Original Article

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Anaesthesia Section

Ketamine versus Dexmedetomidine Sedation in the Attenuation of Surgical Stress Response and Postoperative Pain: A Retrospective Study

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ABSTRACT

Introduction: Surgical procedures cause stress response in the body. This response involves endocrine, metabolic, haematologic and immunologic reactions. Ketamine has an anti-proinflammatory effect as limiting exacerbation of systemic inflammation. Likewise, dexmedetomidine has anti-stress, sedative, analgesic actions and decreases surgical stress response and leads to better stable haemodynamic properties.

Aim: To compare effects of ketamine, dexmedetomidine and determine correlation between postoperative pain scores and serum C-reactive protein on surgical stress response.

Materials and Methods: Electronic records of 121 patients who had inguinal hernia repair were analysed retrospectively. Patients' age, sex, operation time, sedation drug, preoperative and postoperative C-Reactive Protein (CRP) and leukocyte levels, postoperative visual analogue scale scores were recorded. Normality of the variables were analysed by Kolmogorov-Smirnov test and homogeneity was analysed by Levene's test. Mean tests were compared using independent t-test if data distribution was normal or using nonparametric Mann-Whitney U-test if data were not distributed normally. Pearson's correlation was used to analyse correlation between VAS score and postoperative CRP level. The p-value <0.05 was considered statistically significant.

Results: Postoperative mean CRP level was 42.3±9 mg/dL in ketamine group and 65.4±6.6 mg/dL in dexmedetomidine group. Mean visual analogue scale at postoperative 24th hour was 2.6±0.8 in ketamine group and 3±0.7 in dexmedetomidine level. These differences were statistically significant (p<0.05). Leukocyte counts were similar between groups. There was a moderate positive correlation between postoperative 24th hour CRP levels and pain scores.

Conclusion: Ketamine was found to be more effective then dexmedetomidine at attenuation of surgical stress response. Postoperative serum CRP level was correlated with postoperative pain scores.

Keywords: C-reactive protein, Inguinal hernia, Pain, Sedoanalgesia

INTRODUCTION

Surgical procedures cause stress response in bodies. This response involves endocrine, metabolic, haematologic and immunologic reactions. Activating hypothalamic-pituitary-adrenal axis, surgical stress causes increased secretion of endogenous catecholamines and glucocorticoids and inflammatory mediators [1]. Proinflammatory Interleukin-6 (IL-6) is a major cytokine responsible for induction of acute-phase response and produced at the surgical site. The release of Interleukin-1 (IL-1) and IL-6 induces synthesis of CRP from liver. Increase in CRP serum level is closely related to IL-6 level [2].

Neutrophils are also involved in acute inflammatory response due to tissue trauma. Increased number of neutrophils transmigrate to inflammation site through the vascular endothelium for diapedesis [3].

Loix S et al., reported that ketamine inhibits inflammatory exacerbations by reducing IL-6 release at the postoperative period [4]. Ketamine is previously reported to attenuate cytokine response. In an experimental study, Gokcinar D et al., showed ketamine to reduce the level of proinflammatory factors such as IL-6, TNF-α and IL-1β in the rats with acute lung injury [5]. Ketamine was also reported to inhibit the function of lymphocytes, natural killer cells, and neutrophils by several studies providing in vitro data [5]. In a very recent study, low dose intravenous ketamine was applied to patients undergoing caesarean section with spinal anaesthesia and ketamine was determined to reduce CRP levels at the postoperative 24th hour [6].

On the other hand, α-2 adrenoceptor agonists are well known to reduce central sympathetic outflow and attenuate surgical stress response. In a very recent study dexmedetomidine blunts surgical stress responses when used in conjunction with Total Intravenous Anaesthesia (TIVA) without compromising hemodynamic stability and with minimal adverse effects during the intraoperative period [7].

Dexmedetomidine is another anaesthetic agent known to reduce inflammation and mortality by inhibiting cytokine secretion both in human and animal [8]. Li Y et al., reported dexmedetomidine to regulate serum IL-6 and TNF-α levels intraoperatively. Dexmedetomidine also attenuated the endocrine response to surgical stress by suppressing the plasma elevation of cortisol, epinephrine and norepinephrine levels [7].

Through the present research, we tried to determine the effectiveness of low-dose intravenous ketamine 0.3 mg/kg and dexmedetomidine infusion 0.4 μg/kg/hour in attenuating postoperative stress response, especially in patients undergoing unilateral inguinal hernia repair.

