Could Intraoperative Analgesia Attenuate Excessive Neuroendocrine Responses in Surgical Patients?

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Recently, there has been increasing interest among anesthesiologists in the responses to surgical stress because surgical procedures have become more and more invasive. While the responses are natural and protective in themselves, they may have adverse consequences for the patients.[1,2,3] There have been many investigations suggesting that anesthetic techniques such as spinal and epidural analgesia may alter the endocrine response.[4,5] Some measures which block inflammatory reaction are reported to allow modulation of the response.[6,7] In the present study preemptive analgesia for postoperative pain using spinal and extradural blockade, and pre-treatment of cyclo-oxygenase inhibitor indomethacin were applied to patients who underwent upper and lower abdominal operations, and the neuroendocrine and immunological responses were assessed.

MATERIALS AND METHODS

Experiment One

The effect of preemptive analgesia using spinal block and treatment of anti-inflammatory agent on neuroendocrine and inflammatory reactions was observed in patients who underwent lower abdominal operations. Twenty four patients who received radical removal of colonic or sigmoidal cancers were selected for the study. All patients were classified as ASA class 1 or 2 without cardiovascular, respiratory, endocrinological and/or metabolic diseases. They were informed of the details of the study and wrote consent forms.

The patients were divided randomly into three groups. Group 1 was composed of eight patients who received inhalation anesthesia; in group 2, eight patients accepted spinal blockade combined with inhalation anesthesia; and in group 3, eight patients were pretreated orally with cyclo-oxygenase blocker indomethacin 100 mg doses, two times before operation and received inhalation anesthesia.

At 7:30 AM patients were injected intramuscularly with 0.5 mg of atropine sulfate, and hydroxydine hydrochloride as premedications. After thirty minutes patients were brought to the operating room and catheters were introduced via the cubital vein and radial artery under local

anesthesia. A cuff was attached to the left upper arm to measure arterial blood pressure. Three electrodes were attached to the chest wall to monitor a standard 2-lead electrocardiogram. Blood pressure was determined every 2.5 minutes by the oscillometric technique via an automatic sphygmomanometer (Type BX-2, Nippon Kolin, Nagoya, Japan). Electrocardiograms were displayed on a polygraph (Life Scope-6, Nihon Kohden Kogyo, Tokyo, Japan). Five hundred milliliters of isotonic dextran solution (Saviosol, Midorijuuji Pharmaceutical, Osaka, Japan) were infused at the rate of 5-10 mL/kg/h followed by Ringer's lactate solution at the rate of 5-10 mL/kg/h during the study.

After preparation for monitoring, all patients were positioned in the right lateral decubitus position and the skin of the back was sterilized and draped. Lidocaine 1% was injected intradermally and subcutaneously at L2-3. The epidural space was identified with a 17 gauge Tuohy needle inserted cephalad by the paramedian approach. Entry of the needle point into 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. The catheter was used to inject 6 mL of 0.25% bupivacaine and 0.1 mg of buprenorphine after the end of experiments followed by continuous injection of 0.25% bupivacaine 2 mL/h for inhibition of postoperative pain.

Patients in group 1 were induced into general anesthesia by injecting thiamylal sodium 5 mg/kg and muscle relaxation was obtained by giving vecuronium bromide 0.15 mg/kg. After placement of an endotracheal tube into the trachea, anesthesia was maintained by mixed gas of 66% nitrous oxide (N_2O), 33% oxygen (O_2) and 0.5-1.5% isoflurane (I). Patients in group 2 received spinal block after the placement of epidural catheter. The spinal needle was advanced at L3-4 and hyperbaric 0.5% tetracaine hydrochloride mixed with 0.025% phenylephrine hydrochloride was injected intrathecally. The amount of tetracaine hydrochloride injected was calculated by the following formula: injected amount (mg)=[height(cm) -100] x 0.2.

Immediately after injection of the local anesthetic agent, patients were placed at supine recumbent position and the level of analgesia was checked after 10 min. Patients who showed analgesia higher than Th_4 were included in the study. Patients in group 3 were given 100 mg of indomethacin two times at 12 and 3 h before the induction of anesthesia. The anesthesia was induced and maintained as in group 1.

