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ORIGINAL ARTICLE

Immune-Mediatory Response of Intravenous Ketamine Versus Propofol for Elective Open Colectomy: A Prospective Randomised Study

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Background Surgical stress response is a host defense mechanism against tissue injury but its exaggeration can cause postoperative morbidity. Anaesthetics can modulate this response with variable degrees. Therefore, this study was conducted to compare the immune-modulatory effects of intraoperative intravenous infusion of propofol versus ketamine.

Patients and Methods Forty patients scheduled for open colectomy under inhalational based general anaesthesia were included. They were allocated randomly into Group P (n= 20) which was given intravenous propofol 1% at a subanaesthetic infusion dose of 17µg/kg/min, and group K (n= 20) which was given Ketamine 0.3% (150mg/50ml) at a subanaesthetic infusion dose of 5µg/kg/min. The primary outcome was the post-infusion serum IL-6 2 hours after the start of infusion. The secondary outcomes were IL-1β, TLC, absolute neutrophil count and N/L ratio, glucose level, CRP level, postoperative agitation, mean NRS score for pain at rest and movement during the first day, and time to the resumption of GIT function.

Results Post-infusion serum IL-6 after 2 hours was significantly higher in group K (P<0.001). Additionally, Serum IL-1β, glucose and CRP levels were significantly higher in Group K. Postoperative agitation score was significantly higher (P<0.001) and mean postoperative pain score during rest was significantly lower (P 0.003) in group K. Other outcomes were comparable between both groups.

Conclusions Propofol is more effective than ketamine in reducing the surgical stress response as noted by decreased IL-6 and IL-1β, blood glucose, and CRP when compared with ketamine.

Keywords Anaesthetics, C-reactive protein, Immune modulation, Interleukins, Stress.
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INTRODUCTION

"Surgical stress response" is the pathophysiological changes occurring in response to a surgical stimulus [1]. It consists of two main components: the inflammatory-immune component, which is mediated by the inflammatory cells that pass to the surgical trauma region, accompanied by hypersecretion of cytokines (pro-inflammatory), including interleukins (IL) IL-6, IL-8, IL-1β, and tumour necrosis factor-α (TNF- α), and neuroendocrine-metabolic component [2,3]. These inflammatory mediators can reflect the degree of stress the surgical maneuver accompanies [4]. IL-1β is the main controller of the overall reaction to infection throughout the body. IL-6 is primarily responsible for acute phase proteins and C-reactive protein synthesis as a part of hepatic response and activation of immunosuppressive cytokines such as IL-10 and hematopoiesis [5]. Although the surgical stress response is crucial for host defence, an exaggerated response can result in a longer hospitalisation period and an increased risk of morbidity [1].

Intravenous and inhalational anaesthetics can modulate stress response and has anti-inflammatory effects [6]. Propofol improves inflammation by decreasing the formation of pro-inflammatory cytokines TNF-a, IL-1, IL-6, IL-8, IL-10, inducible nitric oxide synthase (iNOS), and inhibiting neutrophil chemotaxis, attachment, phagocytosis, and reactive oxygen species production [7]. Meanwhile, ketamine inhibits macrophage and monocyte functions, endothelium-leukocyte interaction, and IL-6 and IL-8 synthesis [8]. Although the prior two drugs are widely used in anaesthesia, little research has compared their impact on postoperative stress and immunological response. Therefore, this research was conducted to compare the modulatory effect of both propofol and ketamine on surgical stress response and postoperative outcomes.

PATIENTS AND METHODS

All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the Institutional Review Board (IRB) of Faculty of Medicine, Mansoura University on 3rd November 2018 under code (R/18.09.287) and registered at the clinical trial registry (ClinicalTrials.gov) under code (NCT03793075). It was conducted from 10th January 2019 till 15th August 2019. We used the CONSORT reporting guidelines. The privacy rights of patients were always observed. The study was carried out using the principles of the Declaration of Helsinki, 2013, and good clinical practice. All enrolled patients signed informed written consent forms after explaining the detailed protocol. The trial included forty consecutive patients of both sexes, aged 18 to 65 years, with American Society of Anaesthesiologists (ASA) physical status grade I or II, prepared for elective open colectomy via lower para-median incision with supraumbilical extension. Patients who had a body mass index ≥35kg/m^2, ASA III or more, mental illness, bleeding disorders, known allergies to the study medications, recent or concurrent chemotherapy, perioperative immunosuppressive medication in the last six weeks before surgery, refusal to participate, or a requirement for perioperative blood transfusion were ruled out from the study.