MATERIALS AND METHODS

After receiving local Ethics Committee Approval (Biga State Hospital Management Committee approval), the retrospective study was carried out in General Surgery Operating rooms of a State Hospital in September 2014. The patients who underwent unilateral inguinal hernia repair operation with spinal anaesthesia between June 2013 and June 2014, were detected from the hospital database. These operations were selected because repair of unilateral inguinal hernia

was one of the most common surgeries performed under spinal anaesthesia and sedoanalgesia in the hospital. Electronic records of the patients sedated with either ketamine or dexmedetomidine were analysed retrospectively. The exclusion criteria were: physical status ASA III or more, body mass index score higher than 30 kg/m^2, chronic analgesic consumption, substance addiction or application of additional analgesic drug intraoperatively. Patient's age, sex, operation time, sedation drug, preoperative CRP and leukocyte levels, postoperative 24th hour CRP and leukocyte levels and postoperative 24th hour Visual Analogue Scale (VAS) were recorded from the patient files. Spinal anaesthesia was performed with 27-gauge Quincke needle, 15 mg, 0.5% hyperbaric bupivacaine and 20 μg fentanyl was applied to all patients intrathecally. When the patient records were detected, it was found that following spinal anaesthesia, 0.2-0.3 mg/kg ketamine was administered intravenously in the ketamine group and 0.4-0.5 μg/kg/hour dexmedetomidine infusion was started in the dexmedetomidine group. In the postoperative period, patients received 1000 mg paracetamol every eight hours intravenously for analgesia.

STATISTICAL ANALYSIS

Statistical evaluation was performed using the Statistical package for Social Science, version 18.0 (SPSS Inc., Chicago, IL). The descriptive data of the study was specified with mean, standard deviation, and percentage. Normality of the variables were analysed by Kolmogorov-Smirnov test and homogeneity was analysed by Levene's test based on means. A resulting p-value under 0.05 means that variances are not equal. Mean tests were compared using independent t-test if data distribution was normal or using nonparametric Mann-Whitney U-test if data were not distributed normally. Pearson's correlation was used to analyse correlation between VAS score and postoperative CRP level. The p-value <0.05 was considered statistically significant.

RESULTS

In total, 121 patients were enrolled into the study. There were 62 patients in the ketamine group and 59 patients in the dexmedetomidine group.

In conformity with Levene's test, age, sex, operation time, preoperative CRP levels, preoperative and postoperative leukocyte levels and postoperative 24th hour VAS are normally distributed with 95% confidence. Levene's test showed that the variances for CRP in postoperative time were not equal, F (1,119)=4.33, p=0.04.

According to age and sex of the patients, ketamine and dexmedetomidine groups were similar (p>0.05). The mean operation time was 51.6 minutes with a standard deviation of 6.5 minutes in ketamine group and 53.4 minutes with a standard deviation of 6.3 minutes in dexmedetomidine group (p>0.05). In both groups, preoperative CRP and leukocyte levels were in normal range and similar to each other (p>0.05) [Table/Fig-1].

	Groups		p-value
	KET (n=62)	DEX (n=59)	
Age (years)	48.4±10.4	46.8±10.4	0.407*
Sex (female/male)	10/52	12/47	0.550#
Operation time (minutes)	51.6±6.5	53.4±6.3	0.14#
Preoperative CRP (mg/L)	3.3±0.98	3.8±3.3	0.46#
Preoperative leukocyte (10^3/μL)	6.3±1	6.7±1	0.072*

[Table/Fig-1]: Demographic data of the patients.
Values are expressed as mean±SD and median; *independent t-test, #Mann-Whitney U-test;
KET: Ketamine; DEX: Dexmedetomidine; CRP: C-reactive protein; min: minute

Biomarker	Groups		p-value
	KET (n=62)	DEX (n=59)	
Postoperative CRP (mg/dL)	42.3±9	65.4±6.6	<0.001#
Postoperative leukocyte (10^3/μL)	13.4±1	13.2±1	0.454*

[Table/Fig-2]: Postoperative CRP and leukocyte levels of the groups.
Values are expressed as mean±SD and median; *independent t-test, #Mann-Whitney U-test;
KET: Ketamine; DEX: Dexmedetomidine; CRP: C-reactive protein; min: minute

At the postoperative 24th hour, mean CRP level was 42.3 with a standard deviation of 9 mg/dL in ketamine group and 65.4 with a standard deviation of 6.6 mg/dL in dexmedetomidine group. The difference was statistically significant (p<0.001). Whereas mean leukocyte level was 13.4 with a standard deviation of 1 10^3/μL in ketamine group and 13.2 with a standard deviation of 1 10^3/μL in dexmedetomidine group. The difference between the two was not statistically significant (p>0.05) [Table/Fig-2].

Mean VAS score of the patients in ketamine group was 2.6 with a standard deviation of 0.8 and it was 3 with a standard deviation of 0.7 in dexmedetomidine group at the postoperative 24th hour. The difference was statistically significant (p=0.007) [Table/Fig-3].