Blood samples were withdrawn 5 times: before insertion of epidural catheter, after placement of endotrachial tube, 30 min after the start of the operation, at the end of operation, and 1 hour after the operation. Concentrations of glucose; stress hormones, such as ACTH, cortisol, epinephrine (EP) and norepinephrine (NE); and metabolites of prostanoids such as 6-keto-prostaglandin $F_1\alpha$ (6-keto-$PGF_1\alpha$), thromboxane B_2 (TXB_2) and 11-dehydro-thromboxane B_2 (11DTX) were determined. Blood glucose was measured by glucose dehydrogenase method. Plasma levels of ACTH, cortisol, 6-keto-$PGF_1\alpha$, TXB2 and 11DTX were determined by radioimmunoassay. Plasma levels of EP and NE were quantified by high performance liquid chromatography.

Experiment Two

The effect of epidural blockade combined with inhalation anesthesia on the perioperative immune response was observed. Twenty eight patients who received radical removal of gastric cancer were selected for the study. They were evaluated as ASA class-1 or 2 without systemic complications. The patients were divided into four groups on the basis of anesthesia technique. Patients in group 1 received N_2O and isoflurane anesthesia, group 2 received N_2O and sevoflurane (S) anesthesia, group 3 received continuous epidural analgesia combined with N_2O and isoflurane, and group 4 received epidural analgesia combined with N_2O and sevoflurane anesthesia.

Anesthesia protocol was almost the same as in experiment one. In groups 3 and 4, two milliliters of 2% plain mepivacaine were injected as a test dose into the epidural catheter with the patient in the supine recumbent position. 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 on pinprick test after 15 min. The patients showing an analgesia level over Th_4 were given two-thirds of the initial dose at 50 min intervals throughout the operation. In groups 1 and 2, 15-20 mL of saline solution were injected into the epidural space as a control. The catheter was used to inject 6 mL of 0.25% bupivacaine and 0.1 mg of buprenorphine after the research followed by continuous injection of 0.25% bupivacaine 2 mL/h for inhibition of postoperative pain.

Blood samples were taken from arterial catheter before induction of anesthesia, 1 h after the start of the operation, and 1 h after recovery from the anesthesia. Plasma cortisol, EP and NE were determined as

Table 1. Background parameters of patients in part-1 study

Group	1	2	3
Age	53.5±5.4	59.0±7.9	50.4±13.9
Body height (cm)	160.9±12.0	157.6±8.9	156.1±5.7
Body weight (kg)	60.1±12.0	54.3±5.7	55.0±8.8
Duration of operation (min)	159±36	141±48	132±37
Duration of anesthesia (min)	201±41	203±51	179±41
Amounts of isoflurane (MACE • h)	3.3±1.3	3.5±1.3	0.9±0.1*
Fluid infused (mL)	2548±735	2305±735	1938±432
Urine out put (mL)	180±156	180±253	141±91
Bleeding volume (mL)	359±200	256±115	307±243
Lowest BP (mmHg)	66.3±8.7	71.6±10.9	60.8±12.5

* significant difference among 3 groups

indicators of responses to surgical injury. Analysis of these hormones are same as described above. The subpopulation of T lymphocytes was analysed as a quantitative determination of immune response. In the first step. the proportion of inducer/helper T lymphocytes ($CD4^+$ cells) and suppressor/cytotoxic T lymphocytes ($CD8^+$ cells) was 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 operation and 1 h after recovery from anesthesia. Monoclonal antibodies against cell membrane antigen, anti-CD4 and anti-CD8 (OKT4-FITC and OKT8-FITC, Orthodiagnostic System, Raritan, New Zealand), 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 ($CD4^+$ cells/$CD45R^+$ cells) using two color analysis. The combination of monoclonal antibodies against cell membrane antigens, anti-CD4 (CD4-FITC, Becton-Dickinson, Franklin Lakes, New Zealand) and anti-CD45R (2H4-RRD1, Coulter, Miami, Florida), 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 subpopulation to the total number of peripheral lymphocytes. Continuous variables were presented as means with standard deviations when distribution was normal. Difference in three or more groups was tested by one-way analysis of variance, and Student's t-test was used to test the

