Effect of sedation after abdominal surgery in modulating stress response: The impact of dexmedetomidine and midazolam on cortisol level, interleukin 6 (IL-6) level, and blood glucose level

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Abstract

***Objective*: This study compared the effects of dexmedetomidine and midazolam on stress response markers such as interleukin 6 (IL-6) level, cortisol level, and blood glucose level in patients who needed postoperative mechanical ventilation support after abdominal surgery.**

***Design*: Single-center, double-blinded, randomized clinical trial.**

***Setting*: This study was conducted from November 2018 to March 2019 at the Intensive Care Unit (ICU) of Dr. Cipto Mangunkusumo National Central Public Hospital.**

***Patients and participants*: Twenty-two adult patients who underwent abdominal surgeries and received sedation agents in the ICU were divided into Group D (dexmedetomidine) and Group M (midazolam). Inclusion criteria included patients aged 18-65, American Society of Anaesthesiologists (ASA) physical status classification I-III, and indicated the use of mechanical ventilation after abdominal surgery.**

***Interventions*: Each agent was administered after the patient arrived at the ICU without a loading dose.**

***Measurements and results*: Dexmedetomidine and midazolam were unable to lower stress responses due to only significance in one out of three decided parameters statistically. A decrease in blood glucose level occurred in Group M six hours after abdominal surgery (blood glucose before any sedation agent was administered [T0] p=0.470, blood glucose measured 120 minutes after sedation [T1] p=0.870, blood glucose measured 360 minutes after sedation [T2] p=0.028, blood glucose level changes p=0.008), while there were no significant changes in IL-6 level (IL-6 T0 p=0.844, IL-6 T1 p=0.818, IL-6 T2 p=0.768, IL-6 level changes p=0.974) and cortisol level (cortisol T0 p=0.017, cortisol T1 p=0.974, cortisol T2 p=0.577, cortisol level changes p=0.279). Agitation in Group D showed significant differences compared to Group M (p=0.027), while there was no significant difference in anxiety within both groups (p=1.000).**

***Conclusions*: As sedation agents, both dexmedetomidine and midazolam were unable to lower stress responses in a patient with mechanical ventilation after abdominal surgery. The sedation level in Group D showed better results compared to Group M, but both agents could reduce the anxiety level.**

Key words: Sedation agent, stress response, abdominal surgery.

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Introduction

Preoperative, intraoperative, and postoperative factors influence the stress response of surgery. Postoperative factors that influence the onset of stress responses are anxiety, inadequate pain management, and the influence of the care unit, nutrition, and environment. (1) Patients who undergo abdominal surgery generally need respiratory support and require mechanical ventilation. (2)

Patients on mechanical ventilation may need analgesic and sedation agents because anxiety level in those patients is usually very high (about 85%) and the anxiety level tends to be higher in patients who are difficult to communicate. (3) Endotracheal tube (ETT) connected with a mechanical ventilator is one of the factors that causes an elevation in stress response. Anxiety is the main psychological stressor in mechanical ventilation usage with neuroendocrine responses and physical manifestations that can harm patients. (4)

A high level of anxiety activates the sympathetic nervous system causing an increase in heart rate, blood pressure (2) and respiratory rate, and also initiates an unfavorable neurohormonal response. (40 If these stress responses go untreated, it can increase patient morbidity and mortality. (5,6) Sedation agents in patients using mechanical ventilation are used to reduce anxiety and harmonize the patient's breathing under mechanical ventilation. (7)

In 1995 the Society of Critical Care Medicine (SCCM) recommended midazolam and propofol as short-term sedation agents, but in 2013 SCCM recommended propofol and nonbenzodiazepine group as sedation agents in the ICU (level of evidence 2B) (8) because midazolam causes a variety of side effects if used continuously. The ICU of Dr. Cipto Mangunkusumo National Central Public Hospital still uses midazolam as one of its sedation agents.

