Effect of intrathecally administered ketamine, morphine, and their combination, added to bupivacaine in patients undergoing major abdominal cancer surgery a randomized, double-blinded study

<table>
<thead>
<tr>
<th>Journal:</th>
<th>Pain Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>PME-ORR-Jan-17-068.R1</td>
</tr>
<tr>
<td>Manuscript Type:</td>
<td>Original research</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>n/a</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Abd El-Rahman, Ahmad; South Egypt Cancer Institute, Assiut University, Anesthesia Mohamed, Ashraf; assistant professor, anesthesia and intensive care ABD ELBAKY, SAHAR; SOUTH EGYPT CANCER INSTITUTE, Anesthesia, Intensive care, and Pain management Mostafa, Mohamed</td>
</tr>
<tr>
<td>Keywords:</td>
<td>Intrathecal, Ketamine, Morphine, lower abdominal cancer surgery</td>
</tr>
</tbody>
</table>
Effect of intrathecally administered ketamine, morphine, and their combination, added to bupivacaine in patients undergoing major abdominal cancer surgery a randomized, double-blinded study

Ahmad M. Abd El-Rahman*, M.D., Ashraf A. Mohamed**, M.D., Sahar A. Mohamed**, M.D., Mohamed A. M. Mostafa*, M.D.

*Lecturer of anesthesia, ICU, and pain management. South Egypt Cancer Institute, Assiut University, Assiut, Egypt.

**Assistant professor of anesthesia, ICU, and pain management. South Egypt Cancer Institute, Assiut University, Assiut, Egypt.

Corresponding author:
Ahmad Mohammad Abd El-Rahman
Lecturer of anesthesia, ICU, and pain management. South Egypt Cancer Institute, Assiut University, Assiut, Egypt.

E-mail: ahmad23679@gmail.com
Tel.: +201000525368
Fax: +20882348609
Zip code: 171516

The authors have no conflict of interests.

This work was not published in whole or part before.
Abstract:

Objective: Effective postoperative pain control reduces postoperative morbidity. In this study, we investigated the effects of intrathecal morphine, ketamine, or their combination with bupivacaine for postoperative analgesia in major abdominal cancer surgery.

Study design: prospective, randomized, double blinded.

Setting: academic medical center.

Patients and Methods: Ninety ASA I-III patients aged 30-50 years were divided randomly into three groups: Morphine group (group M) received 10 mg of hyperbaric bupivacaine 0.5% in 2 ml volume and 0.3 mg morphine in 1 ml volume intrathecally. Ketamine group (group K) received 0.1 mg/kg ketamine in 1ml volume instead of morphine. Morphine + Ketamine group (group K+M): patients received both 0.3 mg morphine plus 0.1 mg/kg of Ketamine in 1 ml volume intrathecally. Postoperative total morphine consumption, first request of analgesia, VAS, and side effects were recorded.

Results: Total PCA morphine was significantly decreased in group M+K compared to groups M and K. Time to first request of analgesia was prolonged in groups M and M+K compared to group K (p<0.001). VAS in group M+K was reduced from 2 till 24 hours and in group M at 12 and 18 hours postoperatively compared to group K, with an overall good analgesia in the three groups. Sedation was significantly higher in group M+K compared to group M till 6 hours postoperatively. No other side effects observed.

Conclusions: Adding intrathecal ketamine 0.1 mg/kg to morphine 0.3 mg in patients underwent major abdominal cancer surgery reduced the total postoperative morphine consumption in comparison to either drug alone, with an overall good postoperative analgesia in all groups, with no side effects apart from sedation.

Key words: Intrathecal, ketamine, morphine, lower abdominal cancer surgery.

Introduction:
Effective postoperative pain control is an essential component of the care of surgical patients. Inadequate pain control, apart from being inhumane, may result in increased morbidity or mortality \(^{(1,2)}\).

The advantages of effective postoperative pain management include patient comfort and therefore satisfaction, earlier mobilization, fewer pulmonary and cardiac complications, a reduced risk of deep vein thrombosis, faster recovery with less likelihood of the development of neuropathic pain, and reduced cost of care \(^{(3)}\).

Despite extensive discourses, there is still controversy in the literature as to the safety and analgesic efficacy of ketamine through the intrathecal route \(^{(4,5,6,7,8,9)}\). Preservative-free racemic ketamine was shown to be devoid of neurotoxic effects after both single and repeated administration in animals \(^{(4,5,6)}\).