Table 2. Plasma levels of prostanoid metabolites

	Before anesthesia	After induction	30 min of op	End of op	60 min after op
6-keto-PGF1α (pg/mL)					
group-1	6.2±2.7	7.3±3.9	290±21.2*	76.5±52.1*	50.5±34.1*
group-2	6.9±3.6	6.4±3.7	11.5±9.9###!!!	9.5±6.6###!!!	11.9±7.7*##!!
group-3	5.1±3.3	5.0±2.3	227.4±173.4*	77.3±49.3*	51.5±44.5*
TXB2 (pg/mL)					
group-1	21.9±11.3	56.9±28.0*	191.3±82.5*	191.8±127.8*	278.6±241.1*
group-2	9.0±6.4	9.2±7.833	12.4±11.3###!!!	21.2±13.3*###!!!	13.7±11.0###!!!
group-3	20.3±16.9	16.2±6.7##	104.8±41.3*#	189.9±73.6*	112.0±51.3*###
11-DTX (pg/mL)					
group-1	9.1±3.8	11.9± 6.1*	34.6±11.6*	69.6±14.1*	63.4±12.4*
group-2	6.8±2.5	7.9±3.7	7.8±2.8###!	9.4±3.4###!!!	8.8±3,5###!!!
group-3	5.9±2.2	7.4±3.2	15.0±6.1*###	33.1±8.2*###	29.5±9.1*###

*: significant difference ($p<0.05$) compared to values before anesthesia
#,##,###: significant differences ($p<0.05$, $p<0.01$, $p<0.001$) compared to values in group 1
!,!!,!!!: significant differences ($p<0.05$, $p<0.01$, $p<0.001$) compared to values in group 3

Table 3. Changes in stress hormones and catecholamines

	Before anesthesia	After induction	30 min of op	End of op	60 min after op
ACTH (pg/mL)					
group-1	27.1±20.9	24.5±24.7	227.0±144.0*	750.0±354.0*	716.3±371.4*
group-2	19.8±6.6	12.5 ±6.1*	135.3±94.5*	425.0±309.4*	407.9±314.2*
group-3	33.9±31.3	32.5±27.2	229.1±179.1*	513.8±431.0*	434.8±415.6
cortisol (mg/mL)					
group-1	13.3±11.3	11.0±4.8*	23.0±3.6**	30.1±7.4**	31.3±8.6**
group-2	11.5±6.4	9.8±2.5*	18.0±6.3*	26.8±5.1*	29.1±4.8*
group-3	21.6±24.3	15.9±13.0*	20.2±8.4	36.4±26.4*	33.9±18.5*
EP (pg/mL)					
group-1	102±75	22±11**	143±161	244±247*	348±247*
group-2	96±71	28±19*	65±56	230±302	308±323*
group-3	69±48	12±5*##	112±143	101±85	129±96*
NE (pg/mL)					
group-1	128±53	143±40	379±161**	337±233*	361±187**
group-2	182±102	255±116*	649±337*	461±388*	402±349*
group-3	111±53	53±44*##	85±48*##	171±87	159±77#

*,**: differences ($p<0.05$, $p<0.01$) compared to values before anesthesia
#,##: differences ($p<0.05$, $p<0.01$) compared to values in other two groups

Table 4. Changes in blood glucose level

Group	Before anesthesia	After induction	30 min of op	End of op	60 min after op
1	96.1±7.7	93.9±7.0*	127.8±16.5*	141.0±13.6*	146.5±16.3*
2	111.9±17.2	106.9±16.9*	138.9±24.9* ##	137.3±29.1*	145.1±32.7*
3	95.5±14.3	91.0±10.8*	103.0±16.3 #	122.0±20.0*	124.6±23.1*

* difference compared to values before anesthesia
#, ## difference compared to values in groups 1

Table 5. Patient characteristics of the four groups in Experiment Two

Group	1	2	3	4
Number of patients	6	6	8	8
Anesthetic	I + N_2O	S + N_2O	I + N_2O + E	S + N_2O + E
Age	51±5	55±3	56±9	52±4
Height (cm)	165±5	161±8	161±13	161±6
Anesthesia time (min)	285±30	246±26	267±40	263±40
Operation time (min)	196±30	184±20	192±39	203±41
Bleeding volume (mL)	706±288	636±234	676±300	724±260
Infused volume (mL)	2654±816	2456±357	2950±699	3052±540
Urine volume (mL)	260±88	226±93	143±104	346±253

I isoflurane
S sevoflurane
E epidermal blockade

Table 6. Time course of the changes in mean arterial pressure and heart rate

	Before anesthesia	During operation	After operation
Group 1			
MAP (mmHg)	97±8	93±6	91±7
HR (bpm)	74±12	77±14	77±16
Group 2			
MAP (mmHg)	101±9	93±6	92±6
HR (bpm)	73±12	78±9	76±14
Group 3			
MAP (mmHg)	97±14	75±14* #	87±3
HR (bpm)	76±11	78±6	80±14
Group 4			
MAP (mmHg)	93±5	76±11* #	94±17
HR (bpm)	81±18	73±10	73±13

* significance ($p<0.05$) compared to values before anesthesia
# significance ($p<0.05$) compared to values in Groups 1 and 2

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

Experiment One

There were no differences among three groups with regard to age, body weight, body height, duration of anesthesia, bleeding volume, lowest systolic blood pressure during anesthesia (Table 1). Total amount of isoflurane administered was smaller in group 3 than groups 1 and 2 (Table 1). No patient received blood transfusion during anesthesia. The upper limit of analgesia was at Th_4 when checked after ten minutes of spinal block and Th_5 in recovery room. Spinal analgesia was confirmed to continue throughout the operation.

