Effect of monitored anesthesia care using dexmedetomidine on stress hormones and interleukin-6 in patients undergoing arteriovenous fistula formation

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Surgical procedures, as well as anesthetics, affect stress hormones and proinflammatory cytokines. Therefore, we investigated the effect of two different anesthetic techniques on intraoperative hormonal stress responses and interleukin-6 (IL-6) in patients with chronic renal disease undergoing arteriovenous fistula formation. Eighteen patients aged above 20 years were randomly divided into two groups: group A (n=8) with axillary brachial plexus block and group MAC (n=10) with monitored anesthesia care (MAC) using dexmedetomidine. The levels of epinephrine, norepinephrine, cortisol, glucose, IL-6, and heat shock protein 70 (HSP70) were recorded at pre-anesthesia (T0) and end of surgery (T3). No significant differences in epinephrine and HSP70 were observed between these two groups or within each group. Norepinephrine was significantly decreased in group MAC compared with group A at T3 ($p=0.001$), but no significant differences were found within each group. The cortisol level in group MAC significantly decreased at T3 compared with T0 ($p=0.028$). The glucose level in group MAC significantly increased at T3 compared with T0 ($p=0.019$). No significant differences in IL-6 levels were observed within each group. In conclusion, in this study, neither monitored anesthesia nor regional anesthesia influenced stress hormones and pro-inflammatory cytokines in patients undergoing arteriovenous fistula formation, but significant changes in cortisol and glucose levels were observed in the group receiving dexmedetomidine.

Keywords: Brachial plexus block; Dexmedetomidine; Interleukin-6; Chronic kidney failure; Hormones

INTRODUCTION

Surgery-associated stress response causes extensive immunological changes and can be immunosuppressive [1–3]. Catecholamines and glucocorticoids are the major stress hormones and play a key role in stress-induced suppression of the immune system, and the immune suppression is associ-

ated with high risks of infection and postoperative complications [4]. However, recent evidence indicates that the surgery-associated stress might suppress cellular immunity but boost humoral immunity [5,6]. Stress hormones inhibit the production of proinflammatory cytokines but stimulate the production of anti-inflammatory cytokines [5]. Through modulation of pro/anti-inflammatory cytokine balance, stress hormones

may suppress or potentiate the inflammatory response [5]. In addition, one of the interesting stress hormones is extracellular heat shock protein (HSP), which acts as a molecular chaperone and maintains cell homeostasis under physiological and stress conditions [7]. HSP70 has biphasic inflammatory effects: extracellular HSP70 has pro-inflammatory effects, but intracellular HSP70 primarily has anti-inflammatory and anti-apoptotic effects [7].

Stress hormones (such as epinephrine, norepinephrine, and cortisol) and proinflammatory cytokines (such as interleukin-6 [IL-6]) can be affected by surgical procedures [8,9], and they also can be influenced by anesthetics and adjuvants during and after anesthesia [10–12]. It was reported that total intravenous anesthesia and regional anesthesia attenuated the increase of stress hormones more than did inhalational anesthesia. However, it is still debated whether the IL-6 level is affected by different anesthetic techniques [10,13]. Furthermore, no reports have compared levels of stress hormones and pro-inflammatory cytokines during regional anesthesia and monitored anesthesia care (MAC).

Therefore, we hypothesized that MAC with dexmedetomidine and remifentanyl attenuates stress-induced changes in hormones and pro-inflammatory cytokines more compared with regional anesthesia with axillary brachial plexus block. The effect of the anesthetic techniques on perioperative changes of stress hormones (a primary outcome) was investigated.

MATERIALS AND METHODS

This prospective, randomized, controlled, and double-blinded study was approved by the Institutional Review Board of Chosun University Hospital (IRB no. 11S-263). Written

informed consent was obtained from all participants, legal surrogates, or parents or legal guardians of participants who were minors.

A total of 40 patients, who were scheduled to undergo arteriovenous fistula formation because of chronic renal disease, were enrolled in this study. These patients were more than 20 years old and the American Society of Anesthesiologists (ASA) physical status I, II, or III. The patients with preoperative hypertension (above 180 mmHg of systolic blood pressure) or hypotension (below 90 mmHg of systolic blood pressure), preoperative bradycardia (below 50 beats/min), cardiac conduction disorders or arrhythmias, preoperative desaturation (less than 90%), mental disorders, and allergy or resistance to drugs used in this study; those taking medication comprising other sedatives or anxiolytics; as well as pregnant or breastfeeding women were excluded in this study.