Ketamine, a phencyclidine derivative, has recently been found to be effective by epidural and intrathecal routes. It possesses some definite advantages over the conventional local anaesthetic agents as it stimulates cardiovascular system \(^{(10,11)}\) and respiratory system \(^{(12)}\). The onset of anaesthesia (sensory block) and motor paralysis is found to be earlier than the conventional local anaesthetics \(^{(11)}\). Intensity of sensory block is 100% as it is described to be due to potent analgesic effect of ketamine \(^{(13)}\).

Intrathecal opioid administration is an attractive analgesic technique since the opioid is injected directly into the cerebrospinal fluid, close to the structures of the central nervous system where the opioid acts. The procedure is simple, quick, and with a relatively low risk of technical complications or failure \(^{(14)}\).

However, it is known that intrathecal morphine, alone or as an adjuvant to a local anesthetic, increases the risk of respiratory depression. As respiratory depression is a major risk \(^{(15)}\).

The objective of this study was to investigate the effects of intrathecal morphine, ketamine, or their combination when added to bupivacaine for postoperative analgesia in major abdominal cancer surgery.

**Patients and methods:**

This randomized, double-blind study was approved by the ethics committee of South Egypt Cancer Institute, Assiut University, Assiut, Egypt. Registered at (www.clinicaltrials.gov) with identifier no.: NCT02726828. After obtaining written informed consent, 90 American Society of
Anesthesia (ASA) I-III patients aged 30-50 years scheduled for major abdominal cancer surgery were included in the study. Patients with a known allergy to the study drugs, significant cardiac, respiratory, renal or hepatic disease, coagulation disorder, infection at or near the site of intrathecal injection, drug or alcohol abuse, BMI > 30 kg/m², and psychiatric illnesses that may interfere with perception and assessment of pain were excluded from the study.

Preoperatively, patients were taught how to evaluate their own pain intensity using the visual analogue scale (VAS), scored from 0 -10 (where 0 = no pain, and 10 = the worst pain imaginable).

Oral diazepam (5 mg) was given the night before surgery. Up on arrival at the operative theatre, a 16-gauge catheter was introduced intravenously at the dorsum of the hand; lactated Ringer's solution 10 mg/kg was infused intravenously over 10 min before initiation of spinal anesthesia. Basic monitoring probes (electrocardiography, non-invasive blood pressure, O₂ saturation, and temperature) were applied. Patients were placed in the sitting position and a 25-gauge Quincke needle was placed in the L₂-₃ or L₃-₄ interspaces.

Patients were randomly divided, by selecting sealed envelopes into one of three groups 30 patients each:

- The morphine group (group M) patients received 10 mg of hyperbaric bupivacaine 0.5% in 2 ml volume and 0.3 mg morphine in 1 ml volume intrathecally.
- The ketamine groups (group K) patients received 10 mg of hyperbaric bupivacaine 0.5% in 2 ml volume and 0.1 mg/kg ketamine in 1ml volume intrathecally.
- Morphine + Ketamine group (group M+ K) patients received 10 mg of hyperbaric bupivacaine 0.5% in 2 ml volume and 0.3 mg morphine plus 0.1 mg/kg of Ketamine in 1 ml volume intrathecally.

Immediately, after successful spinal anesthesia, the patients were placed in the supine position, general anesthesia was induced with fentanyl 1.5-2 µg/kg, propofol 2-3 mg/kg, and lidocaine 1.5 mg/kg. Endotracheal intubation was facilitated by cis-atracurium 0.15 mg/kg. Heart rate, systolic, and diastolic blood pressure were recorded at 5, 10, 20, 30, 60, 120, 180 minutes. Anesthesia and muscle relaxation were maintained by isoflurane 1- 1.5 MAC in 50% oxygen/air mixture and cis-atracurium 0.03 mg/kg bolus given every 30 min respectively.