The changes in plasma concentration of metabolites of prostanoids are shown in Table 2. The plasma level of 6 keto-$PGF_1\alpha$ depicted peaks at 30 min after the beginning of operation in groups 1 and 3, being followed by significantly higher levels throughout the operation and in recovery room. However, group 2, which was pretreated with indomethacin showed only slight but significant elevation at 60 min after the end of operation. There were remarkable differences between group 2 and the other two groups, at 30 min after the beginning of operation, at end of the operation, and 1 h after the operation. The plasma level of TXB2 elevated significantly after endotracheal intubation, followed by gradual increases throughout the study in group 1. In group 3, the plasma value was significantly elevated at 30 min after the beginning of operation, and showed lower levels than those in group 1. However, group 2 showed slight but significant elevation at 60 min after the end of operation in 6-keto-$PGF_1\alpha$. The changes in 11-DTX in three groups were similar to those in TXB2.

Changes in plasma levels of ACTH, cortisol and catecholamines are depicted in Table 3. The plasma level of ACTH was significantly elevated after 30 min of operation in all groups. There was no difference among the 3 groups at any point. Plasma level of cortisol paralleled as ACTH, showing transit decline after induction of anesthesia. Epinephrine concentration elevated significantly at 30 min after the beginning of the operation, in the recovery room in group 1, and in the recovery room in groups 2 and 3. Norepinephrine concentration increased markedly at 30 min after the beginning of the operation in groups 1 and 2. However, plasma level decreased significantly during the operation in group 3.

Blood glucose concentration increased significantly after the beginning of the operation in group 1 and 2, and in the recovery room in group 2 (Table 4). There were significant differences between group 3 and the other two groups after 30 minutes of operation.

In summary, patients in group 2 who received indomethacin did not show elevation of plasma levels of prostanoid metabolites, but showed increases of stress hormones.

On the other hand, patients in group 3 who received spinal analgesia showed elevation of plasma stress hormones and metabolites of prostanoid, but did not depict high catecholamine levels.

Experiment Two

Background parameters of patients are shown in Table 5. There was no difference among the four groups in all parameters. 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. Mean arterial pressure was significantly lower in groups 3 and 4 during operation than in the preanesthetic controls and matched that in groups without epidural block (Table 6).

The changes in stress hormone concentration are shown in Table 7. Plasma EP concentration increased significantly in groups 1 and 2 during the operation, followed by 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 seen in group 4 at 1 h after recovery from analgesia. Plasma NE was significantly increased in groups 1 and 2 during the operation and after recovery

Table 7. Changes in plasma levels of stress hormones

	Before anesthesia	During operation	After operation
EP (pb/mL)			
Group 1	40±20	80±48* #	220±188* #
Group 2	30±17	90±32* #	230±130* #
Group 3	30±11	20±11	50±37
Group 4	20±14	30±20	70±24*
NE (pg/mL)			
Group 1	140±49	310±230* #	560±320*
Group 2	130±63	390±205	700±428*
Group 3	120±44	110±63	540±318*
Group 4	130±70	110±56	570±344*
Cortisol (μg/mL)			
Group 1	10.1±7.2	18.7±4.0*	25.6±2.8*
Group 2	11.2±4.5	22.7±5.6*	28.0±4.2
Group 3	9.6±3.3	21.2±2.8*	25.1±2.3
Group 4	15.3±4.6	24.1±1.4*	34.1±5.7

* significance ($p<0.05$) compared to values before anesthesia
# significance ($p<0.05$) compared to values in groups 3 and 4

