RESEARCH

Dexmedetomidine Effects on Surgical Stress Hormones

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ABSTRACT

Background: Increased levels of cortisol and catecholamines are the reaction to tissue damage due to surgical trauma. Dexmedetomidine inhibits the synthesis of these two hormones.

Objective: This study aimed to prove that dexmedetomidine reduces the endocrine response to surgical stress.

Methods: 40 patients who underwent total knee or hip replacement surgery with regional anesthesia were involved in the double-blind randomized controlled trial pre-test – post-test design, which was divided into two research groups: the therapy group and the control group. Changes in the body's response to stress during surgery were compared by assessing blood cortisol levels, heart rates (HRs), and mean arterial pressures (MAPs). The beck depression inventory (BDI) was used to evaluate the level of depression. The numeric rating scale is used to evaluate perioperative pain, while the Ramsay scale is used to measure the level of sedation. Data analysis was carried out using the Statistical Program for Social Sciences (SPSS).

Result: The cortisol levels of the therapy group compared to the control group ($p = 0.016$) decreased significantly immediately after surgery. Hemodynamic changes in the study, the heart rate ($p=0.001$), and mean arterial pressure ($p=0.000$) were significantly lower than the control group.

Conclusion: Administration of dexmedetomidine during the surgical period reduces stress hormone responses. These results indicate that dexmedetomidine administration is good to apply, especially in TKR/THR.

Keywords: arthroplasty; dexmedetomidine; elderly; midazolam; surgical stress response

INTRODUCTION

Stress causes an imbalance in an organism; furthermore, stress can threaten survival and even death.[1,2] The surgical stress response is a pattern of physiological and pathophysiological changes that occur in response to a surgical stimulus, consisting of a neuroendocrine-metabolic response and an inflammatory-immune response.[3,4] This response shows broad, local, and systemic effects on tissue damage.[5,6] This mechanism works simultaneously to maintain body homeostasis, so if it is not managed properly, it will disrupt the smooth operation and potentially cause complications due to interactions with the initial values of previous medical conditions.[7-9]

Surgical wounds can trigger a local response with the manifestation of the release of damage-associated molecular patterns (DAMPs), which stimulate macrophages/ monocytes to produce interleukin (IL-6), interleukin 1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α), namely pro-inflammatory cytokines; furthermore, these cytokines together with DAMPs activate and recruit neutrophils and macrophages/monocytes to areas of inflammation. In addition to this local response, surgery also triggers a systemic response by stimulating the sympathetic-adrenal-medullary (SAM) as well as the hypothalamic-pituitary-adrenal (HPA) axes.[10-12]

Activation of the HPA axis that occurs triggers the release of the stress hormone adrenocorticotropic hormone (ACTH), human growth hormone (HGH), antidiuretic hormone (ADH), β-endorphin, prolactin, cortisol, and glucagon. During the stress of major surgery, for example, in heart and extensive blood vessel surgery, colorectal procedures, and total knee replacement (TKR), or hip (total hip replacement/THR), as in this study, a large amount of corticotropin-releasing hormone (CRH) release occurs. CRH affects the sympathetic nuclei in the locus ceruleus of the brain stem, resulting in sympathoadrenal activation.[3,13–15]

The surgical stress response is characterized by the activity of the sympathetic nervous system, as well as an increase in the release of pituitary hormones. Changes in pituitary secretions have secondary effects on target organs. For example, the adrenal cortex will release cortisol as a result of stimulation from the release of the hormone corticotrophin. The posterior pituitary secretes arginine vasopressin and has effects on the kidneys. Insulin secretion is decreased, and glucagon is inhibited in the pancreas. In general, the metabolic impact of hormonal changes increases catabolism by mobilizing substrates for water and salt storage, cardiovascular homeostasis, balancing fluid volume, and providing energy.[3,13-16]

