

Comparison of Hemodynamic Stability of Patients Undergoing Appendectomy under Spinal Anesthesia versus Blend of Ketamine and Midazolam with Spinal Anesthesia

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ABSTRACT

Objective: To compare appendectomy under spinal anaesthesia versus combining Ketamine and Midazolam with spinal anaesthesia.

Study Design: Quasi-experimental study.

Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi, from Jan to June 2022.

Methodology: A sample of 100 patients fulfilling the inclusion/exclusion criteria was collected. A random segregation was made into two equal groups through the lottery method resulting in fifty patients in each Group-50. The Group A patients received spinal anaesthesia while and were given 0.25mg/kg Ketamine and 2mg Midazolam 2 minutes before incision. Group B patients only received spinal anaesthesia. Patients' hemodynamics were monitored throughout surgery. The primary parameter studied was hemodynamic stability, and the secondary parameter was conversion into general anaesthesia.

Results: The primary outcome was hemodynamic stability. 48(96%) patients remained hemodynamically stable in Group A. Only 2(4%) patients showed hemodynamic instability. The Group B patient had lower hemodynamic stability as 29(58%) patients were hemodynamically unstable versus 21(42%) being stable (p -value <0.001).

Conclusion: Using Ketamine and Midazolam as adjuvants to spinal anaesthesia improves hemodynamic stability and success for open appendectomy.

Keywords: Anesthesia, Ketamine, Midazolam, Spinal anesthesia.

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INTRODUCTION

Appendicitis is the most prevalent acute abdominal emergency in the world,¹ with an overall incidence of almost twenty-eight percent with no significant difference in the distribution pattern about gender or age.² In Pakistan, its incidence is 7% in all age groups, and the peak age for appendicitis is between ten to thirty years.^{3,4} Acute appendicitis is the most common form requiring emergent surgical intervention. However, there are case reports regarding the chronicity of appendicitis.⁵ However, whichever may be the case, the treatment is surgical removal, either by conventional open appendectomy (OA) or laparoscopic appendectomy.⁶ Laparoscopic appendectomy has gained more popularity over open appendectomy due to reduced analgesic requirement and early recovery.⁷

Appendectomies are mostly performed under general anaesthesia (GA) with rapid sequence induction, endotracheal intubation and controlled ventilation to prevent pulmonary aspiration and distress due to referred pain. Appendectomy can also be performed

under neuraxial anaesthesia.⁸ In a multicenter study, Mohib et al. Studied six hundred fifty-five patients, of which three hundred and fifty-three received neuraxial anaesthesia, and three hundred received general anaesthesia. Their study showed that neuraxial anaesthesia was related to improved outcomes compared to general anaesthesia.⁹

The rationale of our study was to compare the combination of old drugs: Ketamine and Midazolam, along with spinal anaesthesia, with conventional spinal anaesthesia to study patients' comfort and improvement in outcome. Instead of using these agents as rescue drugs to alleviate patients' anxiety or proprioception once established, we gave these drugs to all patients before surgical incisions to gather scientific evidence. Although these drugs have been used for a long, the evidence of their use in this respect is scarce. Our study will be specifically helpful for resource-limited setups where short-acting opioids (Fentanyl & Remifentanyl) and advanced laparoscopic instruments are unavailable.

METHODOLOGY

The quasi-experimental study was conducted at the Anesthesia Department of Pakistan Emirate Military Hospital, Pakistan, from Jan to June 2022 after

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seeking permission from Hospital Ethics Committee (IERB number: A/28/149/EC/458/2022). The sample size was calculated with a WHO sample size calculator keeping, Expected effect size of 0.2, P1 (anticipated proportion of subjects in treatment Group A) to be 74% and P2 (anticipated proportion of subjects in treatment group B) to be 54%¹⁰.

Inclusion Criteria: Patients having American Society of Anesthesiology (ASA) classification I or II with ages ranging from 25-50 years who came to the operation theatre for an emergency appendectomy and consented to neuraxial anaesthesia were included.

Exclusion Criteria: Patients unwilling to spinal anaesthesia, patients with advanced cardiovascular, pulmonary, renal, hepatic or Cerebrovascular disease, patients having known drug allergy to any of the drugs or contraindications to neuraxial anaesthesia and pregnant ladies were excluded from the study.

A sample of 100 patients fulfilling the inclusion/exclusion criteria was collected through purposive sampling. Segregation was made into two equal groups through the lottery method resulting in fifty patients in each Group-50. The patients were informed about the purpose of the study and the risk of conversion to general anaesthesia. Written informed consent was taken from all the participants. The patients were booked through the emergency and trauma centre of the hospital, and pre-anaesthesia was done at the bedside before shifting to the operation theatre. Once in the operation theatre, all patients were reassured. Standard monitoring was attached, and intravascular access was achieved with the 18-gauge cannula. Preloading was done with Hartmann's solution 10ml/kg body weight, and premedication was done with ondansetron 8 mg and dexamethasone 8 mg. All Group, A patients were helped to maintain a sitting position, back were scrubbed and draped with Hexiprep (Chlorhexidine gluconate skin-prepping solution). Local anaesthesia was given with a 3ml syringe at L3-L4 interspace.