Table 8. Changes in lymphocyte subpopulations

	Before anesthesia	During operation	After operation
$CD4^+$(5)			
Group 1	42.2±8.4	36.4±6.9	35.0±7.7*
Group 2	42.3±7.3	36.0±6.9	33.7±6.9*
Group 3	42.8±8.7	44.6±7.5	38.0±11.4
Group 4	40.0±6.2	39.6±5.1	27.8±8.8*
$CD8^+$(5)			
Group 1	19.1±4.1	21.1±3.9	17.2±4.3
Group 2	24.0±7.8	24.4±6.9	19.9±6.8
Group 3	23.1±5.0	24.5±4.7	20.0±4.9
Group 4	26.6±5.3	28.2±4.5	27.8±6.2
$CD4^+/CD8^+$			
Group 1	2.4±1.1	1.8±0.6	2.2±0.9
Group 2	2.1±1.0	1.6±0.5	2.3±1.2
Group 3	2.1±0.7	2.0±0.5	2.1±0.8
Group 4	1.5±0.6	1.5±0.5	1.1±0.7
$CD6^+/CD29W^+$			
Group 1	26.6±6.7	24.1±5.4	19.9±4.4*
Group 2	27.1±5.3	23.1±7.3	19.6±5.4*
Group 3	24.1±6.6	25.9±7.8	20.7±5.5
Group 4	26.0±4.95	25.6±4.7	17.3±5.8*
$CD4^+/CD45R^+$			
Group 1	12.3±3.5	11.0±2.7	13.3±5.4
Group 2	15.3±5.5	11.2±3.7	14.8±4.5
Group 3	15.1±2.8	14.9±2.5	14.9±2.8
Group 4	13.5±3.1	15.9±5.4	9.7±3.6

* significance ($p<0.05$) compared to values before anesthesia

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. The plasma cortisol level increased significantly during the operation in the 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.

Distribution of the subpopulations of T lymphocytes is shown in Table 8. 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 $CD4^+/CD8^+$ ratio 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.

In summary, EN 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. The $CD4^+/CD8^+$ in blood was maintained unchanged in group 3, which received epidural analgesia during upper abdominal operation.

DISCUSSION

Surgical procedures are injurious to the human body. Surgical invasion into tissues and nerve endings produces noxious stimuli and the stimuli are transmitted to the posterior horn of spinal cord or the trigeminal nuclei. The noxious stimuli reach the posteromedial ventral nucleus of the thalamus via lateral spino-thalamic tract or ventral central trigeminal tract. The pain impulses are transferred to second connector neurons via thalamocortical radiation. The noxious stimuli are also projected to nucleus tractus solitarus and ventro-lateral medulla, reaching ventral hypothalamus and paraventricular nucleus. Coordination of hypothalamic nuclei produces neuroendocrine response against surgical injuries.[8]

Surgical procedures also induce inflammatory reaction. It was observed that there was an increase in the plasma activity of interleukin-1 (IL-1) during major operation.[9] This substance is released by activated human monocytes/macrophages, inducing other cytokines. Several cytokines, especially IL-1, IL-2, IL-6 and TNF activate the adrenal axis, acting at the central nervous system, and at pituitary and adrenal levels.[10]

Hypovolemia, hypoperfusion of vital organs, disturbances of cellular circumstances, coldness, lack in substrate supply and so on, during anesthesia and operation may be stressful for the patients.

The tendency to maintain the relative constancy of certain variables, even in the face of environmental change, is known as homeostasis. The surgical invasion is an environmental change, disturbing homeostasis. The response of the neuroendocrine system and consequent alterations in intermediary metabolism, are aimed at restoring homeostasis in surgical patients. However, excessive responses give rise to pathological conditions such as high fever, increased energy expenditure, lipolysis, depletion of plasma water and defect in host defense.

In the first part of the present study, we tried preemptive analgesia against postoperative pain using spinal block. Plasma EP and NE levels remained unchanged during the operation with concomittantly lower levels in metabolites of prostanoids, compared to control groups. However, plasma concentrations of stress hormones such as ACTH and cortisol showed high values in patients who received spinal block. The facts suggest that inflammatory reactions in the operative field induced pituitary-adrenal gland activation. On the other hand, pretreatment of cyclo-oxigenase inhibitor indomethacin prevented the production of prostanoid metabolites, but could not suppress neuroendocrine reponses. It is suggested that pain impulses play a vital role in inducing neuroendocrine responses.

Modern surgical treatment requires prolonged anesthesia and has a profound effect on the host defense mechanism. Lymphocytes are critical in the development of cell-mediated immune reaction. Functional classification of T cells became possible with the introduction of monoclonal antibodies such as OKT and Leu series. The subpopulation of T cells is divided into inducer/helper T cells ($CD4^+$) and suppressor/cytotoxic T cells ($CD8^+$). The former includes lymphocytes which stimulate an immune reaction, and the latter contains lymphocytes which inhibit immune responses and are cytotoxic.