Stimulation of the sympathetic nervous system in the hypothalamus causes the adrenal glands to produce more catecholamines in the blood, and the presynaptic sarcolemma releases norepinephrine. Norepinephrine is the primary neurotransmitter, but it has also been found that norepinephrine leaks from nerve endings into the circulation. Increased sympathetic activity produces cardiovascular effects in the form of tachycardia and hypertension. In addition, the function of several organs, including the liver, pancreas, and kidneys, is directly influenced by efferent sympathetic stimulation, or

catecholamines circulating in the blood.[11-15]

Patients undergoing surgery using regional anesthesia often experience anxiety. Regional anesthesia can be comfortable but often requires intravenous sedation, one of which is dexmedetomidine.[17-19]
Dexmedetomidine, each of which has the main hypnotic-sedative effect, is commonly used as an adjuvant in regional anaesthesia techniques.[20-22]

A good sedative should be able to calm the patient and reduce anxiety, while a hypnotic can induce drowsiness and help maintain a sleep state that is as close to natural as possible. The endocrine response to the use of dexmedetomidine in TKR and THR has not been clearly reported. Combined dexmedetomidine significantly reduces inflammatory mediators;[23,24] however, in another case, mortality, ventilator-free day, and length of hospital stay did not show a significant impact.[25,26] This study aimed to prove that dexmedetomidine reduces the surgical stress hormones in TKR/THR.

METHOD

This research was designed as an experimental study, a Double-Blind Randomized Controlled Trial Design with a pre-test and post-test, which compared two research groups; it was carried out by comparing changes in the body's response to stress during surgery by assessing blood cortisol levels, heart rate (HR), and mean arterial pressure (MAP) between a combination of midazolam and dexmedetomidine treatment and a control group only receiving midazolam.

Data collection will be carried out throughout 2021. A total of 40 patients (based on the minimum Lameshow sample) from H Soewondo Hospital, Kendal, and Panti Wilasa Citarum Hospital, Semarang, who underwent total knee or hip replacement surgery with regional anesthesia were divided randomly into two research groups, namely the therapy group and control group. All patients underwent TKR/THR using the same surgical technique according to the type of prosthesis. Intraoperative monitoring was performed according to American Society of Anesthesiologists (ASA) standards, using non-invasive blood pressure and pulse oximetry.

All patients got a spinal anesthesia technique using 2 ml of hyperbaric bupivacaine 0.5% plus 20 μg fentanyl and 0.1 mg morphine. After the complete block of motor and sensory, patients in group P received an intravenous bolus injection of midazolam 0.07 mg/kg BW followed by a titration of 1 mg/hour and an intravenous injection of dexmedetomidine 1 μg/kg (for 10 minutes) followed by a titration of 0.2 μg/kg/hour. The treatment of group K was as a control group, which was given an intravenous injection of midazolam 0.07 mg/kg BW bolus followed by titration of 1 mg/hour and normal saline bolus along with titration. All groups received post-operative analgesics, Ketorolac 30 mg and Tramadol 100 mg, intravenously, programmed every 8 hours for 2 days and started during surgery. Patients who complained of pain during and after surgery were given additional analgesic fentanyl 50 μg intravenous bolus. The research subjects had their cortisol levels checked before treatment and immediately after the operation was completed. HR and MAP were also measured as a representation of changes in serum catecholamine levels, measured at T0 (before

induction), T1 (after completion of the dexmedetomidine bolus), and T2 (immediately after completion of surgery).

The numeric rating scale is used to evaluate perioperative pain, while the Ramsay scale is used to measure the level of sedation. If hypotension occurs (blood pressure < 90/60 mmHg), 10 mg i.v. ephedrine injection was given. Anti-emetics are given if there is nausea and vomiting, namely 10 mg i.v. metoclopramide every 8 hours. 0.5 mg i.v sulfasatropine injection is given when bradycardia occurs and is accompanied by a decrease in the dose of sedation medication. Sedation medication is discontinued when consciousness decreases to respiratory depression (RR <8 breaths per minute) and the Ramsay score is more than 3.