Spinal anaesthesia was achieved by 3ml of 0.5% hyperbaric Bupivacaine (Benzocaine spinal 0.5%, Brookes Pharma) at L3-L4 interspace level with a 27-gauge pencil-point spinal needle (B. Braun, 5 inches, Pencan). All the patients were laid supine immediately after the spinal. The block level was checked after 10 minutes with the help of ethyl chloride spray and Bromage score. After that, 0.5mg/ Kg ketamine and 2mg of Midazolam were given to all Group A patients 3 minutes before incision.

Similarly, Group B patients were helped to maintain a sitting position, back were scrubbed and draped with Hexiprep (Chlorhexidine gluconate skin-prepping solution). Local anaesthesia was given with a 3ml syringe at L3-L4 interspace. Spinal anaesthesia was achieved by 3ml of 0.5% hyperbaric Bupivacaine (Benzocaine spinal 0.5%, Brookes Pharma) at L3-L4 interspace level with a 27-gauge pencil-point spinal needle (B. Braun, 5 inches, Pencan).

The primary parameters observed were hemodynamic stability, and the secondary parameter was conversion into general anaesthesia. Hemodynamic stability was measured in the form of the presence or absence of bradycardia (Heart rate <50), hypotension (>30% decrease in Mean arterial blood pressure), use of vasoconstrictor (100ug phenylephrine) and atropine (0.5mg). The other parameters measured were conversion into general anaesthesia, level of block, Bromage score, maximum intraoperative Visual Analogue Score (VAS) and Ramsay Sedation Score (RSS). The decision to convert into general anaesthesia was made in the patients who complained of discomfort, pain and dragging feeling equivalent to visual analogue score (VAS) ≥ 3 .

All the data was analyzed through Statistical Package for the Social Sciences (SPSS) Version 26. Means \pm SD was calculated for continuous variables. Frequency (percentages) and Interquartile range (IQR) were calculated for categorical and discrete variables. Chi-Square test and t-test were applied to draw comparisons. The *p*-value ≤ 0.05 was considered significant.

RESULTS

There were 50 patients in each Group. The primary parameter studied was hemodynamic stability. 48(96%) patients remained hemodynamically stable in Group A. Only 2(4%) patients showed hemodynamic instability. The Group B patient had higher hemodynamic instability, with 29(58%) patients being hemodynamically unstable versus 21(42%) being stable (Table-I). None of Group A patients required conversion to General anaesthesia (100%), while 19(38%) Group B patients were converted to general anaesthesia (*p*-value < 0.001).

The mean age of patients in Group A was 43.88 \pm 11.88 years, and 39.76 \pm 11.19 years in Group B. The mean weight of patients in Group A was 74.68 \pm 6.11 kg and 79.26 \pm 7.72 kg in Group B. The mean height was 160.70 \pm 4.791 cm in Group A and 164.88 \pm 7.38 cm in Group B. The median intra-operative

pain score (VAS) was recorded to be 0 (IQR 1-5) in Group A and 1(IQR 1-7) in Group B. The Ramsay sedation score was 4 (IQR 1-3) in Group A patients and 2 (IQR 0-1) in Group B patients (*p*-value <0.001). This means Group A patients remained comfortable during surgery (Table-II). The frequencies of adverse effects are compared in Table-III.

Table-I: Comparison of Hemodynamic Stability Between Both Study Groups (n=100)

		Group A n=50 n(%)	Group B n=50 n(%)	<i>p</i> - value
Hemodynamic Stability	yes	48(96.0)	29(58.0)	<0.001
	no	2(4)	21(42)	

Table-II: Descriptive Statistics of Continuous Variables of Study Groups (n=100)

	Group A n=50	Group B n=50	<i>p</i> - value
	Mean ±SD	Mean ±SD	
AGE (YEARS)	43.88±11.88	39.76±11.19	<0.001
WEIGHT (KG)	74.68±6.113	79.26±7.727	<0.001
HEIGHT (CM)	160.78±4.791	164.88±7.381	<0.001
	Median(IQR)	Median(IQR)	
Ramsay sedation score (rss)	4(1-3)	2(0-1)	<0.001
Maximum visual analog score (vas)	0(1-5)	1(1-7)	<0.001

Table-III: Frequencies of Different Outcomes of Study Groups (n=100)

Parameter		Group n(%) n=50	Group B n(%) n=50	<i>p</i> - value
Hypotension	Yes	3(6.0)	19(38)	<0.0001
	No	47(94)	31(62)	
Bradycardia	Yes	0(0)	12(24)	<0.001
	No	50(100)	38(76)	
Conversion into general anesthesia	Yes	0(0)	19(38)	<0.001
	No	50(100)	31(62)	
T6 level achieved	Yes	46(92)	46(92)	<0.643
	No	4(8)	4(8)	
Post-operative nausea and vomiting	Yes	1(2)	13(26)	<0.001
	No	49(98)	37(74)	
Atropine	Yes	0(0)	13(26)	<0.001
	No	50(100)	37(74)	
Vasoconstrictor	Yes	3(6)	18(36)	<0.001
	No	47(94)	32(64)	

DISCUSSION

Spinal anaesthesia with a blend of Ketamine and Midazolam proved a reasonably good alternative to general anaesthesia for open appendectomy. Appendectomy can be performed under regional anaesthesia (spinal, epidural, combined spinal-epidural, peripheral

nerve blocks) or general anaesthesia. There is no basis for an overall analysis to demonstrate the differences in mortality between regional and general anaesthesia for appendectomy. However, spinal anaesthesia alone did not prove appropriate in some patients in our study and appeared to be an inferior choice as the sole anaesthetic technique.