All patients were randomly divided into two groups using a random number table obtained via a computer program (Fig. 1): 1) Group A (n=20) with regional anesthesia using axillary brachial plexus block and 2) Group MAC (n=20) with MAC using dexmedetomidine and remifentanyl. Patients and investigators were blinded to the study medications, but a nurse handed out randomized medications (indistinguishable) and numbered syringes using a table of random numbers.

Intramuscular midazolam (0.05 mg/kg) was administered 30 minutes before anesthesia induction. Subsequently, all patients were transported to the operating room. Before the induction of anesthesia, standard patient monitoring devices were administered. Subsequently, a catheter was installed in a radial artery to continuously monitor blood pressure.

In Group A, an axillary brachial plexus block was performed in position with abduction of the arm 90° using a 22-gauge, 100 mm block needle (disposable nerve blockade

Fig. 1. CONSORT flow chart.

needle metal hub; Hakko Co., Ltd, Nagano, Japan) and the M-Turbo System (SonoSite Inc., Bothwell, WA, USA). In order to prevent the technical variants between performers, all studies were performed by one investigator. After identification of axillary artery and brachial plexus using a 13–6 MHz ultrasound transducer (SonoSite Inc.), the needle was inserted in-plane and 0.75% ropivacaine (each 15 mL) was deposited in areas of the radial, ulnar, and median nerve. Finally, the needle was redirected toward the musculocutaneous nerve, and 0.75% ropivacaine (10 mL) was deposited. Subsequently, two syringes filled with normal saline were infused using a target-controlled infusion (TCI) pump (Orchestra[®]; Fresenius Vial, Brezins, France) with the same techniques as used in group MAC.

In group MAC, an axillary brachial plexus block using normal saline was performed with aforementioned techniques. Thereafter, dexmedetomidine and remifentanyl were infused simultaneously. Dexmedetomidine (1 µg/kg) was loaded during 10 minutes, followed by continuous infusion at the infusion rate of 1.0 µg/kg/h using a TCI pump. Remifentanyl was infused at target effect-site concentrations of 2.5 ng/mL using a TCI pump. Dexmedetomidine and remifentanyl concentrations were controlled to maintain the bispectral index score in the range of 40 to 60 and mean arterial pressure changes within $\pm 20\%$.

Fifteen minutes after anesthesia, surgery started under oxygenation via a facial mask and monitor of ET_{CO}₂ so that the proper anesthetic status of each patient was confirmed. If deoxygenation or hypoventilation was happened, the face mask ventilation was administered. If sudden arousal happened, arterial bold gas analysis was performed to evaluate hypercarbia. Systolic hypotension (≤ 90 mmHg) and bradycardia (≤ 50 beats/min) were treated with intermittent bolus injections of ephedrine (10 mg) and atropine (0.5 mg), respectively. Systolic hypertension (≥ 180 mmHg) was treated with intermittent bolus injections of peridipine (1 mg).

The levels of epinephrine, norepinephrine, cortisol, glucose, IL-6, and HSP70 were recorded at pre-anesthesia (T0) and end of surgery (T3). The arterial pressure, heart rate, arterial partial pressure of oxygen (PaO₂), and ET_{CO}₂ at fifteen minutes after anesthetic induction (T1), incision (T2), and end of surgery (T3) were compared with those at pre-anesthesia (T0). Age, sex, height, weight, ASA physical status, operation time, and anesthesia time were also recorded.

Statistical analysis

The necessary sample size was calculated with t-tests of G*Power software (ver. 3.1.9.1) by taking the level of the statistical significance as $\alpha=0.05$ and $\beta=0.2$ using an expected effect size of 0.95. Total 38 patients were required, but 40 patients were enrolled in this study considering the assumption of a 5% dropout rate.