Dexmedetomidine is one of the nonbenzodiazepine groups recommended as a sedation agent and is a potent and selective α-2 agonist that was approved by the Food and Drug Administration (FDA) in the United States at the end of 1999 to be used in humans as a sedation agent and analgesic for short-term (<24 hours) sedation in the ICU. (8,9) Dexmedetomidine is preferred because it produces a sedation pattern that is different from other sedation agents. Patients sedated with dexmedetomidine are easier to stimulate and can be asked to interact with minimal respiratory depression. (8) A growing study of dexmedetomidine concluded that besides affecting hemodynamic changes, dexmedetomidine could reduce postoperative stress responses in patients after major abdominal surgery. (10)

Methods

This double-blinded randomized clinical trial grouped twenty-two adult patients who went through abdominal surgeries and received sedation agents in the ICU into two groups: Group D (dexmedetomidine) and Group M (midazolam). Each agent was administered after the patient arrived at the ICU with the Richmond Agitation Sedation Scale (RASS) of zero and without a loading dose. Inclusion criteria included patients aged 18-65, American Society of Anaesthesiologists (ASA) physical status classification I-III, indicated for the use of mechanical ventilation after abdominal surgery, and required to sign informed consent before any intervention of the study. Exclusion criteria included a history of cardiac diseases, history of liver diseases, history of using antidepressants and analgetic for a long time, pregnancy and breastfeeding, bradycardia, uncontrolled hypertension, history of hyperthyroidism, patients with diabetes mellitus, being on a pacemaker, morbid obesity, unable to communicate, hypersensitivity to dexmedetomidine and midazolam, history of cerebrovascular diseases, being on use of any sedation agents, hypnotic and psychotropic drugs usage, and patients on β-blocker medication.

Patients were administered bupivacaine and morphine with a total volume of 10 ml intravenously after abdominal surgery, then transferred to the ICU. Dexmedetomidine was administered 0.5 µg/kg body weight intravenously with RASS 0 to Group D and continuously for 6 hours. Group M received midazolam 0.05 µg/kg body weight intravenously and continuously for 6 hours.

Measurements

Heat rate (HR), mean arterial pressure (MAP), and blood pressure (BP) were also recorded in ICU every 30 minutes for 6 hours. Plasma levels of interleukin 6 (IL-6), plasma cortisol level, and blood glucose level had been measured before any sedation agent was administered and was regarded as basal level (T0). T1 was measured 120 minutes after sedation, and T2 was measured 360 minutes after sedation. The level of sedation was assessed by RASS and the level of anxiety was assessed by the Facial Anxiety Scale (FAS).

Statistical analysis

Data were analyzed using Statistical Package for Social Scientist (SPSS) version 2.0 for Microsoft

Windows. Numerical data were expressed as mean±standard deviation. Comparison between the two groups was made using a parametric t-test or non-parametric Mann-Whitney. The level of significance adopted for this study was $p<0.05$.

Results

There were no statistically significant differences between the two groups regarding age, sex, body weight, ASA classification, type of surgery, and duration of surgery as shown in **Table 1**.

Baseline values of HR, and BP were comparable in both groups. Intra sedation, the systolic, diastolic, and MAP were significantly lower in Group D compared to Group M as shown in **Figures 1**, **2**, and **3**.

There were no statistically significant differences between the two groups regarding the basal level of IL-6, cortisol, and blood glucose. There was no statistical difference between the two groups as regards the level of IL-6 and cortisol after two hours of continuous sedation. There was a statistical difference in blood glucose levels after six hours of constant sedation, which lowered blood glucose levels in Group M compared to Group D as shown in **Tables 2-4** and **Figures 4-6**.

The RASS was significantly less in Group D compared to Group M during sedation, but the level of anxiety was not statistically significant difference between the two groups as shown in **Table 5**.

Discussion

Physiological changes that occur in mechanical ventilation are mixtures of hemodynamic responses, immune, metabolic, and endocrine which can be harmful. Endocrine changes include the supranormal release of cortisol and elevated blood glucose level. The immune response is multi-factorial and complex but involves the release of pro-inflammatory and anti-inflammatory cytokines. (11)

Therefore, sedation is needed to minimize anxiety in patients with mechanical ventilation. Sedation is needed to make patients feel comfortable and to help synchronize mechanically ventilated breathing. In this study, the effect of sedation using midazolam or dexmedetomidine on IL-6 concentrations was not statistically significant between the two groups in three timestamps ($p=0.438$). IL-6 concentrations after 2 hours of dexmedetomidine and midazolam were similarly increased (T1). There were also differences in IL-6 concentrations after 6 hours of administration (T2), where IL-6 concentration in Group D increased moderately, whereas Group M tended to decrease (**Figure 3**).