Data analysis was carried out using the Statistical Program for Social Sciences (SPSS). A descriptive analysis of age, body mass index (BMI), and cortisol levels is presented through diagrams and average tables. Inferential analysis was carried out according to the homogeneity and normality of the data. This clinical research has received Ethical Clearance approval from the Health Research Ethics Commission number 408/EC/KEPK/FK-UNDIP/X/2021.

RESULTS

Demographic data of the subjects involved in the study (Table 1) shows no significant differences between the two groups. The average age of the patients was 68.78 ± 7.76 years old (y.o); 58 y.o was the youngest age, and the oldest patient was 82 y.o. In the therapy group, the average age of patients was 68.75 ± 7.92 y.o, while in the control group, it was 68.80 ± 7.59 y.o. In the therapy and control groups, the data was normally distributed with a p-value = 0.151, while in the control group, the p-value = 193. The independent T-test on the age variable showed no significant difference between control and treatment (p=0.984).

Table 1. Participants characteristics

Variables	Therapy (n=20)	Control (n=20)	p-value
Ages	68.75 ± 7.92	68.80 ± 7.59	0.984‡
BMI	23.75 ± 2.1	23.10 ± 1.48	0.265‡

Note: BMI and age are displayed as mean ± SD; ‡ independent T-tests

Table 1 also shows that patients had an average body mass index (BMI) of 23.43 ± 1.8, where the average BMI of the therapy group was 23.75 ± 2.1, while the average BMI in the control group was 23.10 ± 1.48. Both groups had normally distributed data, with a p-value of 0.088 for the therapy group, while the control group was 0.374. The independent T-test on the BMI of the therapy and control groups did not show a significant difference (p=0.265) at the start of the study.

The initial heart rates (Table 2) of all samples had an average of 73.75 ± 3.33 beats/minute. In the therapy group, the average HR was 74.70 ± 3.45 beats/minute, while in the control group, the average HR was 72.80 ± 3.21 beats/minute. The therapy and control groups showed normally distributed data with p-values of 0.108 and 0.252, respectively. The independent T-test for the HRs variable of the therapy and control groups showed no significant difference at the start of the study or after

the dexmedetomidine bolus (p-values of 0.925 and 0.470). However, significant differences were shown in post-surgery measurements with a p-value <0.01.

Table 2. Heart rates data

HRs (beats/minute)	Therapy	Control	*p-value*
T0	74.70 ± 3.45	72.80 ± 3.21.	0.925
T1	63.58 ± 2.79	65.32 ± 2.79	0.470
T2	58.20 ± 2.97	67.00 ± 3.08	0.002*

Note: Heart rate data is displayed as the mean ± SD; independent T-test.
* Significant

In the control group, the results of initial mean arterial pressure (MAP) measurements (Table 3) were a maximum of 90 mmHg. In comparison, the minimum was 82 mmHg, and a mean of 88.50 ± 2.04 mmHg. Otherwise, in the therapy group, the results of initial MAP measurements were a maximum of 90 mmHg and a minimum of 84 mmHg with a mean of 87.40 ± 1.96 mmHg. The normality test of the initial MAP data for the two groups shows a normal distribution, with a p-value of 0.000 (control) and a p-value of 0.017 (therapy). The Mann-Whitney U difference test on the two groups showed that the initial MAP data was not significantly different (p=0.146).

At the end of the study, patients who received dexmedetomidine had significantly lower HR and MAP values than the control group. The mean differences with the Independent T-test on the therapy and control groups show a significant impact on both HRs (p-value 0.002) and MAPs (p-value 0.008).