IBM SPSS Statistics for Windows ver. 21.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. All measured values are presented as median (interquartile range), or number of patients. The levels of epinephrine, norepinephrine, cortisol, glucose, IL-6, and HSP70 were analyzed using a Mann-Whitney U test between groups and a Wilcoxon signed ranks test within each group because of skewed distribution of data. The changes of arterial pressure, heart rate, PaO₂, and ET_{CO}₂ were analyzed using a Mann-Whitney U test between groups because of skewed distribution of data. The sex and ASA physical status were analyzed using the Fisher's exact test. The age, height, weight, operation time, and anesthesia time were analyzed using a Mann-Whitney U test. A p-value less than 0.05 indicates a statistical difference.

RESULTS

Eighteen patients were ultimately enrolled in this study because of early termination of this study (Fig. 1). No significant differences in sex, age, height, weight, ASA physical status, operation time, and anesthesia time were found between these two groups (Table 1).

The Mann-Whitney U test and Wilcoxon signed rank test indicated that no significant differences in levels of epinephrine and HSP70 were observed between these two groups or within each group at T0 and T3 (Fig. 2).

The level of norepinephrine significantly decreased in group MAC (median: 107.7 pg/mL, 22 pg/mL) compared with group A (median: 410.4 pg/mL, 496.4 pg/mL) at T0, T3 (U=8.0, 5.0; p=0.003, 0.001) (Fig. 2). Analysis within each group by a Wilcoxon signed rank test showed that the norepinephrine levels were not significantly different between T3 and T0 (Fig. 2).

The Wilcoxon signed rank test revealed that the levels of cortisol statistically significantly decreased at T3 (median: 9.5 µg/dL) compared with T0 (median: 13.2 µg/dL) in group MAC (z=-2.19; p=0.028) (Fig. 2). However, no significant differences

Table 1. Characteristics of patients

Characteristic	Group A (n=8)	Group MAC (n=10)	p-value
Sex (male/female)	2/6	5/5	0.367
ASA physical status (I/II/III)	0/2/6	0/7/3	0.153
Age (y)	64.0 (32.0–68.0)	55.0 (44.8–67.8)	0.829
Height (cm)	158.5 (156.0–167.8)	166.5 (160.5–170.0)	0.360
Weight (kg)	58.8 (53.5–64.0)	56.5 (51.5–65.5)	0.965
Operation time (min)	152.5 (107.5–171.3)	162.5 (112.5–197.5)	0.762
Anesthesia time (min)	180.0 (123.8–191.3)	162.5 (132.5–213.8)	0.633

Values are presented as number only or median (interquartile range). No significant differences were observed between these two groups. $p < 0.05$ was considered statistically significant. ASA: American Society of Anesthesiologists.

Fig. 2. Levels of epinephrine, norepinephrine, cortisol, glucose, interleukin-6 (IL-6), and heat shock protein 70 (HSP70). Outliers are represented by open circles (○), and extreme outliers are represented by closed circles (●). T0, at pre-anesthesia; T3, at end of surgery. * $p < 0.05$ was considered statistically significant when two groups were compared. † $p < 0.05$ was considered statistically significant when the values of T0 and T3 were compared within each group.

in cortisol levels were observed at T3 compared with T0 in group A (Fig. 2).

It was found by a Wilcoxon signed rank test that the levels of glucose significantly increased at T3 (median: 121 mg/

dL) compared with T0 (median: 104 mg/dL) in group MAC ($z = -2.35$; $p = 0.019$) (Fig. 2). However, the glucose levels were not significantly different between T3 and T0 in group A (Fig. 2).

Fig. 3. Intraoperative changes of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and heart rate (HR). Outliers are represented by open circles ($\circ$), and extreme outliers are represented by closed circles ($\bullet$). T0, at pre-anesthesia; T1, at fifteen minutes after anesthetic induction; T2, at incision; T3, at end of surgery.

The levels of IL-6 significantly decreased in group MAC (median: 2.5 pg/mL) compared with group A (median: 10.2 pg/mL) at T0 ($U=16$; $p=0.034$) (Fig. 2). Analysis within each group by a Wilcoxon signed rank test showed that the IL-6 levels were not significantly different between T3 and T0 (Fig. 2).

The levels of arterial pressure, heart rate, PaO_2 , and ETCO_2 were not statistically significantly changed in group MAC compared with group A (Figs. 3 and 4).

DISCUSSION

This study showed that the cortisol and glucose levels were statistically significantly changed in patients receiving MAC using dexmedetomidine and remifentanyl but not in patients receiving regional anesthesia using axillary brachial plexus block at the end of surgery. In addition, the IL-6 level was not significantly altered in both groups.