The concentration of IL-6 is a marker relevant to the extent of trauma, invasive surgical procedures, and duration of surgery performed. (12) IL-6 levels in both Groups between T0 and T1 were similarly increased because the concentration of midazolam and dexmedetomidine had not been able to suppress IL-6 release. According to Tanabe K. et al., both midazolam and dexmedetomidine can cause depression at the IL-6 level depending on their concentration. Midazolam is able to suppress IL-1β which stimulates the release of IL-6. The suppressive effect works at the concentration of midazolam 0.3-3 μM. Peripheral-type benzodiazepine receptors (PBRs) modulate cytokine responses including IL-6 by inhibiting IL-1β, which induces IL-6 release in C6 cells of mouse glioma by suppressing the activation of signal transducers and activator of transcription (STAT) 3. (13)

Dexmedetomidine can also suppress the release of IL-6 at a concentration of 3 μM. Dexmedetomidine inhibits IL-1β which induces synthesis of IL-6 independently of the adenylyl cyclase-cAMP pathway through α2-adrenoceptor in glioma cell C6. (14)

Post-surgical IL-6 levels can be influenced by several factors including the amount of blood loss during surgery, duration of surgery, (15) types of anesthetic gases used, (16) body weight, (17) age, (18) psychological stress, (19) and genetic polymorphism of each individual. (20)

The difference between both agents on blood glucose level was found to be statistically significant, where midazolam was better in reducing blood glucose levels compared to dexmedetomidine.

Increased blood glucose during surgery is a result of the metabolic response to surgical stress, (21) and is proportional to the duration and severity of surgical trauma. Postoperative blood glucose levels can also increase because of inadequate sedation.

Gamma-aminobutyric acid (GABA) has been found in pancreatic β cells, although in smaller amounts than in the adrenal cortex. Research has shown that peripheral benzodiazepine receptors are also found in the pancreatic tissue, and there are mechanisms in which GABA with released insulin can modulate glucagon secretion through GABA receptor stimulation. (22)

Increased blood glucose level was found in Group D at T0 and T1, and it was in effect that the agent had not reached peak effect. The inhibition of α2 adrenoreceptor-mediated insulin secretion that causes hyperglycemic effect can be reversed by sympathoadrenal inhibition mediated by α2 adrenoreceptors, hence the decline in blood glucose levels shown in T1 and T2.

Cortisol levels between T0 and T1 in Group M experienced a slight decrease, whereas in Group D tended to increase. Decreased cortisol levels in Group M occurred because benzodiazepines modulated GABA type A (GABAA) receptors that inhibited the release of corticotropin-releasing factor (CRF) in the hypothalamic mediobasal, thereby inhibiting adrenocorticotropic hormone (ACTH) release, which can ultimately inhibit cortisol secretion. (23) Desborough et al. also proved the direct effect of intravenous midazolam on cortisol levels which decreased 60 minutes after surgery began. (22)

Cortisol levels in T1 and T2 experienced more decline in Group D compared to Group M. This difference was caused by dexmedetomidine reaching its peak effect, and due to the pre and post-synaptic activation effects of α2 adrenoceptors on the central nervous system. (24)

Anxiety is psychological stress which can induce the secretion of the hormone cortisol. CRF plays many physiological roles associated with regulating stress responses at different levels of anatomy. The CRF system acts as a hypothalamic hypophysiotropic factor that stimulates the synthesis and secretion of the pituitary ACTH thus also controlling hypothalamic pituitary adrenal (HPA) axis activity. CRF neurons also innervate the locus coeruleus so it can activate other major stress response axis, noradrenergic in the central nervous system and the sympathetic nervous system. The CRF system plays a role in regulating adrenal steroidogenesis, and it also plays a role in the synthesis and release of catecholamines from the adrenal glands. (25)

Alpha 2 receptors are pre and postsynaptic receptors that are commonly found in the central and peripheral nervous system. Activation of presynaptic and postsynaptic adrenoceptors in the central nervous system affects the sympathoadrenal system, causing CRF activation to suppress ACTH secretion, and finally cortisol secretion is also suppressed. (26)

The decrease in cortisol level in Group D was greater in T1 and T2 compared to Group M because dexmedetomidine works very selectively on α2 adrenoceptors (both in the central nervous system and peripheral nervous system) so that the stress response occurs after surgery or due to anxiety can be suppressed and the secretion of the hormone cortisol can also be suppressed.