At the end of surgery, muscle relaxation was reversed by neostigmine 50 µg/kg and atropine 10 µg/kg. Patients were extubated and transferred to Post Anesthesia Care Unit (PACU) and
monitored for vital signs (heart rate, non-invasive blood pressure, respiratory rate, and \( O_2 \) saturation) immediately postoperative and at 2, 4, 6, 12, 18, and 24 hours postoperative. Total analgesic consumption in the first 24 hours postoperatively and the time of first request of analgesia were recorded. VAS scores were assessed at the same time intervals. Rescue analgesia represented by patient-controlled analgesia (PCA) with intravenous morphine with an initial bolus of 0.1 mg/kg once pain was expressed by the patient, or if VAS is 3 or more (VAS ≥ 3) followed by 1 mg boluses with a lockout period of 5 min. The patient's level of sedation was assessed at the same time points with scores from 0 to 4, where 0 = awake, 1 = easily aroused, 2 = awakens after tactile stimulation, 3 = awakens after verbal stimulation, and 4 = not arousable. The attendant anesthesiologist was blinded to patient assignment to a specific group. Postoperative adverse effects such as nausea, vomiting, hypotension, bradycardia, itching were recorded and treated.

Hypotension is defined as a 15% decrease in systolic blood pressure from baseline. Bradycardia is defined as a heart rate slower than 50 beats per minute or a decrease in heart rate of 20% or more from baseline; whichever is lowest. Hypoxia is defined as an oxygen saturation of less than 90%. Hypotension was treated with intravenous bolus of ephedrine 0.1 mg/kg and normal saline 5ml/kg; the same doses were repeated as required. Bradycardia was treated with intravenous atropine 0.01 mg/kg.

**Statistical analysis:**

**Power of the study:**

The primary end-point was the total dose of intravenous PCA morphine consumption in the first 24 hours postoperatively. Secondary endpoints were the safety profile of the study drugs in terms of predefined adverse effects, nausea, vomiting, and level of sedation during the study period. To detect a difference of one SD \(^{(16)}\) between the mean of the total amount of postoperative morphine consumption between the study groups in the 24 hours, we estimated that 28 patients in each group would be required to have a power of 90% and an alpha error not exceeding 0.05. We included 30 patients in each group to compensate for possible patient drop-outs.

**Data analysis:**

Analysis was performed using statistical package for the Social Sciences software, ver. 20 (SPSS Inc., Chicago IL, USA). Data were presented as mean ± SD, numbers, and percentages. ANOVA followed by post-hoc tests were used for comparison of parametric data. Kruskal
Wallis test was used to compare non-parametric data while Mann-Whitney was used to compare between two groups. Chi-square test was used for comparison between percentages and frequencies. P < 0.05 was considered significant.

**Results**

There were no significant differences between groups in demographic data regarding age, weight, height, BMI and duration of surgery (p>0.05) (table1). There was no significant difference among groups regarding postoperative pulse rate and MBP (p>0.05) (Fig 1, 2). There was a significant increase in sedation score in group M+K compared to group M started from 0 line till 6 hours postoperatively with no significant differences in sedation score between group K and group M+K (p> 0.05) (Fig3). There was a significant reduction in mean VAS score in group M+K compared to group K starting 2 hours till 24 hours postoperatively and in group M compared to group K at 12 and 18 hours postoperative (Fig 4). The time to first request of rescue analgesia was significantly prolonged in group M+K (12.00 ± 2.29 hr) and group M (11.94 ± 1.46 hr) compared to group K (6.42 ± 1.43) (p<0.001) (table2). The mean total consumption of PCA morphine in PACU was significantly decreased in group M+K (6.00 ± 2.10 mg) compared to groups M and K (9.23 ± 3.50 mg, and 12.67 ± 3.49 mg respectively) in the first 24 hours postoperatively (p<0.04) (table 2). Five patients (16.6 %) only requested rescue analgesia in group M+K, while in groups M, and K 14 (46.6%) and 22 (73.3%) patients needed rescue analgesia respectively (table 2). There was significantly higher sedation (p<0.01) in groups K and M+K compared to group M. A part from sedation there was no significant difference in the incidence of other side effects between the three studied groups (Fig 5).

**Discussion:**

In this study, adding intrathecal ketamine 0.1 mg/kg to intrathecal morphine 0.3 mg had the advantage of reducing the total postoperative morphine consumption in comparison to using either drug alone. The three study groups had an overall good
analgesia with the use of postoperative PCA morphine. Sedation scores were higher in the combination group and in intrathecal ketamine group than in morphine group.

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptors. It is used for premedication, sedation, induction, and maintenance of general anesthesia. Central, regional, and local anesthetic and analgesic properties have been reported for ketamine \(^{(17)}\).

