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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Effectiveness of the combination of midazolam and dexmedetomidine on the perioperative stress response evaluated by IL-6, HSP60, and cortisol levels

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ABSTRACT

Background & objective: Stress response to surgery is a reaction to tissue damage with wide-ranging effects in the neuroendocrine and immunological fields. The synergistic effects of midazolam and dexmedetomidine can inhibit this response. We aimed to determine the inhibiting effect of the combination of midazolam and dexmedetomidine on the perioperative stress response compared to midazolam alone.

Methodology: A total of 40 patients scheduled to undergo total knee or hip replacement surgery with regional anesthesia were included in this double-blind, randomized controlled trial with a pre-test and post-test design. The participants were divided into two study groups: the treatment group (Group MD) and the control group (Group M). Changes in body stress response during surgery were assessed by measuring Interleukin 6 (IL-6), HSP60, and cortisol levels in the blood samples using ELISA.

Results: The test results of the subject showed significant differences in the IL-6 ($P = 0.043$), HSP60 ($P = 0.001$), and cortisol levels ($P = 0.016$). Multivariate analysis using Hotelling's T square test showed $P < 0.01$. Furthermore, discriminant analysis showed that combining midazolam and dexmedetomidine significantly reduced HSP60 and cortisol levels.

Conclusion: The combination of midazolam and dexmedetomidine proved more effective than midazolam alone in reducing the perioperative stress response in patients scheduled to undergo total knee or hip replacement surgery under regional anesthesia.

Abbreviations: IL-6 - Interleukin-6; LoS - Length of stay;

Keywords: Surgical stress response; Arthroplasty; Midazolam; Dexmedetomidine

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1. INTRODUCTION

Perioperative stress is a significant and extensively studied concern that may hinder the seamless progression of surgery, potentially giving rise to complications, especially in patients with pre-existing medical conditions or comorbidities.[1] This could lead to an extended length of stay (LOS), elevated morbidity and mortality rates, and a diminished quality of life after surgery.[2]

Surgical wounds can trigger a local response, with manifestations including the release of damage-associated molecular patterns (DAMPs) such as mtDNA (mitochondrial deoxyribonucleic acid) and HMGB1 (high mobility group box 1).[3] These DAMPs activate macrophages/monocytes through toll-like receptors (TLRs) to produce pro-inflammatory cytokines, namely IL-1β (Interleukin-1β), IL-6 (Interleukin-6), and TNF-α (Tumor Necrosis Factor-α).[4] The cytokines and DAMPs prompt the activation and recruitment of neutrophils and macrophages/monocytes to the inflamed area.[5] Surgery not only causes a local reaction but also a systemic one by activating the SAM (sympathetic-adrenal-medullary) axis and an HPA (hypothalamic-pituitary-adrenal) axis, which result in the release of catecholamines (epinephrine and norepinephrine) and cortisol.[6] Hormones like these stimulate immune cells in the bloodstream to generate anti-inflammatory cytokines such as TGF-β (transforming growth factor beta) and IL-10 (Interleukin-10), which trigger a response from regulatory T cells, particularly type 2 T helper (Th2) cells.[7] Heat shock proteins (HSPs) enhance the function of regulatory T cells. As a result, injured tissues show a pro-inflammatory response, while leukocytes in the bloodstream manifest an anti-inflammatory and hypo-reactive profile.[8] Adaptation to surgical stress includes the synchronization of local inflammation with systemic anti-inflammation, ensuring the concentration of activated phagocytes and other effectors solely at the site of injury.[9,10]

Dexmedetomidine is a selective and specific α-2 adrenergic agonist used in anesthesia and for sedation.[11] The application of this drug has been extensively documented for its antinociceptive and sympatholytic properties. Additionally, it shows the potential to synergize with other anesthetic agents, thereby assisting in the control of hemodynamic responses during surgery.[12] Midazolam is a minor tranquillizer and is widely used to allay the anxiety in the patients and to induce sedation when required in the operating rooms or in the intensive care units (ICU). We aimed to determine the inhibiting effect of the combination of midazolam and dexmedetomidine on the perioperative stress response compared to midazolam alone.

2. METHODOLOGY

After approval by the Health Research Ethics Commission (No. 408/EC/KEPK/FK-UNDIP/X/2021), a total of 86 patients, scheduled for either total knee replacement (TKR) or total hip replacement (THR) were recruited for the study. After a thorough selection process, 54 of them met the inclusion criteria. Five patients with decompensated heart failure (NYHA II-III), 4 with a history of asthma and wheezing on physical examination, and 5 with uncontrolled diabetes mellitus (DM) were excluded.