Table 3. Average arterial pressures (MAP) data

MAPs (mmHg)	Therapy	Control	*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	0.008*

Note: MAP data is displayed as the mean value ± SD; independent t; * Significant

The initial serum cortisol level (Table 4) in the control group was a maximum of 292.00 ng/ml, while the minimum was 128.00 ng/ml with a mean of 212.45 ± 48.90 ng/ml. The maximum cortisol level measurement results in the therapy group were 260.00 ng/ml, while the minimum was 80.00 ng/ml with a mean of 205.15 ± 55.24 ng/ml. The distribution of cortisol level data was normal for both groups, namely, a p-value of 0.091 for control and 0.112 for therapy. The two groups did not show significant differences with p = 0.929 using the independent T-test.

The difference in cortisol levels (Table 5) in the control group experienced an average increase of 27.20 ± 15.20 ng/ml. In contrast, the therapy group experienced a decrease of 40.65 ± 21.52 ng/ml. As a result of data exploration of differences in cortisol levels, several outlier data were obtained, so data transformation was carried out. After carrying out the transformation, homogeneous and normally distributed data were obtained.

Table 4. Initial serum cortisol examination data

Variable	Therapy	Control	p-value
Baseline cortisol levels	205.15 ± 55.24	212.45 ± 48.90	0.929‡

Note: Data on initial cortisol levels are displayed as mean ± SD;
‡ independent t-test

Table 5. Data on differences in cortisol levels

Variable	Therapy	Control	*p-value*
Difference in cortisol levels (ng/ml)	↓40.65 ± 21,52	27.20 ± 15.20	0.016*

Note: Data on differences in cortisol levels are displayed as mean ± SD; independent T-test, *significant

The Shapiro-Wilk respiratory rate test showed data results that were not normally distributed, so the test was carried out non-parametrically using the Mann-Whitney U test (Table 6). The test results showed that the data groups compared were statistically insignificant.

Table 7 presents the analysis using Mann-Whitney U because the NRS variable data at rest and movement at pre-surgery, post-surgery, and 24 hours post-surgery are not normally distributed using the Shapiro-Wilk test. The results were statistically significantly different NRS in rest (D) and movement (B) 24 hours after surgery.

The effects that appeared 24 hours after surgery, such as nausea, dizziness, and pruritus, are shown in Table 8. Statistically, the therapy and control groups did not show significant differences. Hypotension and bradycardia showed statistically significant differences. None of the subjects vomited or experienced respiratory depression.

Surgery times, pain score, and depression index were analyzed using the Hotelling' Trace multivariate test as covariates (Table 9). The results of the analysis did not show statistically significant differences in the two groups, namely in the length of operation variable (p=0.531), the pain score variable (p=0.877), and the depression index variable (p=0.753). This means that the influence of the intermediary variable on the dependent variable in both groups is insignificant and can be controlled.

The statistical test used to test the minor hypothesis is multivariate analysis. The mediating factors in this study, namely length of operation, level of pain, and anxiety, were included as covariates. The dependent variable shows homogeneous and normally distributed data (Table 10). Box-M analysis for the equality of variance matrices between variables is p=0.238.

Multivariate analysis used Hotelling's Trace calculations obtained p<0.000. This means that there are therapy and control groups that show different results. The results of the influence test between subjects show that there are significant differences in all dependent variables, namely differences in cortisol levels (p=0.018), HR (p=0.001), and MAP (p<0.01), so the minor hypothesis can be accepted because it shows significant differences variables between the two research groups.

Table 6. Respiratory rates data

Respiratory rates (breaths/minute)	Therapy	Control	*p-value*
T0	12.33 ± 0.778	12.58 ± 0.901	0.245
T1	12.42 ± 0.996	12.83 ± 0.230	0.370
T2	12.50 ± 0.847	12.51 ± 0.905	0.286

Note: Respiratory rate data is displayed as the mean value ± SD; Mann-Whitney U

Table 7. NRS in rest and movement

NRS	Mean Rank		p-value
Rest (D), Movement (B)	Therapy	Control	
NRS D Pre-surgery	21.15	19.85	0.712
NRS D Post-surgery	22.43	18.58	0.247
NRS D 24 hours after	11.85	29.15	0.000*
NRS B Pre-surgery	20.50	20.50	1.000
NRS B Post-surgery	18.50	22.50	0.190
NRS B 24 hours after	15.65	25.35	0.006*

