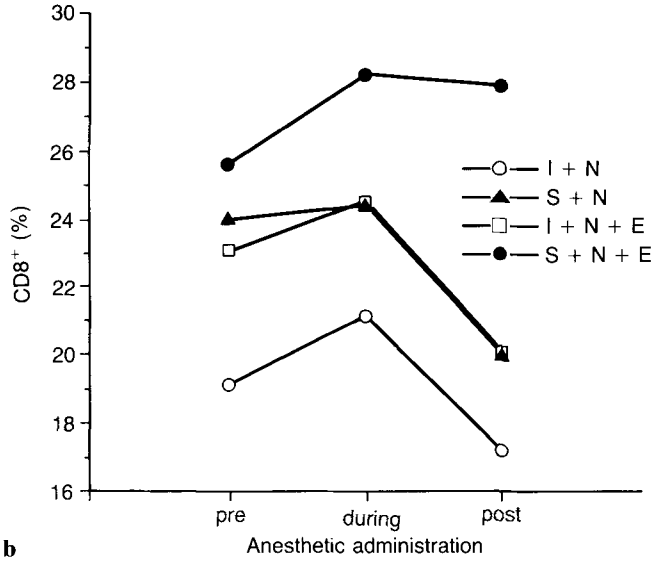
Tokutomi et al. [13] reported that $CD4^†/CD8^†$ rate is significantly decreased in patients anesthetized with inhalational anesthetics. Asakura et al. [14] investigated the changes in $CD4^†/CD8^†$ rate in patients anesthetized with enflurane, isoflurane, and sevoflurane combined with N_2O for various kinds of operations, and found that the rate was significantly decreased in patients who were given sevoflurane and N_2O anesthesia. These investigations were conducted in patients who received surgical manipulation, in whom iatrogenic injury was possible. Tonnessen et al. [15], Slade et al. [16] and Hosokawa et al. [9] investigated the effects of surgical injuries on immune responses and reported that the $CD4^†$ subpopulation of T cells was more markedly reduced in patients receiving major operations than in patients receiving minor operations. Their results indicated that serious surgical injuries can severely depress immune responses. In the present study, the proportion of $CD4^†$ cells was decreased in groups 1, 2, and 4 after recovery from anesthesia compared with the levels before anesthesia. CD^1 cells include various subsets which have many functions. The newly developed antibodies against cell membrane antigens, anti-CD45R and anti-CD29W, have made it possible to separate cells ($CD4^†$, $CD29W^†$), which induce helper T cells and B cells, and cells ($CD4^†/CD45R^†$) which induce suppressor T cells [17].

In the present study, $CD4^+/CD29W^+$ cells were significantly reduced in groups 1, 2, and 4 after anesthesia. The authors thought the changes in $CD4^+/CD29W^+$ cells important enough to suggest that depression of immune response in may have occurred these three groups. On the other hand, the reduction of T cells ($CD4^+$ and $CD4^+/CD29W^+$ cells) was prevented in group 3 patients who received epidural analgesia during and after the operation.

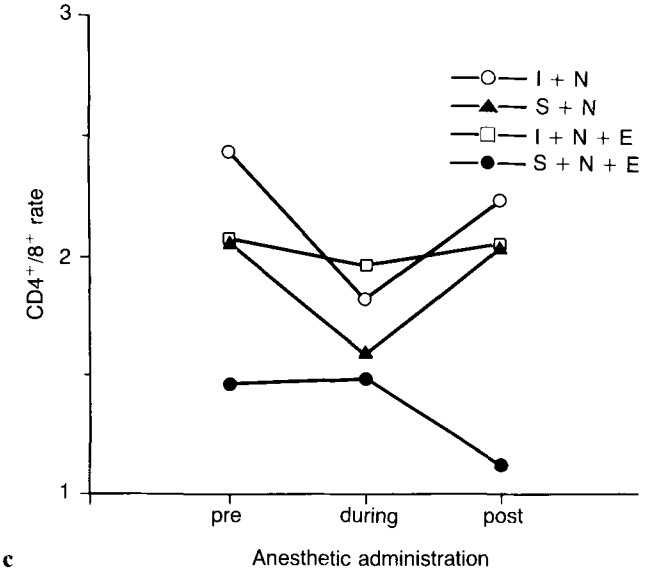
Various kinds of information will be communicated among immune cells such as monocytes, macrophages and lymphocytes when an antigen is taken into the body under ordinary circumstances. Cytokines play central roles in intercellular communication and immune cells react in a stimulating or suppressing way. Immune cells



