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Epidural Anesthesia for Anal Surgeries, Does Ketamine Have a Role?

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ABSTRACT

Background: Performing anorectal operations under epidural anesthesia has multiple advantages. However, such procedures are associated with severe postoperative pain. Ketamine has previously been described to be a potent local anesthetic adjuvant.

Aim of the study: We evaluated if adding ketamine 50mg as an adjuvant to bupivacaine would enhance the postoperative analgesic profile in patients undergoing minor anal surgeries.

Patients and methods: One hundred patients scheduled for anal operations were included in this prospective randomized trial, and they were divided into two equal groups; B group (bupivacaine only) and BK group (bupivacaine and ketamine).

Results: Both basic and clinical criteria of the included patients were comparable between the two groups. However, ketamine was associated with earlier onset of sensory block (11.3 vs. 15.4 minutes in Group B). Also, the adjuvant was associated with a significant reduction of postoperative pain scores, which was evident four hours after surgery till the end of the first postoperative day. Moreover, the need and the total amount of commenced opioids decreased significantly in Group BK. The incidence of postoperative complications, including pruritis, nausea, and vomiting, was significantly reduced with ketamine administration.

Conclusion: Adding ketamine to bupivacaine has multiple advantages in patients undergoing anorectal procedures. It is associated with earlier onset of sensory block, less postoperative pain, and decreased need for postoperative opioids.

Keywords: Epidural anesthesia; Ketamine; Anal surgery.

INTRODUCTION

Minor anorectal procedures, like anal fissures, hemorrhoids, and perianal fistulae, are common entities that are frequently performed in daily general surgical practice [(1,2)].These procedures require deep anesthesia because this region receives a rich nerve supply, including sympathetic, parasympathetic, and somatic innervations[(3,4)].

Although the previous procedures are usually performed under spinal anesthesia or saddle block, some anesthesiologists prefer epidural anesthesia because of its potential advantages. Epidural anesthesia has a low risk for hypotension, minimal motor block, and earlier postoperative mobilization. It is also associated with a lower chance of having postural puncture headaches [(5)].Moreover, it is safer in patients with hemodynamic instability [(6)].

Patients usually complain of severe pain following anorectal procedures. This pain is mainly mediated through the activation of N-methyl D-aspartate (NMDA) receptors in the spinal horn of the spinal cord. This, in turn, leads to central sensitization and severe pain sensation[(7)].

Ketamine is an NMDA inhibitor that has been described as a potent adjuvant to local anesthetics. By its antagonistic actions on NMDA receptors, it activates cholinergic and opioid receptors, together with descending inhibitory monoaminergic pathways. Besides, it also blocks sodium channels like local anesthetics [(8-10)].Although some concerns have been mentioned regarding ketamine neurotoxicity when administered intrathecally, its single and repeated administration through the epidural route has been found safe and devoid of these neurotoxic effects[(11-12)].

AIM OF THE STUDY

It is to evaluate the epidural administration of 50mg ketamine as an adjuvant to bupivacaine would enhance the sensory block and postoperative analgesia and reduce postoperative opioid consumption in patients undergoing minor anal procedures.

PATIENTS AND METHODS

The current prospective trial was conducted over a five-month duration, from May 2021 to September 2021. The study was designed for patients aged between 18 and 60 years, diagnosed with benign anorectal disorder (perianal fistula, hemorrhoids, or fissure in ano), and scheduled for surgery under epidural anesthesia.

We estimated the required sample size via the Priori G Power Analysis, using the data of the previous study published by **Mendonça and his colleagues [(13)]**. Who reported a mean 24-hour pain score of 2.25 ± 1.6 in the ketamine group. A 45-patient sample was required to achieve a 0.6 effect size, 80% power, and 5% type I error. With an expected 10% dropouts, the included patients were increased to 50 patients in each group.

All patients were subjected to the standard preoperative assessment, including history taking and clinical examination, beside routine laboratory and radiological workups. The patients were also assessed by the anesthetic team before surgery, and their physical status was assessed according to the "American Society of Anesthesiologists" or ASA [(14)], and patients with class > II were excluded. We also excluded patients with respiratory tract infections, current smoking,

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pregnancy, bleeding diathesis, or who had any contraindication for regional anesthesia.