*significant

Table 8. Side effects within 24 hours post-operation

Side effects	Therapy N=20	Control N=20	p-value
Nauseous	45%	30%	0.514
Vomit	0	0	
Bradycardia	50%	0	0.002*
Hypotension	50%	10%	0.008*
Respiratory depression	0	0	
Dizzy	35%	10%	0.130
Pruritus	35%	10%	0.548

*significant

Table 9. Descriptive covariance data

Description of Covariance	Therapy	Control	Between Subject Effect test (p)
Surgery time (minutes)	147 ±30.63	141 ±29.36	0.531
Depression Index	7.00±1.00	7.05±0.99	0.877
Pain Score	2.55±0.94	2.45±0.33	0.753

Table 10. Table of variable test results

Test types	P-value
Homogenity (Levene's test)	
MAP	0.474
HR	0.333
Cortisol differs	0.474
Covariance matrix (Box's M)	0.238
Multivariate analysis (Hotelling' Trace)	0,000*
Between-subjects effect test	
MAP	0.000*
HR	0.001*
Cortisol differs	0.018*
Covariance Analysis (Hotelling' Trace)	0.919
Surgery time	0.531
Pain scores	0.877
Index of depression	0.753

* Significant

DISCUSSION

Multivariate analysis of MAP values showed a significant decrease ($p<0.000$) between the two groups compared (therapy and control). Exploration and testing of initial MAP value data before treatment was given showed that the two treatments did not show statistically significant differences ($p=0.146$). This shows that before treatment, all samples had initial mean MAP values that were not different. The results of observing a decrease in the average MAPs indicate changes that occurred during the treatment period. These results are in accordance with theory, where dexmedetomidine administration during surgery will significantly reduce MAP.[27–30]

Multivariate analysis of the mean HR value showed a statistically significant decrease ($p<0.001$) in the therapy group compared to the control group. Exploring and testing the initial HR value data before treatment was given, the results of the two variables were not statistically significantly different ($p=0.925$). This can indicate that before treatment, all samples had initial mean HR values that were not different. Observing a decrease in HR values shows changes during the treatment period. These results are in accordance with theory, where dexmedetomidine administration during surgery will significantly reduce HR.[27–30]

High levels of HR and MAP were positively correlated with catecholamines – dopamine, norepinephrine, and epinephrine. As neurotransmitters and hormones necessary for the autonomic nervous system to maintain homeostasis, catecholamines have significant and intricate roles in human memory, behavior, and cognition. Compared to other amines, norepinephrine has an exceptionally high affinity for adrenaline receptors attached to blood vessels. Norepinephrine significantly controls arousal, attention, and mood, additionally inducing sympathetic reactions to stress, which include elevations in blood pressure and heart rate.[31-33]

The results of hypothesis testing using multivariate analysis showed a significant difference in cortisol levels ($p=0.018$) in the two groups. Before

post-therapy observations were carried out, data had been explored and tested for initial cortisol levels before treatment, and the results showed that cortisol levels between the therapy and control groups were not significantly different (p=0.929). This shows that before treatment, all samples had initial cortisol levels that were not different. The results of observing the difference in final scores show the changes that occurred during the treatment period. These results are in accordance with previous studies findings, where dexmedetomidine will reduce cortisol production.[23,30,34]

ACTH stimulation causes cortisol secretion from the adrenal cortex to increase rapidly after the onset of the disease, depending on the severity of the trauma experienced. Normally, further ACTH release is inhibited as a feedback mechanism due to the resulting increase in blood cortisol levels. However, this mechanism appears to be ineffective after surgery, where concentrations of both hormones remain high. This cortisol response can be modified by anesthetic intervention.[35-37]