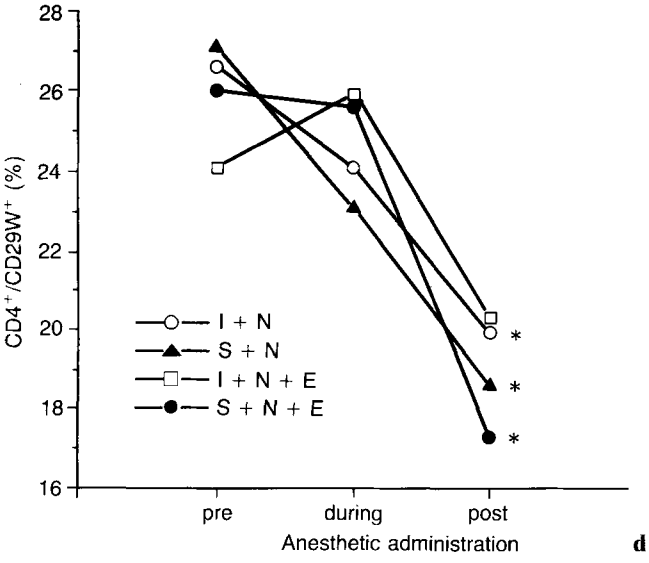
a



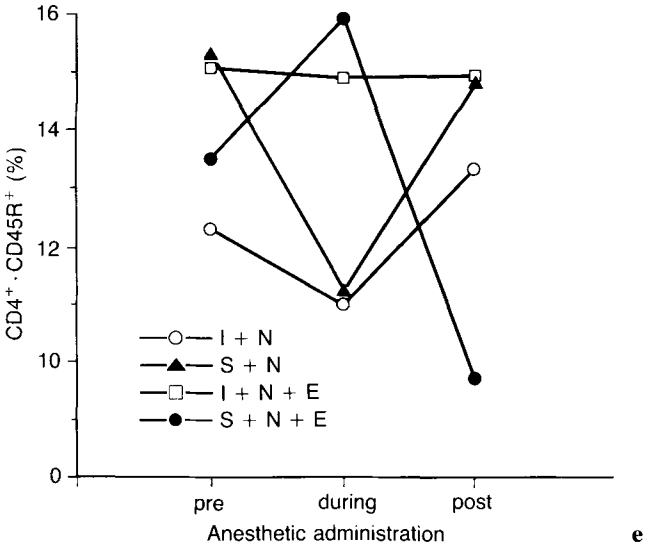
b



c



d



e

Fig. 2. a. Time course of the changes in $CD4^+$ cells. **b** Time course of the changes in $CD8^+$ cells. **c** Time course of the changes in $CD4^+/CD8^+$ rate. **d** Time course of the changes in $CD4^+ \cdot CD29W^+$ cells. **e** Time course of the changes in $CD4^+ \cdot CD45R^+$ cells. $^*P < 0.05$ *vs* control; $^\#P < 0.05$ *vs* groups 3 and 4.

have many receptors on the cell membrane for various substances including cytokines. Neuronal and humoral factors influence the immune reaction through these receptors. The well-known factors are EP and CO. Bruce et al. [18] reported that the $CD4^+/CD8^+$ rate decreased quickly when EP was infused into the circulation in healthy men. Hosokawa et al. [9] found a positive correlation between the plasma CO level and the proportion of inducer/helper T cells ($CD4^+$ cells). However, Tonnessen et al. [15] reported that changes in T cells appeared after several hours when synthesized glucocorticoids were given systemically.

In the present study, elevated concentrations of EP and NE were observed during the operation and after recovery from anesthesia in groups 1 and 2 which received inhalational anesthesia. In the groups which received epidural block, a slight but significant rise EP was observed in group 4. The CO levels increased markedly during the operation and after recovery from anesthesia in all four groups. The present study revealed marked increase in plasma EP, NE, and CO concentration, and concomitantly a reduction of helper/inducer T cells ($CD4^+/CD29W^+$) in patients who received radical gastrectomy.

Although both groups 3 and 4 received epidural analgesia, group 4 showed reductions of $CD4^+$ and $CD4^+/CD29W^+$ cells while group 3 did not. Asakura et al. [14] reported that $CD4^+/CD8^+$ rate was reduced significantly in patients given sevoflurane and N_2O but not in patients given isoflurane and N_2O. This finding suggests that sevoflurane has the ability to induce the proliferation of T cells directly.

If early changes in immune responses are caused by the released EP, measures to reduce surgical injury could prevent these reactions. Giesecke et al. [19] and George et al. [20] reported that a massive dose of opioids, morphine or fentanyl, attenuated hormonal reactions through the hypothalamus-pituitary-adrenal axis caused by surgical stimulation. There are many studies that suggest the superiority of epidural analgesia to inhalational anesthesia from the viewpoint of immune responses [21]. Davis et al. [22] showed that epidural analgesia decreased the mortality rate among geriatric patients with fixation of femoral neck fracture. Yeager et al. [23] pointed out a reduction in the rate of infection in patients with critical illness who recevied surgical treatments under epidural anesthesia and analgesia. Rem et al. [24] observed a larger number of T lymphocytes in patients who received operation under epidural analgesia. Tonnessen et al. [25] reported that epidural analgesia maintained the function of natural killer lymphocytes in patients who received lower abdominal operations. Epidural analgesia maintained the proportion of T cells in patients who were given isoflurane anesthesia after recovery from anesthesia in the present study. These results supported the findings of the earlier reports.

