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The Effect of Combined Epidural and Light General Anesthesia on Stress Hormones in Open Heart Surgery Patients

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Abstract: This study was designed to evaluate the potential advantages of combined epidural and light general anesthesia over the commonly employed general anesthesia during open heart surgery. Twenty-four patients undergoing mitral valve replacement were thus studied. General anesthesia was maintained with an isoflurane–nitrous oxide–oxygen gas mixture and morphine sulfate (0.4 mg/kg i.v. initially) followed by postoperative pain control with morphine in 12 patients (group GA). The remaining 12 patients (group EAA) received continuous epidural bupivacaine (0.125%)–morphine (50 μg/ml) supplemented with the same gas mixture as group GA. Epidural infusion was continued until the third postoperative day. Changes in the serum cortisol and β-endorphin levels together with postoperative pain relief defined as good (scale 0–2), fair (3–4), or poor (5–10) were observed serially. Lower cortisol levels were observed in group EAA than in group GA ($P < 0.05$) just before skin closure, on the second and the third postoperative day. The β-endorphin levels were substantially lower in group EAA than in group GA throughout the observation. The pain scores were good in 2 patients (17%), fair in 6 (50%), and poor in 4 (33%) for group GA, and good in 8 (67%), fair in 3 (25%), and poor in 1 (8%) for group EAA. We thus conclude that a combined epidural and light general anesthesia is considered to attenuate the stress response and thereby provides a better quality of postoperative pain control.

Key Words: epidural anesthesia, open heart surgery, postoperative pain relief, stress hormones

Introduction

Recently, several investigations comparing general anesthesia with combined epidural and light general anesthesia (EAA) have been reported.[1,2] The merits of regional anesthesia include a reduced intraoperative blood loss,[3] a decrease in postoperative catabolism,[4] improved postoperative pulmonary function,[5] and a reduction in the stress response.[6,7] Combined epidural and light general anesthesia has also been associated with less sedation,[8] earlier ambulation,[9] better pulmonary function,[10] improved oxygenation,[8] and better pain control.[11] Although the advantages of a combined technique over general anesthesia alone may be controversial, postoperative pain control with epidural analgesia has been shown to be advantageous over the routine administration of intermittent intravenous opiates.[11,12] The most commonly employed method of pain control for open heart surgery is the systemic injection of opioids, which thus include disadvantages such as unpredictable pain relief, a delay in recovery, and the need for large amounts of opioids.[13,14] The purpose of this study was to determine whether the use of combined epidural and general anesthesia for open heart surgery may improve the quality of perioperative analgesia and attenuate the endocrine response to surgical stress.

Patients and Methods

This study was approved by the Korea University Hospital Ethics Committee, and informed consent was obtained from each patient prior to surgery. Twenty-four patients scheduled for mitral valve replacement were randomly divided into two groups of equal number. Group GA ($n = 12$) was designated as the general anesthesia group, and received the routine intraoperative anesthesia with an oxygen–nitrous oxide–isoflurane gas mixture and morphine. Postoperative pain was controlled with the intermittent intravenous injection of morphine (2–3 mg) as needed. The group EAA patients ($n = 12$) received combined epidural and light general anesthesia, and postoperative pain control with a continuous epidural infusion. Premedication con-