Tokutomi et al.[11] reported that the $CD4^+/CD8^+$ ratio is significantly decreased in patients anesthetized with inhalational anesthetics. Asakura et al.[12] investigated the changes in $CD4^+/CD8^+$ ratio in patients anesthetized with enflurane, isoflurane, and sevoflurane combined with N_2O for various kinds of operations, and found that the ratio was significantly decreased in patients who were given sevoflurane and N_2O anesthesia. Tonnesen et al.,[13] Slade et al.,[14] and Hosokawa et al.[15] 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. Induction of helper T cells and B cells, $CD4^+/CD29W^+$ cells, was significantly reduced in groups 1, 2, and 4 after anesthesia in the present study. On the other hand, reduction of T cells ($CD4^+$ and $CD4^+/CD29W^+$) was prevented in group 3 patients who received epidural analgesia during and after the operation. The results suggest strongly that immune response was sustained in group 3.

CONCLUSION

(1)Pretreatment of cyclo-oxygenase inhibitor indomethacin suppressed inflammatory reaction but did not attenuate neuroendocrine responses in patients who underwent lower abdominal operation. On the other hand, the block of noxious stimuli by spinal analgesia impeded excessive neuroendocrine and inflammatory reactions perioperatively. (2) Prevention of noxious stimuli that originate from the operative field through epidural block could prevent reduction of helper-inducer T cells in patients who were receiving upper abdominal operation under isoflurane-N_2O anesthesia. (3) Freedom from noxious stimuli during and after surgery was very important in preventing excessive response of the neuroendocrine system to surgical stress. STI

REFERENCES

1. Kuntchen FR, Galletti PM, Hahn G, et al. Alterations of insulin and glucose metabolism during cardiopulmonary bypass under normothermia. J Thorac Cardiovas Surg 1985; 89:97-106.
2. Chernow B, Alexander HR, Smallridge RC,

et al. Hormonal responses to graded surgical stress. Arch Intern Med 1987;147:1273-7.
3. Cruickshank AM, Fraser WD, Burns HJG, et al. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. Clin Sci 1990;79:161-5.
4. Shaw JHF, Galler L, Holdaway IM, et al. The effect of extradural blockade upon glucose and urea kinetics in surgical patients. Surg Gynecol Obstet 1987;165:260-5.
5. Simpson PJ, Radford SG, Lockyer JA. The influence of anesthesia on the acute phase protein response to surgery. Anaesthesia 1987; 42: 690-6.
6. Asoh T, Shirasaka C, Uchida I, et al. Effect of indomethacin on endocrine responses and nitrogen loss after surgery. Ann Surg 1987;206:770-6.
7. Schulze S, Sonmer P, Gigler D, et al. Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response after colonic surgery. Arch Surg 1992;127: 325-31.
8. Gann DS, Berieter DA, Dallman MF, et al. Neural interaction in control of adrenocorticotropin. Fed Proc 1985;44:161-95.
9. Naito Y, Tamai S, Shingu K, et al. Responses of plasma adrenocorticotropic hormone, cortisol, and cytokines during and after upper abdominal surgery. Anesthesiology 1992;77:426-32.
10. Imura H, Fukata J, Mori T. Cytokines and endocrine function; an interaction between the immune and neuroendocrine systems. Clinical Endoclinology 1991;35:107-15.
11. Tokutomi Y, Muteki T, Okubo K, et al. Influence of anesthesia on immune system: studies on fluctuation of lymphocyte subpopulation (in Japanese with English abstract). Masui (Jap J Anesthesiol) 1983;32: 1523-8.
12. Asakura Y, Goto F, Fujita T. Effect of inhalational anesthetics on immunological system (in Japanese, with English abstract). Rinshoumasui (J Clin Anesth) 1989;13:603-7.
13. Tonnesen E, Mickley H, Grunnet N. Natural killer cell activity during premedication, anesthesia and surgery. Acta Anaesthesiol Scand 1983;131:1178-81.
14. Slade MS, Simmons RL, Yunis E. Immunomodulation after major surgery in normal patient. Surgery 1975;78:363-72.
15. Hosokawa T, Hori Y, Miyazaki M, et al. Interaction between immunological change and serum cortisol concentration in patients ubdergoing majar and minor surgery. In: Mtuki A, Ishihara H, Oyama T (eds). Endocrine response to anesthesia and intensive care. Elsevier, Amsterdam; 1990. p 157-163.