In conclusion, prevention of noxious stimuli that originate from the operative field through epidural block could prevent reduction of helper-inducer T cells in patients who are receiving upper abdominal operations under isoflurane-N_2O anesthesia.

References

1. Bruce DL, Wingard DW (1971) Anesthesia and the immune response. Anesthesiology 34:271–282
2. Cullen DF, Van Belle GM (1975) Lymphocyte transformation and changes in leucocyte count: Effect of anesthesia and operation. Anesthesiology 43:563–569
3. Walton B (1979) Effect of anaesthesia and surgery on immune status. Br J Anaesth 51:37–43
4. Park S, Brody KJI, Wallace HA, et al. (1971) Immunosuppressive effect of surgery. Lancet i:53–55
5. Agostio D, Cliffton EE (1964) Anesthetic effect on pulmonary metastasis in rat. Arch Surg 88:735–739
6. Uchida A, Kolb R, Micksche M (1982) Generation of suppressor cells for natural killer activity in cancer patients after surgery. J Natl Cancer Inst 68:735–741
7. Metzger Z, Hoffeld JJ, Oppenheim JJ (1980) Macrophage-mediated suppression. HI: Evidence for participation of both hydrogen peroxide and prostaglandins in suppression of murine lymphocyte proliferation. J Immunol 124:983–988
8. Bradley JA, Hamilton DNH, Brown ME, et al. (1984) Cellular defence in circulatory ill surgical patients. Crit Care Med 12:565–570
9. Hosokawa T, Hori Y, Miyazaki M, et al. (1990) Interaction between immunological change and serum cortisol concentration in patients undergoing major and minor surgery. In: Matsuki A, Ishihara H, Oyama T (eds) Endocrine response to anesthesia and intensive care. Elsevier, Amsterdam, pp 157–163
10. Cosimi BA, Colvin BR, Russell SP, et al. (1981) Use of monoclonal antibodies to T-cell subsets for immunologic monitoring and treatment in recipients of renal allografts. N Engl J Med 305:308–314
11. Reinhertz FL, Kung PC, Schlossman SF, et al. (1979) Separation of functional subsets of human T cell by monoclonal antibody. Proc Natl Acad Sci USA 76:4061–4065
12. Kansas GS, Wood GS, Fishwild DM, et al. (1985) Functional characterization of human T lymphocyte subsets distinguished by monoclonal anti Leu-8. J Immunol 134:2995–3003
13. Tokutomi Y, Muteki T, Okubo K, et al. (1983) Influence of anesthesia on immune system studies on fluctuation of lymphocyte subpopulations (in Japanese, with English abstract). Masui (Jpn J Anesthesiol) 32:1523–1528
14. Asakura Y, Gotou F, Fujita T (1989) Effect of inhalational anesthetics on immunological system (in Japanese, with English abstract). Rinshoumasui (J Clin Anesth) 13:603–607
15. Tonnessen E, Mickley H, Grunnet N (1983) Natural killer cell activity during premedication, anaesthesia and surgery. Acta Anaesthesiol Scand 27:238–241
16. Slade MS, Simmons RL, Yunis E (1975) Immunomodulation after major surgery in normal patient. Surgery 78:363–372
17. Morimoto C, Schlossman FS (1987) The human immunoregulatory T cell circuit: recent progress and its clinical implications. Keio J Med 36:351–368
18. Bruce C, Stephen LH, Herbert B, et al. (1983) Epinephrine-induced changes in the distribution of lymphocyte subsets in peripheral blood of humans. J Immunol 131:1178–1181

19. Giesecke K, Hamberger B, Persson B, et al. (1988) High and low-dose fentanyl anaesthesia; Hormonal and metabolic response during cholecystectomy. Br J Anaesth 61:575–582
20. George JM, Reiner LE, Rower JM, et al. (1988) Morphine anesthesia blocks cortisol and growth hormone response to stress in humans. J Clin Endocr Metab 38:736–741
21. Kehlet H (1978) Influence of epidural analgesia on the endocrine-metabolic response to surgery. Acta Anaesthesiol Scand 70:39–42
22. Davis FM, Woolner DF, Thadaka R, et al. (1987) Prospective multicenter trial of mortality following general or spinal anaesthesia for hip fracture in the eldery. Br J Anaesth 59:1080–1088
23. Yeager MP, Glass DD, Brinck JT, et al. (1987) Epidural anesthesia and analgesia in high risk surgical patients. Anesthesiology 66:729–736
24. Rem J, Brandt MR, Kehlet H (1980) Prevention of postoperative lymphopenia and granulocytosis by epidural analgesia. Lancet i:283–284
25. Tonnessen E, Huttel MS, Christensen NJ (1987) Natural killer cell activity in patients undergoing minor gynaecological surgery. Eur J Anaesth 4:119–125