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sisted of morphine (0.1–0.2 mg/kg) and glycopyrrolate (0.03–0.04 mg/kg) 1 h before anesthesia. In all patients, anesthesia was induced with intravenous thiopental (3–4 mg/kg) followed by vecuronium (0.1 mg/kg) to facilitate both intubation and mechanical ventilation. In group GA, anesthesia was maintained with a nitrous oxide (2 l/min)–oxygen (2 l/min)–isoflurane (1.0–2.0 vol%) gas mixture and morphine, initially 0.4 mg/kg i.v., was given followed by supplements as needed. In group EAA, an epidural puncture was performed with an 18-gauge Tuohy needle in the T3–4 intervertebral space in a left lateral decubitus position. After the epidural space was identified, a test dose of 2% lidocaine (3–4 ml) was administered before the induction of anesthesia. Five minutes later, 20 ml of a combination of 0.125% bupivacaine and 6 mg of morphine was given slowly as a bolus dose. The level of the neural block was tested 15 min later, and infusion using an infusion pump (Terumo syringe pump, model stc-523, Tokyo, Japan) was started at a rate of 3–5 ml/h (mixture of 0.125% bupivacaine with 50 μg/ml of morphine). The continuous epidural infusion was then continued until the third postoperative day. An electrocardiogram was made while the arterial blood pressure was monitored by means of radial artery cannulation. In addition, a pulmonary artery catheter (Swan-Ganz) was inserted before the start of surgery to measure the hemodynamic profile with a cardiac output computer (Arrow International, model AI-07350, Reading, PA, USA). Blood samples for stress hormones, including cortisol and β-endorphin, were obtained before induction, 30 min after skin incision, 60 min after induction or before cardiopulmonary bypass (CPB), 30 min after CPB, before skin closure, on the first, second, and third postoperative day (POD). Cortisol was determined by a time-resolved fluoroimmunoassay using a Delphia kit (Wallac, Turku, Finland) while β-endorphin was determined using high pressure lipid chromatography. The blood sample was placed in a cold tube within 5 min after withdrawal and was then centrifuged. The plasma was stored at −20°C until analyzed. After the completion of the operation, each patient was carried to the surgical intensive care unit for postoperative care including mechanical ventilation. The severity of pain was scored according to the visual analog pain scale (VAS) (Table 1) as suggested by Jorgensen et al.[15] The VAS evaluation was performed at 8 A.M. on the first POD and every 12 h after that until the third POD. The quality of pain relief was then evaluated as good, fair, and poor (Table 2). Epidural catheters were removed in all patients at the end of the study. The unpaired Student's *t*-test was used for a statistical analysis. Data comparisons involving the ratios or proportions were performed using the chi-square test. A value of $P < 0.05$ was considered to be statistically significant.

Table 1. Visual analog pain scale[15]

0	No pain
1–2	No pain at rest, slight pain on movement
3–4	Slight pain at rest, moderate pain on movement and coughing
5–6	Moderate pain at rest, severe pain on movement and coughing
7–8	Severe pain at rest, excruciating pain on movement and coughing
9–10	Excruciating pain at rest

Table 2. Quality of pain relief

Quality	Visual analog pain scale
Good	0–2
Fair	3–4
Poor	5–10

Table 3. Postoperative pain relief

Quality of pain relief	Group GA	Group EEA
Good (0–2)*	2 (17%)	8 (67%)
Fair (3–4)	6 (50%)	3 (25%)
Poor (5–10)	4 (33%)	1 (8%)

GA, General anesthesia; EAA, combined epidural and light general anesthesia
* $P < 0.001$, group GA *vs* group EAA

Results

Patient Profile

There was no significant difference between the two groups regarding age (30 ± 5 years for group GA *vs* 35 ± 14 for group EAA), weight (51 ± 8 *vs* 50 ± 13 kg), height (159 ± 6 *vs* 156 ± 10 cm), body surface area (1.57 ± 0.13 *vs* 1.55 ± 0.10 m^2), duration of surgery (332 ± 37 *vs* 366 ± 84 min), or cardiopulmonary bypass (72 ± 16 *vs* 83 ± 18 min).

Plasma Concentration of Cortisol and β-Endorphin

Plasma cortisol levels were significantly lower in group EAA than in group GA before skin closure, on the second POD and third POD ($P < 0.05$). In the plasma β-endorphin levels, no statistically significant differences were observed between the two groups (Fig. 1).

Postoperative Pain

Postoperative pain relief showed a higher percentage of good pain relief in group EAA than in group GA (67% *vs* 17%, $P < 0.001$) (Table 3).