Using the "sealed envelope method", the enrolled participants were divided into two groups; Group B (50 patients), which received only epidural bupivacaine, and Group BK (25 patients), which received bupivacaine in addition to ketamine (50 mg).

On arrival at the operating room, basic hemodynamic monitoring was established, including pulse oximetry, blood pressure measurement, and ECG. An intravenous line was secured in all patients by an 18-gauge cannula inserted into a peripheral forearm vein, and ringer lactate or saline 0.9% was infused as a preload. No pre-medications were administered.

After proper skin sterilization with bovine iodine, epidural anesthesia was performed when the patient was setting, using an 18-gauge Tuohy needle that was inserted into the L4-5 interspace with its bevel directed cranially. The entrance to the epidural space was confirmed by loss of resistance to air. Then, a 22-gauge multi-orifice catheter was inserted into the epidural space. The catheter was then secured to the patents back with adhesive plaster.

Initially, we tested the catheter using 3ml of lidocaine (2%) with adrenaline (1:200000). If there were no signs of subarachnoid or intravascular injection, the long-acting anesthetic was administered according to group allocation. Group B received 15 ml bupivacaine (0.5%), whereas Group BK received the same bupivacaine dose in addition to ketamine (50 mg), which was injected over one minute, half an hour prior to the surgical procedure.

After the procedure, the patients were transferred to Post Anesthetic Care Unit (PACU), then to the surgical ward. Postoperative analgesia was maintained by IV paracetamol (1gm/ eight hours) and IV ketorolac (30 mg/12 hours). Patients were asked to express their pain via the “Numerical Rating Scale” or NRS, which is an eleven-point scale ranging from zero to 10 [(15)],Zero for no pain at all, while 10 for the worst pain ever felt. NRS values were recorded at PACU, then 2, 4, 6, 8, 12, 16, 18, and 24 hours after the operation. If the patient reported breakthrough pain (NRS > 3), IV fentanyl (25 – 50 mcg) was administered. The number of patients requiring rescue analgesia, the duration till reporting the breakthrough pain, and the total postoperative fentanyl consumption were recorded in both study groups.

The main outcome of our trial was postoperative pain (measured by the NRS, whereas secondary objectives included the onset of sensory block, the duration till the first rescue analgesic, total postoperative opioid consumption, and the incidence of postoperative complications.

Ethical Consideration:

Initially, the study protocol was approved by the Institutional Review Board (IRB) of Mansoura University, code R.21.05.1335.R1, and all patients agreed to the terms of our research after explaining the benefits and possible drawbacks of each intervention. An informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association [(16)] (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The previously collected parameters were tabulated and analyzed via the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). We expressed the numerical data as mean and standard deviation, while the categorical ones was expressed as numbers and percentages. When the data of the two groups were compared, we used the student t-test and the Chi-Square tests for the former and latter data sets, respectively. When a p-value less than 0.05 was detected, it was considered statistically significant.

RESULTS

Patients' demographic criteria showed no significant difference between the study groups table (**1**). Patients in Group B had a mean age of 34.92 years compared to 36.06 years in Group BK ($p = 0.502$). Regarding their gender, men represented 52% and 38% of the included patients in the previous two groups, respectively, while the remaining patients were women ($p = 0.159$). The mean weight of these cases was 89.4 kg in Group B versus 87.62 kg in Group BK ($p = 0.447$).

Patients with ASA class I represented 94% and 86% of the participants in Groups B and BK, respectively. The remaining cases were classified as ASA class II ($p = 0.182$). Preoperative diagnosis and the duration of the operative procedure were statistically comparable between the two groups. The latter had a mean duration of 21.7 minutes in Group B versus 22.2 minutes in Group BK ($p = 0.523$). However, Group BK showed earlier onset of anesthesia (11.3 versus 15.4 minutes in Group B – $p < 0.001$). Table (**1**) illustrates the previous data.

Table (1): Demographic characteristics, ASA classification, diagnosis, the onset of anesthesia, and surgery duration in the two groups.