It has been known that the catecholamine concentration was significantly elevated in patients with chronic renal failure compared with age-matched normal controls, and the concentration of plasma epinephrine and norepinephrine was 77 pg/dL and 330 pg/dL, respectively, in patients with renal disease [14,15]. Patients with end-stage renal disease also showed increased levels of pro-inflammatory cytokines (such as IL-1, IL-6, and tumor necrosis factor [TNF]- α), cortisol, and glucose

Fig. 4. Intraoperative changes of arterial partial pressure of oxygen (PaO_2) and end-tidal partial pressure of carbon dioxide (ETCO_2). Outliers are represented by open circles ($\circ$). T0, at pre-anesthesia; T1, at fifteen minutes after anesthetic induction; T2, at incision; T3, at end of surgery.

[16–18]. Particularly, cortisol levels in serum were significantly higher in patients with impaired glomerular filtration rate [19]. In the present study, the baseline values of catecholamines were similar to those in previous published reports, and the baseline values of other parameters were within upper normal ranges in patients with end stage renal disease.

Dexmedetomidine, an α -2 adrenoceptor agonist, induces a biphasic cardiovascular response with an initial short-term increased blood pressure followed by a long-lasting decreased blood pressure and heart rate [20]. Dexmedetomidine reduces the circulating catecholamines (such as epinephrine and norepinephrine) on average by approximately 70%, and the role may be associated with its negative inotropic effect [21,22]. In addition, dexmedetomidine significantly decreases the levels of cortisol and glucose, although the levels of catecholamines increase significantly relative to baseline values after surgery, which was aimed to prevent adverse hemodynamic changes [23–25]. Dexmedetomidine-induced stress hormonal changes significantly reduce the levels of pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6, and stimulate the production of anti-inflammatory cytokines [5,12,26–30].

Patients with chronic renal disease have upregulated HSP70, which might play a role in initiation and/or progression of atherosclerosis [31]. HSP70 protects cell and tissue against stress damage, and particularly, extracellular HSP70 has been reported to have a pro-inflammatory effect [7,32]. Any kind of stress may influence expression of HSP70, but the association of circulating HSP70 with post-surgery complica-

tions is poorly understood [33,34]. The HSP70 level increased immediately after surgery and was significantly correlated with the IL-6 level [33], and patients with more aggressive surgery had a significantly increased HSP70 level [35].

It has been reported that total intravenous anesthesia attenuates the postoperative increase of cortisol, epinephrine, norepinephrine, and glucose more than does inhalational anesthesia [10,13,36]. Regional anesthesia, such as epidural anesthesia, is also associated with less increased stress hormones levels compared with general anesthesia [11,37]. However, it is still unknown whether the IL-6 level is affected by different anesthetic techniques [10,13,36]. Furthermore, no reports have compared the levels of stress hormones and pro-inflammatory cytokines between regional anesthesia and MAC.

In this study, no significant changes in catecholamines, cortisol, glucose, IL-6, and HSP70 were observed during regional anesthesia using axillary brachial plexus block. However, the cortisol level significantly decreased, and the glucose level significantly increased in patients receiving MAC using dexmedetomidine, although no significant changes in catecholamines, IL-6, and HSP70 were found.

This discrepancy of results regarding stress hormones, IL-6, and HSP70 between previous published reports and our present study may be explained as follows. First, we could not enroll enough patients as planned for the calculated sample size in this study. Thus, this study did not satisfy the initial assumed statistical power (0.8). Analysis of stress hormones, IL-6, and HSP70 had low statistical powers, which were between 0.06 (IL-6) and 0.72 (glucose). Second, the sub-group analysis could not be performed according to the first redo procedure because of low statistical powers. Third, some baseline parameters were significantly different between these two groups because of small sample size, as mentioned above.

In conclusion, in this study, neither monitored anesthesia nor regional anesthesia influenced stress hormones and pro-inflammatory cytokines in patients undergoing arteriovenous fistula formation, but significant changes in cortisol and glucose levels were found in the group receiving dexmedetomidine. Patients with MAC using dexmedetomidine showed significantly decreased cortisol and increased glucose level at end of surgery compared with before surgery. Therefore, further studies, with increased sample size, are needed for more exact interpretation of this study's results.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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