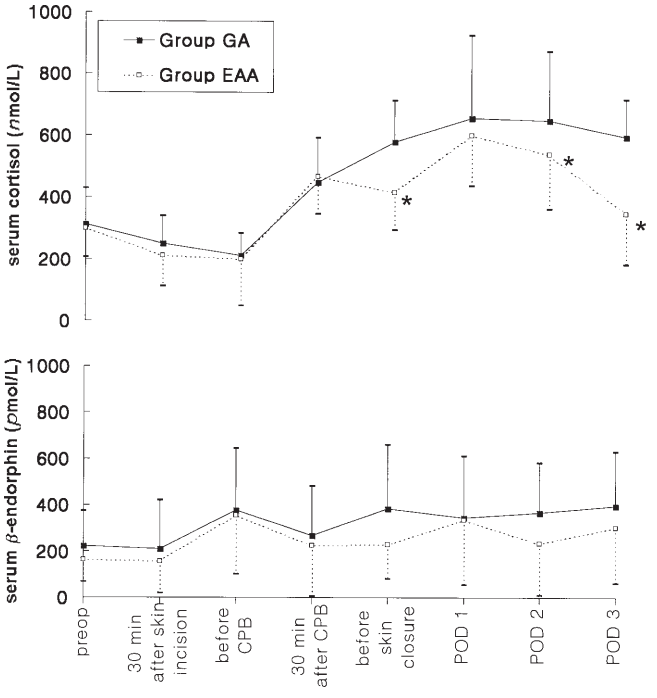

Fig. 1. Changes in serum cortisol and serum β-endorphin in both *group GA* and *group EAA*. Values were recorded preoperatively, 30 min after skin incision, before cardiopulmonary bypass (*CPB*), 30 min after CPB, before skin closure, postoperative day (*POD*) 1, POD 2, and POD 3. Each point and error bar shows mean and SD. $*P < 0.05$ *vs* group GA

Discussion

In the 1970s, several studies on intrathecal and epidural opiates resulted in the widespread clinical application of pain control.[16] Since then, there has been growing interest in the use of regional anesthesia in combination with general anesthesia for the management of high-risk surgical patients scheduled for major abdominal or vascular surgery.[1,2] These studies have shown that the advantages of EAA include a reduction in the overall complication rate with a lowed incidence of cardiovascular failure and major infectious complications, with less need for prolonged ventilatory support, improved pulmonary function and postoperative analgesia, and a reduction in the release of stress hormones.[5,17,18] In spite of such favorable outcomes, the overall merit of EAA over general anesthesia remains controversial.[19]

A significant reduction in the total dose of intraoperative morphine in the EAA group is predicted since epidural anesthesia, even with a low dose of morphine and bupivacaine, can abolish the nociceptive pathways to provide adequate anesthesia.[20,21] Our study of an epidural block extending from T1 to T10 showed a relatively stable hemodynamic profile. The hemodynamic stability seen in this study results from the low concentration of bupivacaine given. Bupivacaine at a concentration of 0.125% does not cause a profound sympathetic block. In addition, it reduces the total amount of bupivacaine in the circulation. Large doses of local anesthetics themselves may also cause physiologic derangement as a result of the direct pharmacological effects of the circulating blood concentrations.