		Group B (n= 50)	Group BK (n= 50)	P
Age (years)		34.92 ± 8.752	36.06 ± 8.173	0.502
Gender	**Male**	52.0% (26)	38.0% (19)	0.159
	Female	48.0% (24)	62.0% (31)	
Weight (kg)		89.40 ± 11.245	87.62 ± 12.056	0.447
ASA	**I**	94.0% (47)	86.0% (43)	0.182
	II	6.0% (3)	14.0% (7)	
Diagnosis	**Hemorrhoids**	34.0% (17)	44.0% (22)	0.264
	Anal fissure	56.0% (28)	40.0% (20)	
	Anal fistula	10.0% (5)	16.0% (8)	
The onset of anesthesia (minutes)		15.40 ± 6.376	11.30 ± 4.608	**< 0.001**
Surgery duration (minutes)		21.70 ± 4.117	22.20 ± 3.665	0.523

Ketamine administration was associated with a marked decline in postoperative NRS, and that was evident four hours after surgery till the end of the first postoperative day (Table **2**).

Table (2): NRS in the study groups.

VAS score	Group B (n= 50)	Group BK (n= 50)	P
PACU discharge	0.00 ± 0.0	0.00 ± 0.0	-
2 hours	0.00 ± 0.0	0.00 ± 0.0	-
4 hours	0.08 ± 0.274	0.00 ± 0.0	**0.042**
6 hours	0.56 ± 0.577	0.12 ± 0.328	**< 0.001**
8 hours	1.18 ± 0.748	0.60 ± 0.606	**< 0.001**
12 hours	1.80 ± 0.728	1.52 ± 0.677	**0.044**
16 hours	2.72 ± 0.701	2.42 ± 0.609	**0.023**
18 hours	3.30 ± 0.953	2.84 ± 0.934	**0.013**
24 hours	4.26 ± 1.259	3.28 ± 1.051	**< 0.001**

Postoperative opioids were required in 94% of patients in Group B, compared to only 80% in Group BK (p = 0.037). Additionally, the amount of commenced postoperative fentanyl decreased significantly in association with ketamine (112.2 vs. 141.06 µg in Group B, p = 0.001). The duration to the first analgesic request had mean values of 14.91 and 16.43 minutes in Groups B and BK, respectively (p = 0.001). The previous analgesic parameters were in favor of Group BK (Table **3**).

Table (3): Postoperative analgesic profile of the study groups.

	Group B (n= 50)	Group BK (n= 50)	P
Patients who required IV fentanyl	94.0% (47)	80.0% (40)	**0.037**
First analgesic rescue (hours)	14.91 ± 3.432	16.43 ± 3.234	**0.039**
Amount of fentanyl (µg)	141.06 ± 40.283	112.20 ± 35.108	**0.001**

Apart from urine retention, which has a comparable incidence between the two groups after the operation (p = 0.401), there was a significant increase in the incidence of nausea, vomiting, and pruritis in Group B. We did not encounter any cases of bradycardia or hypotension in the current study (Table **4**).

Table (4): Postoperative complications in the two groups.

	Group B (n= 50)	Group BK (n= 50)	P
Nausea	22.0% (11)	6.0% (3)	**0.021**
Vomiting	8.0% (4)	0.0% (0)	**0.041**
Bradycardia	0.0% (0)	0.0% (0)	-
Hypotension	28.0% (14)	22.0% (11)	0.488
Hallucination	0.0% (0)	0.0% (0)	-
Pruritus	8.0% (4)	0.0% (0)	**0.041**
Urinary retention	12.0% (6)	18.0% (9)	0.401

DISCUSSION

The current study was conducted to elucidate if ketamine is a potent adjuvant for bupivacaine injected during epidural anesthesia for patients undergoing anal surgery. Initially, the reader could notice no significant difference between our two study groups as regards preoperative and operative characteristics, indicating our proper randomization technique. Moreover, that should also decline any bias skewing our findings in favor of one group rather than the other.

Our findings showed that ketamine was a potent adjuvant for bupivacaine, as its administration was associated with a faster sensory block during epidural anesthesia (11.3 vs. 15.4 minutes in controls, $p < 0.001$). This could be secondary to the inhibition of action potentials via affecting sodium and potassium channels, which are mediated by ketamine in a similar way to local anesthetics [17].This is in accordance with **Kawana *et al*** [18] .who reported that epidural ketamine administration was associated with a significantly faster onset of epidural anesthesia.