All participating patients had the same standard preoperative bowel preparation; no premedication was administered. The "Numerical Rating Scale" (NRS) for pain was explained to them as 0 no pain and 10 for the highest pain. They were randomly allocated into two equal groups by using a computer-generated randomisation table. Group P (n= 20) was given intravenous propofol 1% at a subanaesthetic infusion dose of 17µg/kg/min, and group K (n= 20) was given Ketamine 0.3% (150mg/50ml) at a subanaesthetic infusion dose of 5µg/kg/min. The group allocation was sealed in sequentially numbered opaque envelopes opened by an assistant not included in the study upon patient arrival to the pre-anaesthesia room. Both drugs were prepared under a complete aseptic technique in a 50ml syringe by a pharmacist not involved in the study. They were entirely wrapped with its line by a non-transparent cover to keep the working anaesthesiologist blinded to the infused medication.

The standard monitoring equipment was connected in the operating room, and baseline data were obtained. A venous cannula (20-gauge) was inserted, and 10 ml venous blood sample was aspirated. It was divided into two ml added into an ethylenediamine tetraacetic acid (EDTA) tube for measuring basal total leucocytic count (TLC), absolute neutrophil count and Neutrophil-Lymphocyte-Ratio (N/L ratio) [9], four ml into a plane tube to measure basal serum glucose and CRP, and four ml into another plane tube for measuring basal IL-6 and IL-1β. For assaying both IL-6 and IL-1β, the third blood sample was left to coagulate and centrifuged for 10min, and the supernatant serum was stored at -20°C until tested using enzyme-linked immunosorbent assay (ELISA) kits (Dia Source, Louvian –laNeuve, Belgium). These laboratory parameters were then measured after 30 minutes, two, eight, and 24 hours from start of infusion. In addition, CRP was ordered after 24 hours.

After preoxygenation, general anaesthesia was induced by IV 2µg/kg fentanyl, then 5mg/kg of thiopental sodium, and endotracheal intubation was facilitated by atracurium 0.5mg/kg. Maintenance of anaesthesia was achieved by inhalation of dialed concentration of 2% to 3% sevoflurane in 50%-50% oxygen-air mixture at flow rate of 2L/min via closed breathing circuit to achieve a bispectral index of 40. The Ventilator Settings were adjusted to keep end tidal carbon dioxide (ETCO2) around 35mmHg. Atracurium incremental dose of 0.1-0.2mg/kg were given till the elimination of spontaneous breathing attempts when needed. According to group allocation, propofol or Ketamine IV infusions were started just after the intubation. The infusion continued until the start of abdominal wall closure, and then 1g paracetamol was infused intravenously. Inadvertent events as hypotension, bradycardia or hypoxemia were monitored and managed. Hypotension was defined as mean blood pressure (MBP) <60mmHg and was treated by IV boluses of ephedrine 0.1mg/Kg, bradycardia was defined as heart rate (HR) <50bpm and was treated by IV atropine 0.01mg/Kg, and hypoxemia was defined as SPO2 <94% and was treated by lung recruitment and increasing inspired oxygen fraction. If MBP or HR increased by >30% of basal values, a bolus of IV 1µg/kg fentanyl was given. When skin closure was finished, the sevoflurane was discontinued, and IV 0.04mg/kg neostigmine mixed with 0.02mg/kg atropine was used to reverse the residual neuromuscular blockade. The same surgical team performed the surgery.

After extubation, the patients were transferred to the postanaesthesia care unit (PACU). Postoperative agitation was assessed via the "Riker Sedation-Agitation Scale" [10]. When their Aldrete score [11] became ≥9, they were discharged to the ward. The postoperative pain during rest and movement was assessed by NRS every two hours, and the mean of each throughout the first day was calculated. According to the local policy of analgesia, patients received IV 1g paracetamol every eight hours during the first 48 hours and morphine (1mg/ml) IV at a dose of 0.05mg/kg lean body weight up to 4mg per dose to be repeated if the pain score was or persisted ≥4. The time to the first detection of bowel sounds or passing flatus, indicating resumption of bowel function was recorded. Outcomes were assessed by an anaesthesiologist who was blinded about patient group.

The primary outcome was the serum IL-6 level measured after two hours from the start of either propofol or ketamine IV infusions. Other immune-inflammatory indicators including IL-1β, TLC, absolute neutrophil count and N/L ratio, glucose level, CRP level, postoperative emerging agitation, mean NRS score at rest and movement during the first day, and time to the resumption of GIT function were the secondary outcomes.