2.1. Study procedure

The study method used was a double-blind randomized controlled trial with pre-test-post-test design. The patients were scheduled for TKR/THR procedures. Intraoperative monitoring was conducted according to ASA standards, which included non-invasive blood pressure and pulse oximetry. The amount of bleeding during the procedure was calculated. Patients were randomly divided into Groups MD and Group M.

All patients received spinal anesthesia with 2 ml of hyperbaric 0.5% bupivacaine, supplemented with 20 µg of fentanyl and 0.1 mg of morphine. After completing motor and sensory blockade, the participants in Group MD were administrated a bolus of midazolam 0.07 mg/kg IV, followed by infusion of 1 mg/h. Then dexmedetomidine was administered at 1 µg/kg for 10 min, followed by an infusion of 0.2 µg/kg/h. Group M, the control group, received midazolam 0.07 mg/kg IV, followed by infusion of 1 mg/h, plus a bolus of normal saline followed by infusion. All groups received postoperative analgesics, 30 mg ketorolac, and 100 mg intravenous tramadol, administered every 8 hours. Patients who complained of pain during and after the surgery were given additional analgesic, specifically fentanyl 50 µg IV. IL-6, HSP60, and cortisol levels were examined in the subjects before and immediately after the treatment was completed. Mean arterial pressure (MAP) and heart rate (HR) were assessed as markers of variations in serum catecholamine levels. Changes in body stress response during surgery were assessed by measuring IL-6, HSP60, and cortisol levels in the blood using ELISA.

2.2. Data analysis

SPSS Statistics version 17.0 was used to analyze the data, and significance was set at $P < 0.05$.

3. RESULTS

The groups had no significant differences in patient demographics, as shown in Table 1. The average age of the entire sample was 68.78 ± 7.76 y, with the youngest

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Table 1: Demographic characteristics

Variables	Group MD (n = 20)	Group M (n = 20)	p-value
Age (y)	68.75 ± 7.92	68.80 ± 7.59	0.984‡
Gender (F:M)	12:08	10:10	0.525£
Education status			
-Elementary;	10	11	0.766£
-Junior High School	08	06	
-Senior high school	02	03	
Employment status			
-Employed	04	04	0.569£
-Housewife	10	07	
-Unemployed	06	09	
BMI (kg/m^2)	23.75 ± 2.1	23.10 ± 2.1	0.265‡

Data shown as numbers or mean ± SD; ‡independent t-test. £chi-square

Table 2: Comparative heart rate data

Heart rate (beats/min)	Group MD	Group M	p-values
T0 h	74.70 ± 3.45	72.80 ± 3.21.	0.146
T1	63.58 ± 2.79	65.32 ± 2.79	0.470
T2	58.20 ± 2.97	67.00 ± 3.08	0.000*

*Data shown as mean ± SD; Shapiro-Wilk, Mann Whitney-U, or independent t-test, * significant*

Table 3: MAP data

MAP (mmHg)	Group MD	Group M	p-value
T0	87.40 ± 1.96	88.50 ± 2.04	0.146
T1	88.00 ± 1.59	91.34 ± 1.52	0.470
T2	78.00 ± 2.97	84.00 ± 2.90	0.000*

*Data shown as the mean ± SD; Mann-Whitney U; *significant*

Table 4: Preliminary data

Variable	Group MD	Group M	P-values
Baseline IL-6 levels	27.10 ± 19.24	25.57 ± 15.97	0.766‡
Baseline HSP60 levels	73.68 ± 21.83	76.91 ± 23.90	0.441‡
Baseline cortisol levels	205.15 ± 55.24	212.45 ± 48.90	0.929£

Data on baseline IL-6 and HSP60 levels are shown as mean ± SD; ‡ Mann Whitney-U. £ independent t-test

and oldest being 58 and 75 y, respectively. Specifically, the average age in the Group MD was 68.75 ± 7.92, and in the Group M it was 68.80 ± 7.59 y. The Shapiro-Wilk test for ages shows the normal distribution for the Group MD (P = 0.151) and the Group M (P = 0.193); however, there were no statistical differences in the two groups' age features according to an independent T-test for mean age (P = 0.984).