Our findings showed that ketamine administration was associated with better pain control and lower pain scores during the first postoperative day. Of course, the initial two readings, which were comparable between our two groups, could be explained by the action of bupivacaine itself. Once its action faded, the advantage of ketamine became more obvious.

The diffusion of ketamine from the epidural space to the cerebrospinal fluid and to the systemic circulation also plays a role in its analgesic effects[19], as it performs this analgesic action by its supraspinal effects, NMDA receptor antagonism, and activation of the descending inhibitory monoaminergic pathways [19] .These theories of diffusion were previously confirmed in animal and human studies[20, 21] .It was noted that ketamine diffusion to the CSF makes it have a longer half-life[20], while its systemic diffusion provides 80% bioavailability[20].

Himmelseher *et al* [22]. agreed with our findings, as their participants expressed significantly lower pain scores when ketamine was used as an adjuvant to ropivacaine in epidural anesthesia during knee arthroplasty procedures. This effect was more evident at 24- and 48-hour readings. **Sethi *et al*** [11]. Also confirmed the previous findings in patients undergoing abdominal operations, and the effect was evident starting from six hours after surgery till the end of the second postoperative day.

In the current study, not only did the number of patients requiring opioid analgesia decrease with ketamine but also the total opioid consumption significantly diminished. The previous findings agree with **Ozyalcin and his coworkers** [8] ,who reported that ketamine not only decreases peripheral nociceptive stimuli but also it enhances the response to opioid analgesics and decreases its tolerance by preventing central sensitization. **Sethi and his colleagues** [11] agreed with our findings, as morphine consumption significantly declined in the group receiving ketamine as an adjuvant to local epidural anesthesia.

In our study, the decreased postoperative pain and opioid consumption had a positive impact on the incidence of complications manifested by the decreased incidence of nausea, vomiting, and pruritis. It is known that uncontrolled postoperative pain is a documented cause of nausea and vomiting, as pain stimulates the vomiting center[23].

Opioid administration could induce nausea and vomiting, which are reported in up to 40% and 25% of patients, respectively, after opioid administration[24]. This occurs secondary to the activation of the vomiting center, vestibular apparatus, chemoreceptor trigger zone, and the gastrointestinal tract itself [25]. Pruritus could also occur with opioid administration, and histamine release has been incriminated in that side effect. However, the clear mechanism is still unknown [26].A previous study also found a decreased incidence of the same three complications with epidural ketamine [11].

Limitations of the study:

We collected our patients from a single surgical center and the sample size was relatively small.

CONCLUSION AND RECOMMENDATION

Adding ketamine to bupivacaine has multiple advantages in patients undergoing anorectal procedures. It is associated with earlier onset of sensory block, less postoperative pain, and decreased need for postoperative opioids. This combination is recommended in such patients to enhance patient outcomes. Also, we recommend conducting more studies, including more cases from multiple centers in the future. These studies should also compare ketamine with other adjuvants and compare epidural anesthesia with other anesthetic techniques to define what is best for these patients.

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REFERENCES

1. **McCullough T , Wichmann M (2019):** Anorectal Disorders. Gastroenterology For General Surgeons. https://doi.org/10.1007/978-3-319-92768-8_4.
2. **Gardner I , Siddharthan R , Tsikitis V (2020)**: Benign anorectal disease: hemorrhoids, fissures, and fistulas. Ann Gastroenterol., 33(1): 9-18.
3. **Sundel M , Voltaggio L, Leeds I *et al.*** (2019): Anatomy and Histology of the Anus. Anal Cancer: A

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Comprehensive Guide. https://doi.org/10.1007/978-3-030-20253-8_1.