VAS	Groups		p-value
	KET (n=62)	DEX (n=59)	
Postoperative 24th hour (cm)	2.6±0.8	3±0.7	0.007#

[Table/Fig-3]: VAS scores of the groups at postoperative 24th hour.
Values are expressed as mean±SD and median; #Mann-Whitney U-test.
KET: Ketamine; DEX: Dexmedetomidine; VAS: Visual analog scale; Postop: Postoperative; cm: centimetre; Dex: Dexmedetomidine

VAS		
Postoperative CRP	r	0.636
	p	0.001
	n	121

[Table/Fig-4]: The correlation between postoperative CRP and VAS at the postoperative 24th hour.
Spearman test; Abbreviations; CRP: C-reactive protein; VAS: Visual analog scale; r: correlation coefficient; n: number of subjects

Pearson's test was performed to analyse the correlation between postoperative CRP levels and VAS scores at postoperative 24th hour. There was a moderate positive correlation with a correlation coefficient of 0.636. The correlation was statistically significant [Table/Fig-4].

DISCUSSION

In the current study, ketamine sedation was found to decrease CRP levels and VAS scores much more than dexmedetomidine sedation at postoperative 24th hour. There was a moderate correlation between CRP levels and VAS scores and this correlation was statistically significant.

Surgical stress response is believed to be a significant risk factor for unsatisfactory outcome, especially in patients with cardiovascular, endocrine, metabolic and immune disorders. Intraoperative modulation of stress response has been suggested to reduce postoperative complications and morbidity [9]. Therefore, perioperative inhibition of IL-6 and production of CRP from liver have great importance.

In the current study, we compared the effects of ketamine and dexmedetomidine on acute-phase reactants CRP and leukocyte levels. Although, leukocyte levels were similar in both groups, the increase in CRP levels was less in ketamine group.

Both anaesthetic drugs are known to decrease the release of IL-6 and TNF-α levels during surgical stress. The data about the effects of dexmedetomidine on cytokines is limited. Dexmedetomidine is believed to have a modulation effect of cytokine production by macrophages and monocytes [10]. Peng M et al., reported that dexmedetomidine suppressed polysaccharide induced inflammation in activated microglia and inhibited the release of nitric oxide, prostaglandin E2, IL-1β and TNF-α [11]. On the other hand, ketamine is reported to inhibit leukocyte reactivity and suppress superoxide anion produced by neutrophils and subsequently lead a different anti-inflammatory effect after coronary artery bypass grafting [12]. In other studies, ketamine is also proved to inhibit signal pathway and

transcription factors for pro-inflammatory cytokines [13], reduce macrophage functions, expression of adhesion molecules on surface of immune cells [14], activation of inflammation response by lipopolysaccharide binding protein, preserve IL-2 response [13-15].

In a very recent study, Bulow NM et al., compared Total Intravenous Anaesthesia (TIVA) and TIVA with dexmedetomidine infusion on release of cytokines and CRP after mini-cardiopulmonary bypass. Although, they found dexmedetomidine infusion to reduce IL-1, IL-6, TNF-α and interferon-γ levels, the CRP levels at postoperative 24th hour were similar between groups [16]. However, Senapathi TG et al., reported that ketamine managed to reduce the increase in CRP levels after caesarean section, but leukocyte levels were similar between groups [6]. These results are congruent with the present study. In the present study, postoperative CRP levels were significantly lower in the ketamine group, whereas leukocyte levels were similar.

Postoperative pain is believed to aggravate inflammatory reactions of stress response related to surgery. When postoperative pain can't be controlled, patients may suffer from prolonged hospitalisation, poor long-term outcomes and dissatisfaction [17]. In previous studies dexmedetomidine was reported to manage pain control successfully during postoperative period [18,19]. In a recent study, dexmedetomidine was shown to have morphine sparing effect with or without loading dose [20]. Ketamine has long been known to prolong postoperative analgesia and spare additional analgesic needs [21,22]. In the study of Garg N et al., small dose ketamine and dexmedetomidine infusions were compared at postoperative period to evaluate pain-free period, pain scores and rescue analgesic requirements. Mean pain-free period in the ketamine group was 860 minutes while it was 580 minutes in dexmedetomidine group. Both at the postoperative 24th and 48th hours, rescue analgesic requirements were lower ketamine group [18]. The present results were similar with previous study. VAS scores at postoperative 24th hour was significantly lower in ketamine group.

Senapathi TG et al., has suggested postoperative VAS to be related with postoperative CRP levels and they have found a weak correlation between them with a correlation coefficient of 0.374 [6]. In the present study, we found a moderate correlation with a correlation coefficient of 0.636 and this relation was meaningfully significant. In present study, suppression of IL-6 and subsequently CRP production resulted in better postoperative pain management.

Retrospective design is the main limitation of the current study. First, we obtained VAS scores from patient files. So, validity of VAS scores depends on the validity of nurse care records. On the other hand, preoperative and postoperative CRP and leukocyte levels were recorded from electronic database of the hospital. Secondly, we could assess stress response with limited biomarkers. As cortisol, interleukins, TNF-α or other stress response markers are not checked routinely at preoperative and postoperative period, we could analyse only CRP, leukocyte and VAS levels.

CONCLUSION

In the current study, ketamine sedation was found to be more effective than dexmedetomidine sedation at attenuation of surgical stress response. Postoperative serum CRP as an acute-phase protein was determined to be correlated with postoperative pain scores.

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