The depth of sedation in the two treatment groups was assessed using RASS. The group treated with dexmedetomidine showed a statistically significant difference (p=0.027) compared to Group M. All patients who were sedated with dexmedetomidine achieved good levels with a sedation depth of zero, where the patient was still calm and awake. Four out of 11 patients, who were sedated with midazolam, experienced deeper sedation with a scale of -1, where the patients weren't fully awake and woke up slowly (>10 seconds) with sound eye contact.

Relationship between cortisol and anxiety

The main goal of many therapies in the ICU is to maintain physiological stability including the administration of sedation agents. This study also assessed the relationship effect of sedation on anxiety in patients using mechanical ventilation using the FAS. Statistically, there were no differences in anxiety scores between dexmedetomidine and midazolam. Midazolam is a benzodiazepine that has specific benzodiazepine receptors that are capable of inducing changes in the GABAA receptor. Anxiolysis effect of midazolam results from the presence of a BZ2 receptor consisting of α2 isoforms that mediate anisolysis. (27) Dexmedetomidine is a highly selective α2 adrenergic agonist. It suppresses the activation of the sympathoadrenal system through two pathways, namely: through the activation of presynaptic α2 adrenoceptors to inhibit norepinephrine secretion and the activation of postsynaptic α2 adrenoreceptors in the central nervous system to inhibit sympathetic activity, so it can reduce postoperative anxiety. (24)

Limitations

In this study, we did not measure baseline cortisol and IL-6 levels before surgery, so it was difficult to know whether cortisol and IL-6 levels were indeed high, because in patients who already had malignancies IL-6 levels were higher than patients who didn't have malignancy.

Sedation measurements used in these patients were only the RASS. Although it is commonly used, sedation measurements from RASS are subjective.

This study can provide information that both midazolam and dexmedetomidine can be used for sedation in postoperative patients who use mechanical ventilation for 6 hours based on consideration of the pharmacodynamics of each drug. We found that sedation with midazolam at a dose of 0.05 mg/kg body weight intravenous continuously was more stable in maintaining hemodynamics. Patients did not experience anxiety (FAS score 0) and the effect of sedation was not too deep (RASS -1 to 0). Nevertheless, midazolam was less effective in patients suffering from hypertension because the patient's BP remained high even though it had been sedated with midazolam. The use of dexmedetomidine in patients with hypertension was more effective because BP during sedation was relatively stable, so the patient didn't need any anti-hypertension during sedation.

Conclusion

Both dexmedetomidine 0.5 μg/kg body weight/hour intravenously and midazolam 0.05 mg/kg body weight/hour intravenously were not able to reduce stress responses caused by mechanical ventilation. Both dexmedetomidine and midazolam in this study could reduce anxiety, whereas for the level of sedation dexmedetomidine was found to be better than midazolam.

Author's contribution

AS was the study's primary investigator, who designed the study, subject enrollment, and follow-up. AM, AS, and IM were responsible for supervising the study, analyzing the data, and correcting the manuscript.

All authors had full access to all the study data, contributed to drafting the manuscript or critically revised it for correction, approved the final version of the manuscript, and took responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Table 1. Demographic and characteristic data of the Dexmedetomidine group and Midazolam group

Characteristic	Sedation agents		p-value
	Dexmedetomidine, n (%)	Midazolam, n (%)	
Sex - Male - Female	 4 (36.4%) 7 (63.6%)	 1 (9.1%) 10 (90.9%)	0.127
ASA - 1 - 2 - 3	 0 (0.0%) 7 (63.6%) 4 (36.4%)	 1 (9.1%) 4 (36.4%) 6 (54.5%)	0.391
Type of surgery - Digestive - Obstetry	 5 (45.5%) 6 (54.5%)	 3 (27.3%) 8 (72.7%)	0.375
Age (years), mean±SD	41.91±9.73	42.91±9.617	0.965
Duration of surgery (min), mean±SD	421.81±104.31	348.18±91.98	0.095

Legend: ASA=American Society of Anaesthesiologists physical status classification; SD=standard deviation.