Sample size:

G*power program version 3.1.9.7 was used for sample size calculation depending on the results extracted from an internal pilot study, which included six patients enrolled in each group who were not included in the study. The mean (SD) of serum level of IL-6 measured after two hours of infusion as a primary outcome was 264.33(22.13) in the propofol group and 284.83(46.63) in ketamine group. By using 2-tailed *t* test for power analysis, an effect size of 0.42, α error= 0.05 and power= 80% achieved a sample size of 40 patients: 20 patients in each group.

Statistics:

The SPSS version 22 (SPSS, Inc, USA) tabulated and analyzed the previously collected data. We used the means and standard deviations to express numerical data, while categorical ones were expressed as numbers and percentages. The student t-test was used to compare the numerical data, while the Chi-square or Fisher exact tests were used to compare the other types of data. If the P value was less than 0.05, the difference between the groups was considered significant.

RESULTS

Patient recruitment started from 10th January 2019 till 15th August 2019. Sixty patients were enrolled in the study, but ten patients were excluded because of blood transfusion before surgery for correction of anemia, another six patients received preoperative neoadjuvant chemotherapy, and four patients refused to participate. Thus, forty patients were enrolled and completed the study. Trial phases are shown in the CONSORT chart in Figure (1). Demographic data were comparable between both groups, as shown in Table (1).

Table 1: Patients' characteristics and surgical data of the studied groups:

	Group P (*n*= 20)	Group K (*n*= 20)	95% CI	Mean CI	*p*-value
Age (years)	50.40(9.77)	55.15(8.88)	0.735, -0.758	-0.0115	0.116
Sex					0.519
Male	13(65%)	11(55%)	-2.05, -10.72	-6.385	
Female	7(35%)	9(45%)			
Body mass index (kg/m^2)	28.66(3.52)	28.18(4.31)	-2.05, 2.99	0.47	0.706
Surgical duration (min)	188.65(46.80)	174.05(49.35)	-16.18, 45.38	14.6	0.343

Age: body mass index and surgical duration are expressed as mean (standard deviation); while sex is expressed as frequency (percentage); P: Propofol; K: Ketamine; 95% CI: 95% confidence interval of the mean difference between both groups.

Table (2) shows that the baseline measurements of IL-6, IL-1β, TLC, neutrophils, NLR, and glucose showed no significant difference between the two groups. Nonetheless, post-infusion Il-6 exhibited statistically higher readings at all time points in group K than group P except at 30-minute timepoint. Additionally, IL-1β and serum glucose exhibited statistically significant higher readings in Group K at all assessment time points except at 30-minute timepoint for serum glucose. In addition, postoperative serum CRP exhibited a statistically significant higher reading in Group K compared to Group P (*P* 0.019).

Table (3) shows that agitation scores were significantly lower in Group P compared to group K (*P*<0.001). The mean of NRS scores during rest was statistically higher in Group P than in Group K (*P* 0.003), but during movement NRS scores were not significantly different (*P* 0.072). The time to resume bowel function expressed no significant differences between the two groups as detected by bowel sounds (*P* 0.424) or passing the first flatus (*P* 0.759).

Table 2: Serum levels of IL-6, IL-1β, TLC, ANC, N/L ratio, Plasma glucose and CRP at the pre-specified perioperative measurement points:

	Time		Group P (n= 20)	Group K (n= 20)	95% CI	Mean CI	P
IL-6 (pg/ml)	Pre-infusion	Basal	39.70(12.62)	41.00(13.42)	-9.6, 7.0	-1.3	0.754
	Post-infusion	30min	89.45(39.52)	86.95(35.11)	-21.4, 26.4	2.5	0.834
		2hs	207.80(34.04)	308.90(28.21)	-121.1, -81.1	-101.1	<0.001*
		8hs	189.05(17.19)	232.40(39.05)	-62.7, -24.0	-43.35	<0.001*
		24hs	122.80(28.71)	148.00(28.83)	-43.6, -6.8	-25.2	0.009*
IL-1B (pg/ml)	Pre-infusion	Basal	7.55(2.24)	8.70(1.75)	-2.44, -0.135	-1.2875	0.078
	Post-infusion	30min	17.90(5.73)	36.60(14.11)	-25.6, -11.8	-18.7	<0.001*
		2hs	57.30(20.51)	72.70(26.47)	-30.6, -0.2	-15.4	0.047*
		8hs	44.55(11.65)	66.75(31.57)	-37.4, -7.0	-22.2	0.005*
		24hs	24.10(10.45)	49.40(34.49)	-41.6, -9.0	-25.3	0.003*
TLC (cells/mm^3)	Pre-infusion	Basal	7.78(1.17)	7.17(1.61)	-0.3, 1.5	0.6	0.179
	Post-infusion	30min	9.78(1.74)	8.73(2.25)	-0.2, 2.3	1.05	0.106
		2hs	12.80(1.86)	16.83(12.72)	-9.8, 1.8	-4	0.169
		8hs	12.65(2.16)	15.93(11.79)	-8.7, 2.1	-3.3	0.229
		24hs	11.75(1.94)	14.78(10.89)	-8.0, 2.0	-3	0.228
ANC (cells/mm^3)	Pre-infusion	Basal	5.12(0.83)	4.59(1.01)	-0.1, 1.1	0.5	0.083
	Post-infusion	30min	6.30(1.11)	5.670(1.58)	-0.2, 1.5	0.65	0.152
		2hs	8.16(1.23)	10.89(8.07)	-6.4, 1.0	-2.7	0.142
		8hs	8.11(1.35)	10.23(7.08)	-5.4, 1.1	-2.15	0.196
		24hs	7.24(1.09)	9.72(7.04)	-5.5, 1.0	-2.25	0.128
N/L ratio	Pre-infusion	Basal	2.02(0.48)	1.850(0.49)	-0.1, 0.5	0.2	0.279
	Post-infusion	30min	2.37(0.51)	2.15(0.41)	-0.1, 0.5	0.2	0.134
		2hs	3.17(0.65)	4.06(2.70)	-2.1, 0.4	-0.85	0.163
		8hs	2.99(0.70)	3.70(2.59)	-1.9, 0.5	-0.7	0.247
		24hs	2.81(0.52)	3.630(3.01)	-2.2, 0.6	-0.8	0.237
Serum glucose (mg/dl)	Pre-infusion	Basal	115.10(13.95)	115.25(12.92)	-8.8, 8.5	-0.15	0.972
	Post-infusion	30min	122.08(16.43)	121.81(12.92)	-9.2, 9.7	0.25	0.954
		2hs	131.58(16.86)	148.76(30.87)	-33.1, -1.3	-17.2	0.035*
		8hs	131.41(17.01)	147.03(29.69)	-31.1, -0.1	-15.6	0.048*
		24hs	129.09(17.64)	145.04(29.99)	-31.7, -0.2	-15.95	0.047*
CRP (mg/l)	Pre-infusion	Basal	2.92(0.95)	3.60(1.22)	-1.38, -0.013	-0.6965	0.054
	Post-infusion	24hs	9.56(4.719)	15.17(9.06)	-10.2, -1.0	-5.6	0.019*

Data are expressed as mean (standard deviation); P: Propofol; K: Ketamine; IL-6: Interleukin-6; IL-1β: interleukin-1β; TLC: total leucocytic count; ANC: Absolute neutrophil count; N/L ratio: Neutrophil-lymphocyte-ratio; CRP: C-reactive protein; 95% CI: 95% confidence interval of the mean difference between both groups; *: Significance (P<0.05) between the two groups.

Table 3: Postoperative sedation, pain and bowel function criteria of the studied groups:

Postoperatively	Group P (n= 20)	Group K (n= 20)	95% CI	Mean CI	P
RSAS	3.75(0.64)	4.45(0.51)	-1.1, -0.3	-0.7	<0.001*
NRS at rest for the first 24 h	4.20(1.15)	3.15(0.93)	0.4, 1.7	1.05	0.003*
NRS at movement for the first 24 h	6.30(1.34)	5.50(1.39)	-0.1, 1.7	0.8	0.072
First auscultation of bowel sounds (day)	1.33(0.47)	1.45(0.51)	-0.4, 0.2	-0.1	0.424
First passage of flatus (day)	1.73(0.44)	1.78(0.57)	-0.4, 0.3	-0.05	0.759

Data are expressed as mean (standard deviation); P: Propofol; K: Ketamine; 95% CI: 95% confidence interval of the mean difference between both groups; RSAS= Riker Sedation-Agitation Scale; NRS= Numerical Rating Scale; *: Significance (P<0.05) between the two groups.