No participants had attained bachelor's or postgraduate education levels. In total, 21 (52.5%), 14 (35%), and 5 (12.5%) were elementary school graduates or equivalent, junior high school graduates or equivalent, and high school graduates or equivalent. The distribution of employment in the entire sample in this study included 8 (20%) farmers/laborers, 17 (42.5%) housewives, and 15 (37.5%) unemployed. The average Body Mass Index (BMI) of the entire sample was 23.43 ± 1.8. The Group MD's BMI (P = 0.088) and that of the Group M (P = 0.374), and both followed a normal distribution.

The average initial HR for the entire sample was 73.75 ± 3.33 beats per minute. The Group MD's HR data (P = 0.108) and the Group M's HR data (P = 0.252) demonstrate a normal distribution, according to the Shapiro-Wilk test. The two groups had no significant differences, according to an independent T-test performed at the start of the administration (P = 0.925) (see Table 2).

Table 3 shows that the initial MAP measurements ranged from a maximum of 90 mmHg to a minimum of 82 mmHg, with an average of 88.50 ± 2.04 mmHg for the Group M. Meanwhile, the Group MD ranged from 90 mmHg to 84 mmHg, with an average of 87.40 ± 1.96 mmHg. The initial MAP data were not normally distributed; the control (P = 0.000) and the Group MD (P = 0.017) were subjected to a Shapiro-Wilk test. No significant differences were found between the two groups according to the Mann-Whitney U test (P = 0.146).

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Table 5: Data on differences pre- and post-surgery in IL-6, HSP60, and cortisol levels

Variable	Group MD	Group M	P-values
Difference in IL-6 levels (pg/ml)	↓ 0.94± 4.83	0.84 ± 0.20	0.043*
Difference in HSP60 levels (ng/ml)	↓ 14.20 ± 8.17	↓4.03 ± 2.24	0.001*
Difference in cortisol levels	↓ 40.65 ± 21.52	27.20 ± 15.20	0.016*

Data on differences in IL-6, HSP60 and cortisol levels are showed as mean ± SD; P < 0.05 considered as significant

Table 6: Covariate analysis between both groups in length of operation, pain scores, and depression index

Statistics	P-values
Homogeneity (Levene's test)	
○ IL-6 difference	0.474
○ HSP60 Difference	0.333
○ Cortisol Difference	0.474
Covariance matrix (Box's M)	0.238
Multivariate analysis (Hotelling' Trace)	0.000*
Between-subjects effect test	
○ IL-6 difference	0.043*
○ HSP60 Difference	0.001*
○ Cortisol Difference	0.016*
Covariance analysis (Hotelling' Trace)	0.919
Length of operation	0.531
Pain Score	0.877
Depression Index	0.753

Table 4 shows the preliminary data of baseline levels of IL-6, HSP60, and cortisol levels. The Shapiro-Wilk test revealed that the baseline IL-6 values in both the Group MD (P = 0.001) and Group M (P = 0.046) were normally distributed. Finally, there were no significant differences in the two groups according to the Mann-Whitney U test (P = 0.766). The baseline HSP60 values in the Group MD (P = 0.029) and Group M (P = 0.011) were not normally distributed. There were no significant differences between the two groups according to the Mann-Whitney U test (P = 0.441). Cortisol data for the control (P = 0.091) and the Group MD (P = 0.112) were normally distributed in the Shapiro-Wilk test. An independent t-test conducted showed no significant differences in cortisol levels in the 2 groups (P = 0.929).

Table 5 shows the differences in IL-6, HSP60, and cortisol levels between pre- and post-surgery levels. IL-6 levels in the Group MD were decreased, while In the Group M were increased. HSP60 levels were decreased in the Group MD and Group M. Furthermore, the cortisol levels were decreased in the Group MD, whereas in the Group M increased the difference. Multivariate analysis showed significant differences in the deviation of IL-6, HSP60, and cortisol levels before and after surgery.

A covariate analysis of the influence of length of operation, pain score, and depression index is presented in Table 6. Hotelling's trace for the two groups did not show statistically significant differences (P = 0.919). Likewise, the Mann-Whitney U test results for length of operation, pain score, and depression index did not show statistical differences.

Table 7 shows the strength of the variables, namely the difference between cortisol and HSP60 levels as a function of differentiation between the two groups. The largest variable interaction was the difference in HSP60, followed by cortisol. Meanwhile, the difference in IL-6 had no statistical interaction with the group.