Table 2. Changes in IL-6 levels between the Dexmedetomidine group and Midazolam group

	Sedation agent						p-value
	Dexmedetomidine			Midazolam			
	Median	Minimum	Maximum	Median	Minimum	Maximum	
IL-6 T0	221.0	44.0	454.0	254.0	47.0	461.0	0.844
IL-6 T1	264.1	46.0	481.0	325.0	36.0	439.0	0.818
IL-6 T2	340.0	71.0	460.0	285.0	26.0	451.0	0.768
IL-6 level changes	6.00	-78.00	175.00	8.70	-35.00	131.60	0.974

Legend: IL-6=interleukin 6; T0=IL-6 at basal level; T1=IL-6 level at 120 minutes after sedation; T2 IL-6 level at 360 minutes after sedation.
Mann-Whitney test, significant if p-value<0.05.

Table 3. Blood glucose measurement in accordance with sedation agents used

	Sedation agent						p-value
	Dexmedetomidine			Midazolam			
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Blood glucose T0 (mg/dl)	170.0	103.0	216.0	186.0	129.0	360.0	0.470
Blood glucose T1 (mg/dl)	198.0	98.0	316.0	190.0	109.0	322.0	0.870
Blood glucose T2 (mg/dl)	167.0	108.0	276.0	134.0	90.0	275.0	0.028
Blood glucose level changes	5.00	-90.00	60.00	-49.00	-121.00	1.00	0.008

Legend: T0=blood glucose at basal level; T1=blood glucose level at 120 minutes after sedation; T2=blood glucose level at 360 minutes after sedation.
Mann-Whitney test, significant if p-value<0.05

Table 4. Changes in cortisol level between the Dexmedetomidine group and Midazolam group

	Sedation agent						p-value
	Dexmedetomidine			Midazolam			
	Median	Minimum	Maximum	Median	Minimum	Maximum	
Cortisol T0 (μg/dl)	254.3	81.0	825.0	302.0	244.5	706.0	0.017
Cortisol T1 (μg/dl)	312.3	131.0	535.0	285.0	85.0	825.0	0.974
Cortisol T2 (μg/dl)	229.9	80.0	676.0	286.0	97.0	825.0	0.577
Cortisol level changes	3.50	-489.00	286.10	-30.00	-193.00	119.00	0.279

Legend: T0=cortisol at basal level; T1=cortisol level at 120 minutes after sedation; T2=cortisol level at 360 minutes after sedation.
Mann-Whitney test, significant if p-value<0.05

Table 5. Comparison of FAS and RASS between the Dexmedetomidine group and Midazolam group

	Sedation agent		p-value
	Dexmedetomidine, n (%)	Midazolam, n (%)	
FAS - 0 - 1	 10 (90.9%) 1 (9.1%)	 10 (90.9%) 1 (9.1%)	1.000
RASS - -1 - 0	 0 (0.0%) 11 (100.0%)	 4 (36.4%) 7 (63.6%)	0.027

Legend: FAS=Face Anxiety Scale; RASS=Richmond Agitation Sedation Scale.
Fisher test, significant if p-value<0.05.

Figure 1. Comparison of systolic blood pressure between the Dexmedetomidine group and Midazolam group