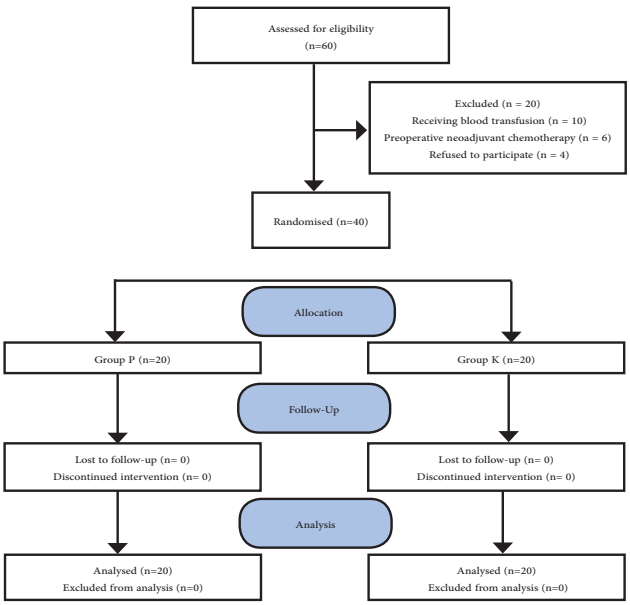

Figure 1: CONSORT flow chart showing trial phases.

DISCUSSION

This study was conducted as a prospective randomised double-blinded clinical trial. It compared the impact of propofol and ketamine infusions on the levels of postoperative stress and immune responses. Propofol was more effective than ketamine in reducing the physiological stress response in patients undergoing open colectomy surgery. Propofol has a notable effect in attenuating the pro-inflammatory cytokines (IL-6 and IL-1β), blood glucose levels, and acute phase reactants (CRP), as well as a more effective sedative effect. However, ketamine has a notable effect on the management of postoperative pain but with similar impacts on gastrointestinal function.

In the current study, propofol significantly attenuated both IL-6 and IL-1β, which are pro-inflammatory cytokines that increase significantly in association with surgical trauma compared to ketamine. Propofol and ketamine have an inhibitory effect on the release of pro-inflammatory cytokines [8,12]. However, no previous study has elucidated which agent is more effective. The mechanism by which propofol reduces these cytokines may be attributed to activating the GABA-A receptor, it causes an increase in the Nuclear factor erythroid 2-related factor (Nrf2) in the cytoplasm. This Nrf2 then moves into the nucleus, preventing the inflammatory response during the polarisation of human macrophages [13].

The enhanced suppressive effect of propofol on stress response was also manifested in the decrease in postoperative serum CRP levels. CRP is a well-known acute phase reactant that increases in the serum after tissue injury or inflammation. CRP is produced by the liver cells under the influence of IL-6 [14]. Therefore, CRP levels were lower with propofol infusion as this group expressed lower levels of pro-inflammatory cytokines, including IL-6. However, NLR expressed no significant difference between the two groups. The rise of that ratio has been reported in patients with severe trauma [15], postoperative complication [16], and bacterial or fungal infections [17,18]. Eochagáin *et al.,* noticed a significant decline in NLR in the propofol group compared to inhaled anesthetics after the operation [19]. However, the previous authors did not use ketamine in the other group, and studies evaluating the effect of ketamine on that parameter are scarce in the current literature.

Additionally, elevated blood glucose levels after major surgery are expected to be found secondary to the release of stress hormones like cortisol and adrenaline, as well as increased hepatic gluconeogenesis and glycogenolysis [1,20,21]. Our results showed lower values of postoperative glucose with propofol infusion, which could reflect a decreased stress response compared to ketamine.

The current study noted a significant decline in postoperative agitation score with propofol infusion because it induces sedation by decreasing the dissociation of γ-Aminobutyric acid, an inhibitory neurotransmitter, from its receptors [22]. On the other hand, ketamine is known for its sedative effects mediated by the dissociation between the cortical and limbic systems. Still, it may induce recovery agitation, delirium, and even hallucinations that may occur in up to 25% of patients [23-25]. Despite the effective sedative effects of propofol, it does not have an analgesic effect [26]. Our findings showed a significant decline in postoperative pain scores during rest with ketamine infusion as it induces analgesia via its antagonistic action on N-methyl-D-aspartic acid receptors [27].

Despite this handling of a rare anesthetic topic, this study has some limitations. The sample size may be small for evaluating the secondary outcomes. Further studies may be needed to determine the lowest effective dose to reduce the stress response (dose-response study).

CONCLUSION

Propofol is more effective than ketamine in reducing the physiological stress response in patients undergoing open colectomy surgery. It is linked to a notable decrease in pro-inflammatory cytokines IL-6 and IL-1β, blood glucose levels, and acute phase reactant CRP when compared with ketamine.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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