Spinal anaesthesia is frequently employed for surgical anaesthesia in the lower abdomen and lower limbs, and it is associated with improved fetal and maternal outcomes when given for lower-segment cesarean section.¹⁰ Afolayan *et al.* Studied intrathecal tramadol and fentanyl to mitigate the discomfort of dragging and proprioception during spinal anaesthesia. They studied one hundred and eighty-six patients who underwent open appendectomy. The incidence of intraoperative hypotension was almost twenty-four per cent in both study groups, with itching in the fentanyl group and statistically significant post-operative nausea and vomiting in both groups.¹¹ Fentanyl and remifentanyl or not available in our setup.

We used Ketamine as the only drug used as the sole anaesthetic agent, which causes analgesia, amnesia, akinesia and sedation. The rationale for giving Ketamine was to use its analgesic, sedative, amnestic and pressor effect to prevent pain and hemodynamic compromise. Apart from being a good anaesthetic agent, Ketamine is not devoid of side effects like mydriasis, nystagmus, palpitations, tachycardia, hypertonia, psychomimetic and psychomotor reactions. These side effects are revealed along with respiratory depression and apnea when used at high doses.^{12,13} We were well aware of this adverse profile of Ketamine; therefore, we decided to counterbalance these effects using Midazolam. One study conducted on 30 patients who were given Midazolam (0.02mg/kg) as premedication and Ketamine (1mg/kg), which was given as an induction agent for general anaesthesia. The results of the study showed that there was no significant hemodynamic compromise and psychomimetic effects in 24 out of 27 patients. Their study differed from ours as we used Ketamine 0.25mg per kg, and they used it as 1mg/kg. The mode of anaesthesia they used was general anaesthesia, while we used neuraxial anaesthesia.¹⁴

Midazolam is a drug with an array of clinical effects. It causes anxiolysis, which is mediated through the inhibitory neurotransmitter glycine. Its anticonvulsant effect is attributed to Gama amino butyric acid (GAMA) in central nervous system motor neuronal

centres.¹⁵ As mentioned earlier, the two actions are centrally mediated, while the muscle relaxation caused by Midazolam is due to its action on the spinal cord through glycine receptors.¹⁶ The muscle relaxation caused by Midazolam potentiated Bupivacaine-induced muscle relaxation. It counteracted the hyper-tonia caused by Ketamine, resulting in smooth surgery as 45 out of 50 patients did not require conversion into general anaesthesia.

The combined use of Ketamine and Midazolam in our study was useful in producing sedation with a Ramsay sedation score of 4 in almost 28(56%) patients, which was beneficial in those patients who were willing to sleep during the surgery. This combination of drugs also proved effective against post-operative nausea and vomiting, as only one Group A patient developed nausea. It was associated with profound hypotension necessitating the use of a vasoconstrictor. General anaesthesia is an independent risk factor for PONV, with an incidence as high as 43% without using any premedication.¹⁷ The use of regional anaesthesia excluded this risk factor. Midazolam infusion has been used in the treatment of refractory PONV.¹⁸ At the same time, Ketamine has also been associated with a decreased incidence of PONV compared to placebo in a randomized controlled trial by Modir et al.¹⁹

The other advantage of using spinal anaesthesia over general anaesthesia in our study was that the patients were awake and oriented at the end of the procedure due to the short duration of action of Ketamine, which is 30 min, and Midazolam, which is 60 min. Less pain was experienced due to the residual effects of neuraxial anaesthesia. The patients who received spinal anaesthesia tend to ambulate earlier than patients who received general anaesthesia. Finally, complications related to intubation and/or extubation are avoided in spinal anaesthesia, which is of specific benefit to patients with pulmonary disease who may benefit from fewer effects on pulmonary function and oxygenation. It also had the added advantage of opioid-sparing and the potential to reduce blood loss and perioperative deep venous thrombosis. Spinal anaesthesia is a less invasive technique with lower morbidity and mortality rates than general anaesthesia. Perioperative deep venous thrombosis.

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LIMITATION OF STUDY

We did not use specialized equipment for objective sedation measurement, like a bi-spectral index. The sampling

technique was purposive sampling which can be a source of bias.

CONCLUSION

We concluded that using Ketamine and Midazolam as adjuvants to spinal anaesthesia improves its hemodynamic stability and success as a mode of anaesthesia for open appendectomy.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

KM: & UEM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AH: & FH: Study design, drafting the manuscript, data interpretation, concept, approval of the final version to be published.

HM: & NUS: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Hemodynamic Stability of Patients

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