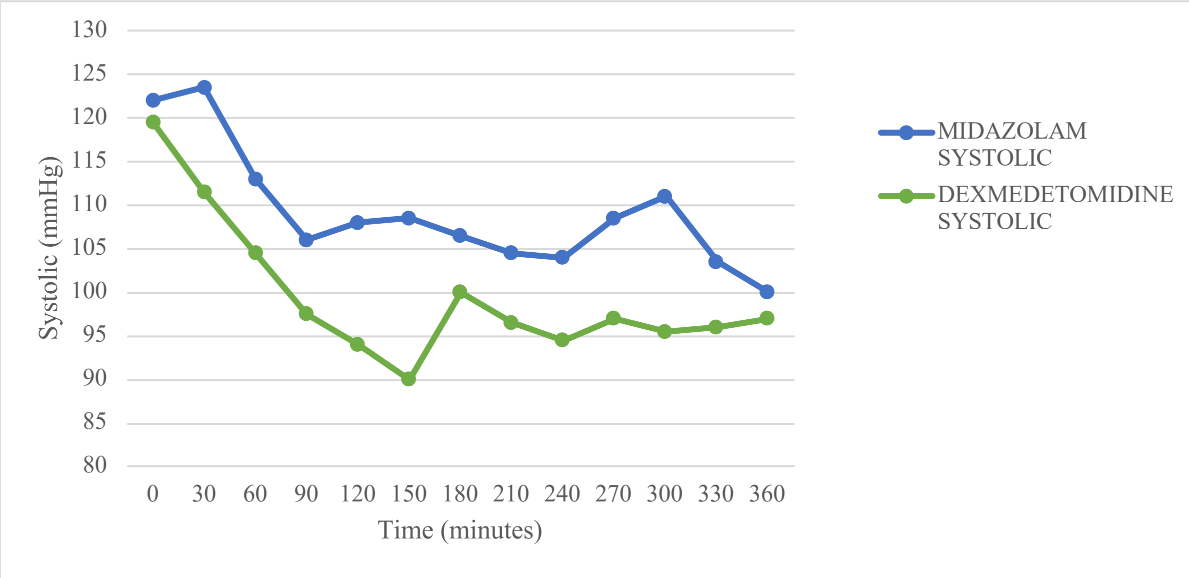


Figure 2. Comparison of diastolic blood pressure between the Dexmedetomidine group and Midazolam group

