ORIGINAL RESEARCH   **REGIONAL ANESTHESIA**

Comparison of analgesic efficacy and safety of bupivacaine plus ketamine versus bupivacaine alone in rectus sheath block for midline laparotomy

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ABSTRACT

Background & Objective: Addition of ketamine affects pain modulation through multiple mechanisms and may enhance the analgesic effect of local anesthetics in rectus sheath block (RSB). However, limited studies have evaluated the analgesic efficacy and safety of ketamine added to RSB for midline laparotomy. We aimed to evaluate the analgesic efficacy and safety of ketamine as an adjuvant to 0.25% bupivacaine in ultrasound-guided RSB following major abdominal or gynecological surgery with midline incision.

Methodology: Fifty-four patients of American Society of Anesthesiologists class I–II, aged 18–65 y, who underwent midline laparotomy under general anesthesia were studied. The patients were randomly allocated to two groups: ultrasound-guided RSB was performed in the control group (n = 28) with 40 ml of 0.25% bupivacaine, while in the ketamine group (n = 28) it was performed with 40 ml of 0.25% bupivacaine plus ketamine 1 mg/kg. Postoperatively, both groups received IV morphine patient-controlled analgesia. The Numeric Rating Scale (NRS) pain scores at rest and on movement were assessed at 0, 1, 12 and 24 h postoperatively. The total 24-h postoperative morphine consumption and psychomimetic side effects were recorded.

Results: The mean NRS pain score on movement was significantly lower in the ketamine group at most time points compared to the control group ($P < 0.05$). The ketamine group had a significantly reduced total 24 h postoperative morphine consumption (14.3 ± 6.55 mg) compared to the control group (21.86 ± 15.46 mg) ($P < 0.05$). No psychomimetic adverse effects were reported in both groups.

Conclusion: The addition of ketamine to bupivacaine in RSB resulted in effective postoperative analgesia by reducing postoperative pain scores on movement in patients who underwent midline laparotomy. Such combination also reduced postoperative morphine requirement without serious side effects.

Abbreviations: ERAS - Enhanced Recovery After Surgery; LA - Local anesthetics; NRS - Numeric Rating Scale; PAC - Patient-controlled analgesia; RSB - Rectus sheath block;

Key words: Ketamine; adjuvant; rectus sheath block; laparotomy

Citation: Hassan SK, Thang PY, Wan Shukeri WFWM, Ismet S. Comparison of analgesic efficacy and safety of bupivacaine plus ketamine versus bupivacaine alone in rectus sheath block for midline laparotomy. Anaesth. pain intensive care 2023;27(2):154–160.

1. INTRODUCTION

Postoperative pain remains a major challenge in the management of surgical and gynecological patients. Major surgeries requiring midline laparotomy incision are associated with severe pain, requiring treatment with strong opioids. A study in Malaysia showed that regardless of the current pain management practices, the majority of laparotomy patients still experienced moderate to severe pain in the first 24 h after surgery, which may delay postoperative mobilization and return to daily activities. A large proportion of these patients also reported severe pain that interfered with their activities in bed, and out of bed, as well as emotional disturbances.[1]

Effective multimodal analgesic strategies are crucial to aid these patients in recovery after surgery while reducing opioid-related side effects, such as sedation, respiratory depression, nausea, vomiting and ileus. Local anesthetics (LA) based techniques have gained popularity in the era of Enhanced Recovery After Surgery (ERAS) for their opioid-sparing effects. While epidural analgesia showed evidence of superior postoperative pain relief compared to systemic analgesia,[2] its use may be limited due to perioperative anticoagulant therapy and undesirable complications such as hypotension.

The rectus sheath block (RSB) is an appropriate technique in multimodal analgesic regimen to provide somatic pain relief after midline laparotomy. The anterior abdominal wall is innervated by anterior branches of the intercostal nerves (T6−T11), subcostal nerve (T12), and iliohypogastric/ ilioinguinal nerves (L1). These nerves travel in the neurovascular plane between the internal oblique and transversus abdominis muscles. The terminal anterior cutaneous branches then enter the rectus sheath at its lateral margin and run deep to the posterior surface of the rectus abdominis muscle to form a longitudinal rectus sheath plexus.[3,4] RSB aims to deposit the LA within the posterior rectus sheath bilaterally to provide somatic analgesia over the middle anterior abdominal wall structures superficial to the peritoneum, from the xiphoid process to symphysis pubis.[4] The advancement of the ultrasound-guided RSB technique enables direct visualization of anatomical landmarks, accurate needle placement, and observation of LA spread, which leads to higher block success rate, shorter onset time, and reduced complications.[4]

On the other hand, ketamine affects pain modulation through multiple mechanisms of action. It is a non-competitive N-methyl-d-aspartate (NMDA) receptor antagonist, which exerts an anti-hyperalgesic effect by decreasing central sensitization and reducing the wind-up phenomenon in the postoperative period.[5] Ketamine has been shown to exhibit LA-like effects by inhibiting neuronal ion channels.[6,7] It demonstrates immunomodulating and anti-proinflammatory properties due to its interaction with inflammatory cell recruitment, cytokine production, and inflammatory mediator regulation.[8–10] However, limited studies have evaluated the analgesic efficacy and safety of ketamine addition to RSB for patients undergoing major surgeries requiring midline laparotomy.

We aimed to evaluate the analgesic efficacy and safety of ketamine 1 mg/kg as an adjuvant to 0.25% bupivacaine in ultrasound-guided RSB following major abdominal or gynecological surgeries with midline incision. We hypothesized that the addition of ketamine to bupivacaine in RSB would provide more effective pain relief in these patients compared to bupivacaine alone and would, therefore, improve postoperative pain scores and reduce 24 h postoperative morphine consumption.