4. **Carmichael J , Mills S (2022):** Anatomy and Embryology of the Colon, Rectum, and Anus. The ASCRS Textbook of Colon and Rectal Surgery. https://doi.org/10.1007/978-3-030-66049-9_1.
5. **Vadhanan P, Rajendran I, Rajasekar P (2020)**: Ultrasound-Guided Caudal Epidural Anesthesia in Adults for Anorectal Procedures. Anesth Essays Res.,14(2): 239-242.
6. **Grass J A (2000)**: The role of epidural anesthesia and analgesia in postoperative outcome. Anesth Clin North Am.,18(2): 407-28, viii.
7. **Bell R , Dahl J , Moore R *et al*. (2005)**: Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). Acta Anaesthesiol Scand., 49(10): 1405-28.
8. **Ozyalcin N , Yucel A, Camlica H *et al*. (2004)**: Effect of pre-emptive ketamine on sensory changes and postoperative pain after thoracotomy: comparison of epidural and intramuscular routes. Br J Anaesth., 93(3): 356-61.
9. **Mion G, Villevieille T (2013)**: Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther., 19(6): 370-80.
10. **Zorumski C, Izumi Y, Mennerick S (2016)**: Ketamine: NMDA Receptors and Beyond. J Neurosci., 36(44): 11158-11164.
11. **Sethi M, Sethi N, Jain P *et al*. (2011)**: Role of epidural ketamine for postoperative analgesia after upper abdominal surgery. Indian J Anaesth., 55(2): 141-5.
12. **Allen C , Ivester J (2017)**: Ketamine for Pain Management-Side Effects & Potential Adverse Events. Pain Manag Nurs., 18(6): 372-377.
13. **Mendonça F, Almeida M, Guimarães C *et al*. (2013)**: Comparative study between epidural ketamine and morphine in patients submitted to mastectomy. Revista Dor., 14: 169-173.
14. **Apfelbaum J, Connis R, Nickinovich D *et al*. (2012):** Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology,116(3): 522-38.
15. **Pool J, Ostelo R, Hoving J *et al*. (2007)**: Minimal clinically important change of the Neck Disability Index and the Numerical Rating Scale for patients with neck pain. Spine (Phila Pa 1976), 32(26): 3047-51.
16. **Idänpään-Heikkilä J (2001)**: Ethical principles for the guidance of physicians in medical research--the Declaration of Helsinki. Bulletin of the World Health Organization,79(4): 279-279.
17. **Collins J (1986)**: Effects of ketamine on low intensity tactile sensory input are not dependent upon a spinal site of action. Anesth Analg., 65(11): 1123-9.
18. **Kawana Y, Sato H, Shimada H *et al*. (1987)**: Epidural ketamine for postoperative pain relief after gynecologic operations: a double-blind study and comparison with epidural morphine. Anesth Analg., 66(8): 735-8.
19. **Erol İ, Özdoğan L, Örnek D *et al*. (2014)**: Effect of Ketamine on the Quality of Anesthesia and Postoperative Analgesia in Epidural Anesthesia. J Exper Clin Med., 6(3): 83-89.
20. **Pedraz J, Calvo M, Gascon A *et al*. (1991)**: Pharmacokinetics and distribution of ketamine after extradural administration to dogs. Br J Anaesth., 67(3): 310-6.
21. **Pedraz J, Lanao J, Calvo M *et al*. (1987)**: Pharmacokinetic and clinical evaluation of ketamine administered by i.v. and epidural routes. Int J Clin Pharmacol Ther Toxicol., 25(2): 77-80.
22. **Himmelseher S, Ziegler-Pithamitsis D, Argiriadou H *et al*. (2001)**: Small-dose S(+)-ketamine reduces postoperative pain when applied with ropivacaine in epidural anesthesia for total knee arthroplasty. Anesth Analg., 92(5): 1290-5.
23. **Shaikh S, Nagarekha D, Hegade G *et al*. (2016)**: Postoperative nausea and vomiting: A simple yet complex problem. Anesth Essays Res., 10(3): 388-396.
24. **Mallick-Searle T, Fillman M (2017)**: The pathophysiology, incidence, impact, and treatment of opioid-induced nausea and vomiting. J Am Assoc Nurse Pract., 29(11): 704-710.
25. **Porreca F, Ossipov M (2009)**: Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options. Pain Med., 10(4): 654-62.
26. **Reich A, Szepietowski J (2010)**: Opioid-induced pruritus: an update. Clin Exp Dermatol., 35(1): 2-6.