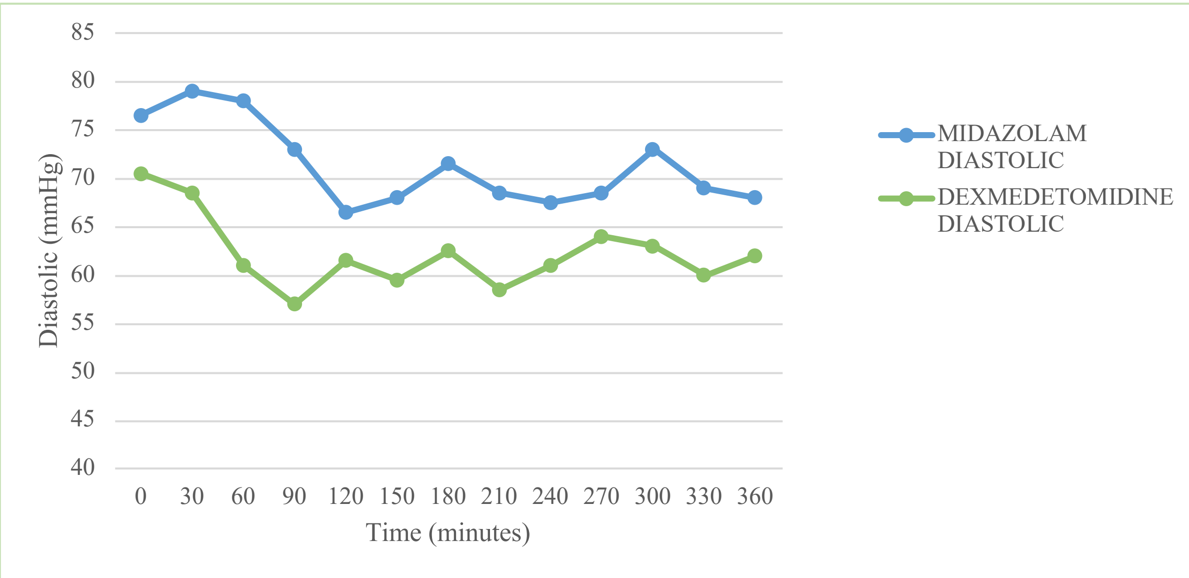
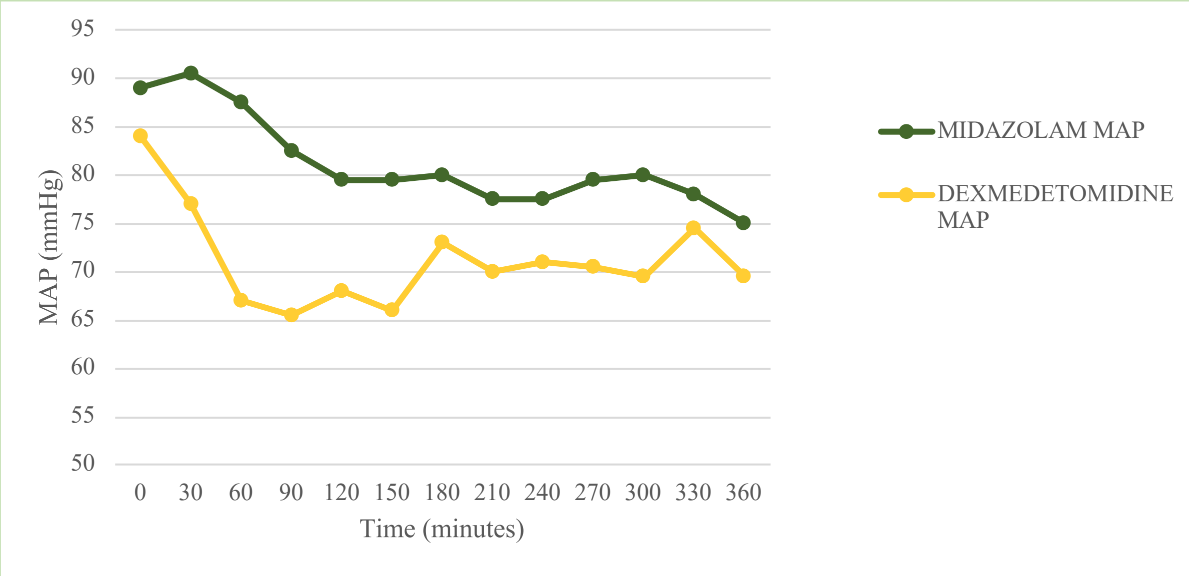
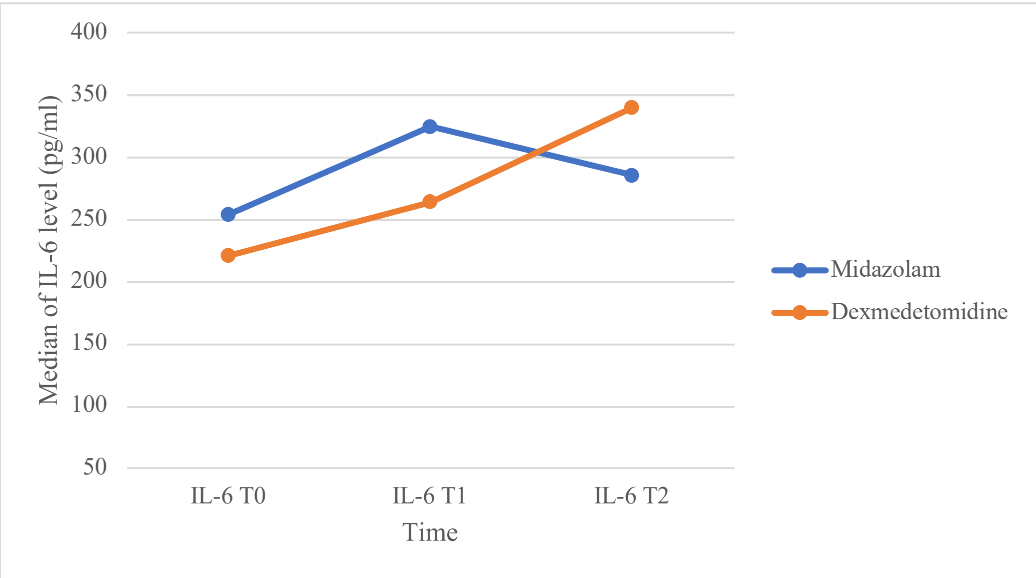


Figure 3. Comparison of MAP between the Dexmedetomidine group and Midazolam group