In response to immune and neuroendocrine reactions, metabolic responses occur simultaneously. Increased cortisol and catecholamines affect the balance of glucagon and insulin. Hyperglycemia, protein catabolism with breakdown of body muscle resulting in negative protein balance and increased fat breakdown, is a manifestation of the metabolic response.[35-37]

In stressful situations, cortisol secretion increases. Cortisol is an essential hormone because it plays a role in facilitating the work of catecholamines and preventing excessive immune reactions during trauma, supplying glucose from the muscles to the brain. The length and severity of the surgery undertaken generally accumulate positively with cortisol levels.[13,38]

Regional anesthesia can prevent endocrine and metabolic responses to surgery of the pelvis and lower extremities. A spinal or epidural block occurring from the Thoracic 4 to Sacral 5 dermatome segments, created before the start of surgery, can prevent the increase in cortisol resulting from TKR/THR. Both afferent input from the operating site of the central nervous system and the hypothalamic-pituitary axis, as well as efferent autonomic neurons leading to the liver and adrenal medulla, are blocked, resulting in the adrenocortical response to the deletion being terminated.[22,28,29,34,38]

Dexmedetomidine is a selective and specific α-2 adrenoceptor agonist. Its use in the field of anesthesia has been widely reported based on its antinociceptive, sympatholytic, and potential capabilities with other anesthetic preparations, so it is useful for controlling hemodynamic responses during disease.[20,28]

The NRS score did not show a statistically significant difference in the movement or stationary periods during pre-surgery or post-surgery. The plasma level of the analgesic drug administered is still high and is also influenced by previous analgesics, causing the patient to be pain-free. After 24 hours after surgery, there was a significant difference in NRS between stationary and moving conditions. Several previous studies have shown that pain and immune factors, especially pro-inflammatory cytokines, interact and influence each other. In the present study, the significantly lower NRS

scores in the treatment group may be due to the antinociceptive effect of dexmedetomidine, which results in anti-inflammatory effects.[39,40]

Nausea, dizziness, and pruritus were side effect parameters within 24 hours after surgery, and the differences were not statistically significant. Hypotension and bradycardia were statistically significant differences. No subjects vomited or experienced respiratory depression. Hypotension causes the brain stem to lack blood supply, causing hypoxemia and hypoperfusion in the chemoreceptor trigger zone of the medulla oblongata as the center for vomiting. This can increase the potential for nausea and vomiting.[41,42]

The response to surgery stress results in endocrine, metabolic, and immunological structural/compositional changes in the patient. Several studies have shown that anesthesia can dramatically improve the outcome of surgical patients by increasing/reducing the hormonal stress response, consistent with the findings of this study. The differences in cortisol, MAP, and HR values in this study were significant in bivariate and multivariate analyses.

Dexmedetomidine, a potent α2 adrenergic agonist, is gentler than clonidine and has a broad range of action. Both HR and MAP as a representation for serum catecholamine levels at the end of surgery were lower in the treatment group than in the control group, and this was thought to be due to central sympatholytic effects due to stimulation of α2 adrenoceptors and subsequent relative stimulation of cholinergic activity.

In this study, cortisol levels decreased by 40% compared to the average initial value in the therapy group, while the control group increased by 27%. This is in accordance with previous studies where dexmedetomidine significantly ($p<0.05$) reduced cortisol levels compared to controls. The HR and MAP values during surgery were significantly lower than controls ($p<0.05$).[43]

CONCLUSION

Administration of dexmedetomidine during surgery reduces the endocrine stress hormone response. Dexmedetomidine in this study was proven to reduce HR, MAP, and cortisol levels compared to controls, and maintained respiratory rate. The 24-hour postoperative pain was also lower with dexmedetomidine, especially in Bradycardia and Hypotension, compared to controls. These results indicate that dexmedetomidine administration is good to apply, especially in TKR/THR. The weakness of this research is that it does not reveal much about other hormonal influences, so it can be used as a study for future researchers to obtain more comprehensive data.

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