Surgical trauma results in endocrine and metabolic changes as evidenced by the acute rise in stress reactant hormones such as catecholamines, cortisol, glucagon,[22] and β-endorphin.[23] Recognizing the factors precipitating the stress response and applying appropriate therapeutic methods to minimize these changes are important, because morbidity in high-risk surgical patients may be reduced by inhibiting the surgically induced endocrine response, hypermetabolism, and increased demands on the body mass and physiologic reserve.[24] High-dose opiate anesthesia has been commonly used for cardiovascular procedures because of the hemodynamic stability offered, and it has also been shown to be initially effective in preventing most endocrine and metabolic responses to surgery. This effect, however, lasted only until the cardiopulmonary bypass procedure, and no effect was seen in the postoperative period.[25,26] In addition, the use of high-dose narcotics also results in prolonged central narcosis and prolonged recovery.[12] Although morphine is ineffective when given alone, studies have shown that morphine enhances and prolongs the block achieved by bupivacaine.[27,28] We selected a combination of low-dose bupivacaine and morphine for this study. Afferent neurogenic blockade with epidural anesthesia using a local anesthetic has been demonstrated to inhibit or prevent most of the endocrine and metabolic changes following lower abdominal surgery.[29] However, epidural anesthesia is less efficient in attenuating the response associated with major upper abdominal surgery.[30,31] Bromage et al.[30] postulated that the failure to stop the increase in cortisol levels in upper abdominal or thoracic surgery was due to the vagal impulses to the hypothalamus where ACTH is released, thus causing cortisol to be released from the adrenal cortex. However, Traynor et al.[31] showed that a vagal nerve failed to inhibit the increase in the cortisol blood level in upper abdominal surgery under epidural anesthesia. The stress associated with upper abdominal or thoracic procedures may be so great that it is difficult for an epidural or spinal block to inhibit all nociceptive pathways. Our study established an epidural block from T1 to T10, and found that the cortisol levels were significantly lower in the EAA group before skin closure, on POD2, and POD3, and although no significant differences were seen in β-endorphin levels, the EAA group showed consistently lower levels throughout the study. This shows that the T1–T10 block with low concentra-

tions of bupivacaine and morphine can attenuate the stress response to surgery.

Effective pain control is essential for the optimal care of surgical patients. Epidural infusion of a local anesthetic agent acts by blocking neural conduction in the mixed spinal nerves to provide effective, segmental spinal analgesia, and improves postoperative respiratory and cardiovascular functions.[25] However, the potential side effects include motor paralysis and the loss of autonomic nervous functions such as bradycardia and hypotension caused by sympathetic block.[20]

Epidural opioids bind to the opiate receptors in the substantia gelatinosa of the posterior spinal cord gray matter and cause selective blockade of nociceptive pathways, providing profound, prolonged, and selective pain relief without a neuronal blockade. Large epidural doses of morphine, however, show a high incidence of nausea, vomiting, pruritus, urinary retention, and respiratory depression.[23,32] Although low-dose epidural morphine has been shown to provide adequate pain relief after pulmonary operations with minimal side effects, pain relief is incomplete with occasional episodes of severe pain.[20]

A combination of local anesthetic agents and opioids has been shown to provide an excellent analgesic effect.[33] The analgesia obtained is more rapid in onset, more prolonged, and more complete.[34] This combination allows a reduction in the total dose of each agent, thus reducing the risk for side effects while still providing adequate pain relief. This combination also attenuates the adverse neuroendocrine and stress responses to surgery. In our study, the use of 0.125% bupivacaine mixed with morphine (50 μg/ml) given as a continuous infusion provided superior analgesia over intramuscular morphine. Sixty-seven percent of the patients with epidural infusion reported a good quality of pain relief, while those with intramuscular morphine reported good pain relief in only 17%.

Reservations about the use of epidural anesthesia combined with general anesthesia for open heart surgery is due mainly to the risk of epidural hematoma, since open heart surgery involves heparin anticoagulation. Rao and E1 Etr,[35] in a large-scale study of 3146 patients receiving heparin during vascular surgery, demonstrated the safe use of epidural analgesia without any associated epidural hematoma or neurologic damage. However, DeAngelis[36] and Crawford[37] consider epidural analgesia to be a contraindication for patients receiving anticoagulants. Although our study, which cosisted of only 24 patients, is far from sufficient to determine whether such a procedure is safe, no cases of epidural hematoma were seen.

In conclusion, a combination of epidural and light general anesthesia was found to be safe and effective for open heart surgery patients, and its beneficial effects were an attenuation of the stress response and a better quality of postoperative pain control. As an attractive alternative to general anesthesia, a further careful clinical application of combined anesthesia is thus warranted, based on the findings of this study.

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