Other possible peripheral mechanisms of action of ketamine include binding to multiple opioid receptors (ORs) \(^{(18)}\); binding to monoamine transporters \(^{(19)}\); binding to muscarinic and nicotinic cholinergic receptors and inhibition of function \(^{(20)}\); binding to D2 and 5-HT2 receptors \(^{(21)}\); inhibition of ion channels (Na\(^{+}\), Ca\(^{2+}\), K\(^{+}\)) \(^{(22, 23)}\); decreased activation and migration of microglia \(^{(23)}\); and finally, inhibition of production of inflammatory mediators \(^{(24)}\).

Despite extensive discourses, there is still controversy in the literature as to the safety and analgesic efficacy of ketamine through the intrathecal route \(^{(4-6, 8, 9)}\). When intrathecal ketamine has been evaluated as a sole anaesthetic agent \(^{(25, 26)}\), its psychomimetic disturbances and inadequate analgesia precluded its use for this purpose.

Intrathecal ketamine has been studied extensively in animals. Borgbjerg and Svenssson \(^{(6)}\) administered preservative-free ketamine 5 mg intrathecally to rabbits for a period of 14 days and concluded that it has no harmful neurotoxic effects, even after repeated injections. On the contrary, Vranken et al. \(^{(8)}\) found that repeated administration of preservative - free S(+)-Ketamine for 7 days resulted in histopathologic spinal cord changes. However, they argued that with the finding that there was no significant difference in neurologic status between the two groups after 7 days of intrathecal treatment, and that not all animals given intrathecal preservative - free S(+)-Ketamine developed neurologic deterioration despite histologic evidence of neurotoxicity. They also postulated that the spinal cord of rabbits may be more sensitive than that of humans. In our opinion, it is the dose of intrathecal ketamine used and the repetition of exposure to ketamine that might play the major role in the resulting neurotoxicity.
changes, as the authors used a dose of 0.7 mg/kg of ketamine given daily for successive 7 days.

Data from the above, and similar studies had led to the concept that multiple factors, like preservatives (chlorobutanol and benzethonium chloride), the use of multiple drugs for a long period, and the use of intrathecal catheters may be responsible, in part, for neurological complications (4-6, 8), in addition to the doses and concentrations used. By contrast, Yu et al. (9) reported that ketamine provided potent protective effects against the ischemic reperfusion in spinal cord injuries.

Khezri et al. (27) have reported that using ketamine intrathecally at a concentration of 0.1 mg/kg could be a proper alternative to achieve postoperative analgesia, as it resulted in no side effects.

A major mechanism of spinal opioids analgesia is inhibition of transmitter release from C-fiber primary afferent terminals. The pre-synaptic action of opioids along with the post-synaptic location of NMDA receptors is the rationale for combination of these two drugs. The ketamine interacts as agonist with opiate receptors (28, 29) by producing synergistic effect; to achieve the desired level of post-operative analgesia, with concomitant reduction of side effects. This was the rationale for choosing morphine and ketamine in this study.

Sandler et al. (30) suggested that epidural ketamine may have an additive effect on opioids and local anesthetics. Long after that, this was studied by Arati and colleagues, and they concluded that combining ketamine with morphine epidurally provided a synergistic effect with good analgesia and facilitated early mobilization. The side effects like nausea, vomiting and sedation were minimal in the group comprising of morphine 0.3 mg/kg with ketamine 0.25mg/kg (31).

Combining intrathecal morphine with other drugs might not give similar results, Abdel-Ghaffar et al. (32), studied the combination of 0.5 mg morphine and 5 µg dexmedetomidine and their results didn’t support improved analgesia despite the absence of significant adverse effects.
The selection of intrathecal ketamine dose of 0.1 mg/kg was based on the fact that several previous studies showed that the use of such dose could prolong the duration of analgesia without additional side effects\(^{(33-35)}\).

In our study, VAS scores in the three groups were kept within a narrow range. Thus, we can say that the three groups had an overall equal analgesia but on the expense of the total amount of rescue PCA morphine.

Our findings support the hypothesis of improved analgesia, when giving these two drugs intrathecally in combination. But, we think that further work on this specific drug combination is needed with trying different doses of both drugs, in different surgical situations, and, of course, with larger sample size if possible to reach optimal analgesia with the least possible untoward effects.