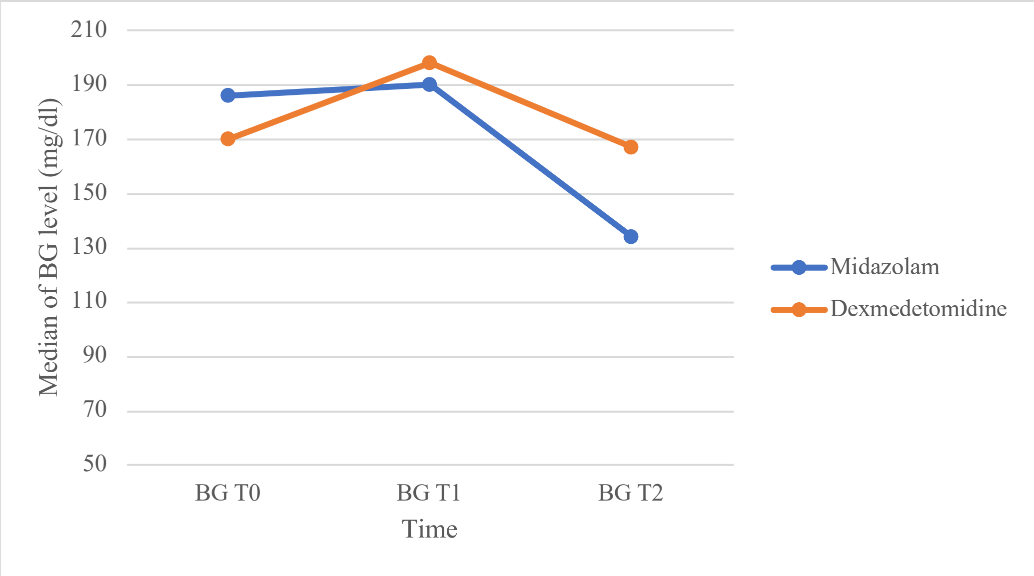
Legend: MAP=mean arterial pressure.

Figure 4. IL-6 level between the Dexmedetomidine group and Midazolam group at T0, T1, and T2 (p=0.438)



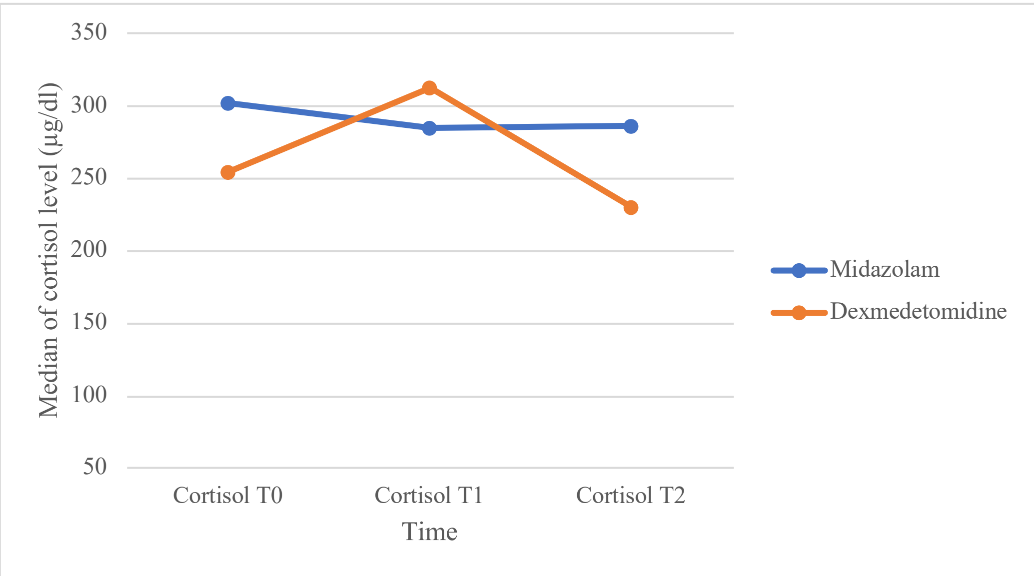
Legend: IL-6=interleukin 6; T0=IL-6 at basal level; T1=IL-6 level at 120 minutes after sedation; T2 IL-6 level at 360 minutes after sedation.

Figure 5. BG level between the Dexmedetomidine group and Midazolam group at T0, T1, and T2 (p=0.019)



Legend: BG=blood glucose; T0=blood glucose at basal level; T1=blood glucose level at 120 minutes after sedation; T2=blood glucose level at 360 minutes after sedation.

Figure 6. Cortisol level between the Dexmedetomidine group and Midazolam group at T0, T1, and T2 (p=0.522)



Legend: T0=cortisol at basal level; T1=cortisol level at 120 minutes after sedation; T2=cortisol level at 360 minutes after sedation.

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