Table 7: Fisher's coefficient of difference in cortisol and HSP60 levels

Classification Function Coefficients	Group MD	Group M
Differences in cortisol levels (ng/ml)	0.028	0.038
Differences in HSP60 levels	0.158	0.236
Constant	-5.798	-11.063

4. DISCUSSION

No significant differences were found between the Group MD and Group M (P = 0.766) in the chi-square test for education levels. The two groups had no statistical differences according to the chi-square test for the occupation distribution (P = 0.569). Statistically, there were no significant differences between the two groups according to the independent T-test (P = 0.265).

Following surgery, the HR and MAP were lower in Group MD than those of the Group M. This is likely due to central sympatholytic effects resulting from α2 adrenergic receptor stimulation and subsequent relative enhancement of cholinergic activity, leading to cholinergic anti-inflammatory effects.[13,14] It may be possible that antinociceptive activity of dexmedetomidine results in anti-inflammatory benefits.[15]

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A significant decrease was shown in multivariate analysis in the difference in IL-6 levels ($P < 0.043$) in the comparison of Group MD and Group M. This reduction implies changes that occurred during the treatment period. Exploration and testing of initial IL-6 levels data of the samples before treatment showed no significant difference ($P = 0.766$). These results were in accordance with the theory, where administration of dexmedetomidine during surgery reduced IL-6 levels significantly.[16-18] However, in step 2 of the discriminant analysis, this variable was no longer included in the calculation. This means that statistically, it has a small interaction with other variables.

When it comes to the inflammatory reaction following trauma and surgery, cytokines are crucial; by initiating systemic alterations and mediating and sustaining the anti-inflammatory response to tissue injury, they produce local effects. The primary cytokines produced following major surgery are TNF-α, IL-6, and IL-1.[19,20] The first response in injured tissue is the production of TNFα and IL-1 by monocytes and macrophages. This release causes more cytokines to be produced and released, especially IL-6, which is in charge of causing acute phase responses in the body.[21] The concentrations of this protein circulating in the blood were usually very low and undetectable. IL-6 concentrations start to rise 30–60 min after surgery starts, reaching a considerable level in 2-4 h. Lower release of cytokines occurs with less traumatic and less invasive procedures like laparoscopic surgery because levels of cytokine production correlate with the degree of tissue stress. The highest increase in IL-6 occurred in major surgery such as joint replacement, as well as vascular and colorectal surgery. After this surgery, cytokine concentrations reach their peak in 24 hours and stay high for 48–72 hours after the surgery.[20–22]

A substantial reduction ($P < 0.01$) in HSP60 was seen in the Group MD as compared to the Group M based on multivariate analysis. Prior to therapy, investigation of the original HSP60 level revealed no discernible difference ($P = 0.441$). The results of the observation of a decrease in the difference showed the changes that occurred during the treatment period. These results are in accordance with theory, where administration of dexmedetomidine during surgery reduced HSP60 levels significantly.[23]

When cells experience stress, there is an increase in HSP expression as it tries to protect the cell from changes in the formation of protein structures. HSP is a protein molecule that helps maintain the structural and functional homeostasis of cells under normal conditions and during times of stress. HSP60 acts as a signaling molecule when the body is under stress, triggering the secretion of pro-inflammatory cytokines and the expression of adhesion molecules in various myeloid cell types, including vascular smooth muscle cells. It has anti-apoptotic effects by repairing damaged cells to restore their normal function. The increased levels of HSP counteract the effects of ischemia and increase the production of ROS (reactive oxygen species). In the event of changes during protein folding, the body tries to maintain homeostasis through various mechanisms, including protein repair and denaturation.[14,24-26]

Cortisol levels in the both groups differed significantly ($P = 0.016$) according to multivariate analysis. In preliminary measurements, there were no statistical differences in the research groups ($P = 0.929$). This suggests that, before treatment, all samples had similar initial cortisol levels. The observed decrease in the final difference values showed changes that occurred during the treatment period. These results were consistent with previous studies, where dexmedetomidine administration reduced cortisol production.[27]

At the onset of surgery, there is a rapid increase in cortisol secretion from the adrenal cortex due to stimulation by ACTH. Depending on the extent of surgical injuries, the elevated concentration can rise from 400 nmol/liter to >1,500 nmol/L in 4-6 h. This is altered by anesthetic interventions.[22,27,28] Under normal conditions, feedback mechanisms play a role in inhibiting further release of ACTH due to the increased concentration of circulating cortisol in the blood.[29] However, following surgery, when both hormone concentrations are still high, this mechanism does not seem to work.[30]