In conclusion, adding intrathecal ketamine 0.1 mg/kg to morphine 0.3 mg in patients underwent major abdominal cancer surgery reduced the total postoperative morphine consumption in comparison to either drug alone, with an overall good postoperative analgesia in all groups, with no side effects apart from sedation.

References:


4- Malinovsky JM, Lepage JY. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? Anesthesiology 1993; 78: 109e15.


16- Bakr MA, Amr SA, Mohamed SA, Hamed HB, Abd El-Rahman AM, Mostafa MA, et al. Comparison Between the Effects of Intravenous Morphine, Tramadol,


21-Kapur S, Seeman P. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D (2) and serotonin 5-HT (2) receptors-implications for models of schizophrenia. Mol Psychiatry 2002; 7:837-44.


27-Khezri MB, Tahaei E, Atlasbaf AH. COMPARISON OF POSTOPERATIVE 
ANALGESIC EFFECT OF INTRATHECAL KETAMINE AND FENTANYL 
ADDED TO BUPIVACAINE IN PATIENTS UNDERGOING CESAREAN 
SECTION: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY. 
28-Kehlet H, Dahl JB. The value of multimodal or balanced analgesia in 
29-Smith DJ, Westfall DP, Adams JD. Ketamine interacts with opiate receptor as 
30-Sandler AN, Schmid R and Katz J. Epidural ketamine for postoperative 
31-Arati S, Ashutosh N, Kirti B. Efficacy of epidural morphine versus morphine 
with two different doses of ketamine in postoperative analgesia in abdominal 
32-Abdel-Ghaffar HS, Mohamed SA, Fares KM. Combined Intrathecal Morphine 
and Dexmedetomidine for Postoperative Analgesia in Patients Undergoing 
ahead of print].
33-Shrestha SN, Bhattarai B, Shah R: Comparative study of hyperbaric bupivacaine 
plus ketamine vs bupivacaine plus fentanyl for spinal anaesthesia during 
34-Murali Krishna T, Panda NB, Batra YK, Rajeev S: Combination of low doses of 
intrathecal ketamine and midazolam with bupivacaine improves postoperative 
35-Yanli Y, Eren A: The effect of extradural ketamine on onsettime and sensory 
Table (1): Demographic data in different groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Group “M” (n = 30)</th>
<th>Group”K” (n = 30)</th>
<th>Group”M+K” (n = 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Age</td>
<td>41.50±3.90</td>
<td>41.23±4.12</td>
<td>41.70±3.80</td>
<td>P=0.903 n.s</td>
</tr>
<tr>
<td>2- Weight</td>
<td>69.73±8.48</td>
<td>69.43±8.58</td>
<td>70.10±8.33</td>
<td>P=0.954 n.s</td>
</tr>
<tr>
<td>3- Height</td>
<td>163.03±11.85</td>
<td>162.20±12.04</td>
<td>162.83±11.35</td>
<td>P=0.960 n.s</td>
</tr>
<tr>
<td>4- BMI</td>
<td>26.93±7.95</td>
<td>27.28±9.83</td>
<td>27.04±7.30</td>
<td>P=0.987 n.s</td>
</tr>
<tr>
<td>5- Duration of</td>
<td>2.68±0.30</td>
<td>3.67±1.01</td>
<td>2.71±0.33</td>
<td>P=0.483 n.s</td>
</tr>
</tbody>
</table>
Table (2): Time to first request of rescue analgesia, total morphine consumption in different groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Group “M”</th>
<th>Group ”K”</th>
<th>Group ”M+K”</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first request (hrs)</td>
<td>11.94±1.46</td>
<td>6.42±1.43</td>
<td>12.00±2.29</td>
<td>P&lt;0.001**</td>
</tr>
<tr>
<td>No. of patients requested</td>
<td>14 (46.6%)</td>
<td>22 (73.3%)</td>
<td>5 (16.6%)</td>
<td>------</td>
</tr>
<tr>
<td>rescue analgesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total morphine dose (mg)</td>
<td>9.23±3.50</td>
<td>12.67±3.49</td>
<td>6.00±2.10</td>
<td>P&lt;0.04*</td>
</tr>
<tr>
<td>Range of total morphine dose (mg)</td>
<td>7-13</td>
<td>9-16</td>
<td>6-9</td>
<td>------</td>
</tr>
</tbody>
</table>
Figure (1): HR in different groups.
Figure (2): MBP in different groups
Figure (3): Sedation Score in different groups
Figure (4): VAS score in different groups.
Figure (5): side effects in different groups.
Dear editor,