The metabolic response is a simultaneous reaction to immunological and neuroendocrine responses. Increased cortisol and catecholamines affect the balance between glucagon and insulin. This metabolic response is characterized by hyperglycemia, protein catabolism, increased fat breakdown (lipolysis), and resorption of bones.[31] In stressful conditions, there is an increase in cortisol secretion.[32] The concentration is directly proportional to the duration and severity of the surgery.[33]

Regional anesthesia using local anesthetics can prevent the endocrine and metabolic responses in pelvic and lower limb surgery.[27] When given prior to the commencement of surgery, spinal or epidural blocks covering the T4 to S5 dermatomal segments minimize the rise in cortisol and glucose levels linked to TKR/THR. Adrenocortical and glycemic reactions to surgery are minimized by inhibiting efferent autonomous neurons to the liver and adrenal medulla, as well as afferent inputs from the surgical site to the central nervous system and the hypothalamic-pituitary axis.[27,34]

Dexmedetomidine can suppress sympathetic tone, both centrally and peripherally. In this study, cortisol levels

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decreased by 20% compared to the average initial value in the therapy group, while in the control group these increased by 12%. This is in accordance with previous studies where dexmedetomidine reduced cortisol levels by up to 30% compared to controls. Dexmedetomidine can suppress sympathetic tone, both centrally and peripherally.[27,35]

The differences in cortisol and HSP60 have a positive role or interaction in both groups. Among the variables, the most remarkable is the difference in HSP60, followed by cortisol. In contrast, the difference in IL-6 levels does not show a statistically significant interaction with the groups. The classification analysis results show the same discriminating power in the original grouped and cross-validated grouped data, amounting to 95%. This implied that the variable removed from the analysis (the difference in IL-6) has limited interaction with cortisol and HSP60 despite yielding significant results in bivariate analysis. As a result, the IL-6 variable has an individual discriminatory function but interacts only slightly with cortisol and HSP60. In discriminant analysis, IL-6 also appears to have a small contribution.

Surgical trauma causes significant physiological abnormalities, such as immunological, inflammatory, and metabolic responses, which affect several organ functions. The overall effects are generally referred to as surgical stress response. Activation of strong inflammatory mediators, such as cytokines or afferent sympathetic nervous system nerves, caused this reaction. Pro- and anti-inflammatory cytokines are in balance in healthy people. Nevertheless, when this protein is secreted excessively after sepsis, trauma, or neoplasms, the balance is upset, increasing morbidity and death.[15,36,37]

The suppression of harmful aspects of inflammation in the context of surgery and anesthesia is a critical method for improving surgical outcomes. This study also investigates dexmedetomidine's anti-inflammatory effects on patients subjected to surgical stress and anesthesia. The difference in IL-6 levels was significantly lower in the Group MD compared to the control. This shows that dexmedetomidine mitigates the inflammatory response during surgery accompanied by stress.[38] Strong α2 adrenergic agonist have a broader spectrum of activities, including anxiolysis, sedation, analgesia, and sympatholytic effects; however, it is more selective than clonidine.[11,39] Current research shows that dexmedetomidine may potentially have anti-inflammatory properties. Previous studies on animals have shown that the medication reduces cytokine secretion and recommend its preemptive administration before surgical stress occurs.[11,27,38,39] Consequently, the initial dose was given before surgery.

In this study, the significantly reduced need for additional analgesics in the therapy group may be attributed to the antinociceptive effect of this medication. The spinal method and anesthetic agents used (bupivacaine, fentanyl, and morphine) may relatively contribute to the lack of prominent cytokine response, as both are known to weaken systemic inflammatory response on and post-surgery. Anesthesia-related factors support this concept, as they affect both groups, but there is a clear difference in cytokine concentrations. Consequently, it seems that the produced anti-inflammatory impact is reflected in the variations in cytokine levels.

5. CONCLUSION

The combination of midazolam and dexmedetomidine proved more effective than midazolam alone in reducing the perioperative stress response. Further studies are required to determine the effect of dosage on the efficiency of dexmedetomidine.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The authors declare no conflict of interest; and no external or industry funding was involved in this study.

10. Authors' contribution

RHS, LBS, MSH: conception and design

RHS: data collection

RHS, LBS, MSH, HS, SB, E: analysis and interpretation

RHS: manuscript preparation

All authors reviewed the results and approved the final version of the manuscript.

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