It is a pleasure to write to you our response to the reviewer comments. We agree to almost all of them and we find most of them a necessity to improve the quality of our work. Here is our detailed response:

**Reviewer # 1:**

Many thanks to you for your valuable comments, inquiries, and suggestions. We find them very useful in order to improve the level of our work and present it to readers in a better and clearer form.

a) **Study power:** the primary outcome is opioid consumption. I do not see any previous reference on previous opioid consumption beside assumption of a SD of 1? I am not sure that this is sufficient. I think this study is potentially underpowered for the primary outcome.

**Response:** Our sample size calculations were based on data from previous work on regional techniques. We included in the revision a reference at the statistical analysis section in the manuscript for a recent study that used similar primary end point for detection of a difference of 1 SD in the mean of total amount of opioid consumption between the groups, and we modified the text into a clearer form and highlighted it. In addition, other references using total amount of postoperative morphine consumption as a primary endpoint were stated in the discussion section (the last two references).

b) **Pain score analysis.** At 6 hours – VAS score range was 1.3-1.7 with not much change till 24 hours postoperatively. I cannot really tell from this chart whether patient in any group had a significantly better analgesia. I can deduce that all of the three groups had equally good analgesia. I would suggest that to be reflected in discussion. Furthermore I do not believe that such low pain scores have sufficient resolution to detect clinically meaningful differences.

**Response:** This is true, most of the patients at the study had an overall good-analgesia, this actually one of our ethical concerns, but the important issue is the amount of rescue analgesia used to achieve this good analgesia. The first request of
rescue analgesia was at 6 hours postoperative, where patients at this group started to receive PCA morphine repeatedly according to their VAS scores. Thus, from this time point there was no large difference in the VAS between the three study groups; other groups had their first request for rescue analgesia at approximately 12 hours postoperative. We reported this in the revision at the discussion section to add our point of view and explain these findings and we highlighted the text added.

c) The first dose request is not different between M and M+K group [11.94 vs 12 hours]. This should be stated clearly in the discussion. Furthermore it is likely that the difference in opioid consumption could be the fact that patients had more time to use the PCA [less sedated in M than the M+K group]. If you consider the dose of the rescue bolus 0.1 mg /kg and the average weight of ~ 70 kg [7mg morphine bolus], it appears that the M+K group barely used the PCA on demand during the first 24 hrs.

Response: We clarified that in the discussion as you suggested. In order to answer the second part of your question, we added to table 2 the number of patients that requested rescue analgesia, and the range of total morphine dose used. Actually, we now think that adding this to the results section should have been done from the start as it provides the reader with important information that make our findings and, hence, our conclusion reasonable.

Looking to this added information, we find that only five patients asked for rescue analgesia in group (M+K). Moreover, the five patients received initial bolus of 0.1 mg/kg morphine, but only one patient needed further dose of morphine (1 mg) in the remaining 24 hours of the follow up period. We added that to the results section and commented upon it in the discussion, and all new text was highlighted.

We changed the conclusion text into a more informative, clear and representative form, and highlighted it.

Minor editorial:

There are many instances thought the manuscript that space needs to be inserted between words. I have noted only a few of them.

Page 4, line 12: “safetyand”: needs space
Page 5, line 12: “wasgiventhe”: separate – spaces
Page 5, line 19: “setting”: correct – sitting position

Page 7, line 54: “pre-synaptic action” needs space-separate

Page 8, line 5: “concomitant reduction”; needs space -separate

Response: Suggested corrections are made, and the whole manuscript was reviewed for similar mistakes, and we highlighted the corrected words.

Reviewer # 2:
Excellent work. I would ask to spend more time discussing literature surrounding the administration of intrathecal ketamine, with discussion of dose or concentration limits, despite safety data in animals. Also grammatical errors are scattered through the manuscript, so please provide a careful proof read.

Response: Thank you very much for your comments and remarks, we wish to have fulfilled your suggested changes.
We expanded the part of the discussion commenting on intrathecal ketamine use regarding dose, concentrations, and safety and highlighted the new text.
Manuscript was reviewed for grammatical errors, and it was corrected.