2. METHODOLOGY

2.1. Study design

This was a randomized controlled trial conducted at a university affiliated hospital in Malaysia over a one-year period from October 2020 to October 2021, and approved by institutional Human Research Ethics Committee (No. USM/JEPeM/20060342).

2.2. Study population

Adult patients, aged 18−65 y, American Society of Anesthesiologists (ASA) class I−II who were scheduled for elective or emergency midline laparotomy under general anesthesia (GA) were enrolled in this study after obtaining written informed consent. Patients with previous paramedian laparotomy, history of bleeding disorder, obstructive sleep apnea, pre-existing peripheral neuropathy or chronic pain, weight < 50 kg, relevant drug allergy, opioid dependence, those with psychiatric illnesses that would interfere with perception and assessment of pain, and those who refused or requested for other modes of analgesia, were excluded from the study. Patients were withdrawn from the study if the duration of surgery exceeded 4 h.

2.3. Randomization, allocation concealment and blinding

Patients were randomly assigned into two groups (28 patients each) using a computer-generated table.

Randomization and allocation concealment were done by an independent person who was not involved in the study. The randomization detail was kept in a sealed envelope, which was only revealed to a second assisting anesthetic resident. Both the primary investigator and patients were blinded to the group allocation to minimize the potential bias.

2.4. Study procedure

Preoperatively, the patients learnt how to rate pain intensity using the Numeric Rating Scale (NRS), scoring from 0−10 (where 0 = no pain and 10 = worst pain imaginable). Patients were educated on the correct usage of IV morphine patient-controlled analgesia (PCA).

On arrival to the operating room, standard monitoring was applied according to ASA guidelines, including electrocardiography, non-invasive blood pressure, pulse oximetry, and end-tidal carbon dioxide level. Induction of anesthesia was performed using fentanyl 2 μg/kg and propofol 2−4 mg/kg, followed by rocuronium 1 mg/kg to facilitate endotracheal intubation. Inj. dexamethasone 8 mg was given at induction for postoperative nausea and vomiting (PONV) prophylaxis.

An assistant then prepared the LA solution under aseptic technique. The control group received 20 ml of 0.25% bupivacaine, injected on each side of the rectus sheath plane under direct ultrasound visualization. The ketamine group were given ketamine hydrochloride 1 mg/kg plus 0.25% bupivacaine 20 ml solution injected over each side of rectus sheath plane under direct ultrasound visualization.

All blocks were performed in the operating room under aseptic technique after induction of anesthesia and before surgical incision by the primary investigator. The rectus muscle and two hyperechoic railway-like lines beneath it (posterior rectus sheath and fascia transversalis) were identified using a 5−12 MHz linear array ultrasound probe in transverse orientation at or immediately above the level of the umbilicus. A 20−22G insulated nerve block needle (Stimuplex® A) was introduced under direct ultrasound visualization using an in-plane technique and advanced to the desired position between the rectus muscle and posterior rectus sheath. After confirmation of needle tip position by hydro-location with 3−5 ml isotonic saline, 20 ml of prepared LA solution was injected to hydro-dissect the rectus muscle away from the posterior rectus sheath. The injection was then repeated on the contralateral rectus sheath. Any procedure-related complications (hematoma, puncture of vessels, puncture of intraperitoneal viscera, inadvertent intravascular injection of LA, and systemic LA toxicity) were recorded.

The surgeon performed the skin incision 10 min after RSB. GA was maintained by 0.8−1.2 minimum alveolar concentration of sevoflurane or desflurane in oxygen/air mixture and boluses of IV rocuronium. Intraoperatively, both groups received morphine 0.05−0.1 mg/kg and paracetamol 15 mg/kg (maximum 1 g) IV. Rescue analgesia, with boluses of fentanyl, was administered as required to keep arterial blood pressure within 20% of the baseline values. Inj. ondansetron 4 mg was given for PONV prophylaxis 30 min before the end of surgery.

After completion of the surgery, muscle paralysis was reversed using neostigmine 2.5 mg and glycopyrrolate 400 mcg. Patients were extubated and transferred to the post-anesthesia recovery area. Pain assessment was performed using the NRS pain score and morphine PCA was commenced. If the subject expressed a pain score of ≥ 4, an initial bolus of morphine 1 mg IV was administered, followed by 1 mg bolus with a lockout period of 5 min without any background infusion. All subjects were prescribed regular paracetamol 1g infusion 6 hourly and oral celecoxib 200 mg 12 hourly before transfer to the ward.

After extubation, patients were assessed at 0-min, 1 h, 12 h, and 24 h postoperatively by acute pain service nurses. The NRS pain scores at rest and on movement, as well as total morphine consumption over 24 h postoperatively were recorded. Any psychomimetic adverse effects related to ketamine, e.g., hallucinations, delirium, or unpleasant dreams) were documented. Other side effects, e.g. shivering, sedation and hypotension requiring vasopressors were noted.

2.5. Study outcomes

The primary outcome was the NRS pain score at rest and on movement at 0-min, 1 h, 12 h, and 24 h postoperatively (efficacy outcome). The secondary outcomes were total morphine consumption over 24 h postoperatively (efficacy outcome) and psychomimetic adverse effects related to ketamine (safety outcome).

2.6. Statistical analysis

We determined that we needed to study at least 42 patients (21 patients for each group) using repeated-measures ANOVA test, between factors, at α 0.05, power 0.8, and effect size 0.4 for the primary outcome, including a 20% potential drop-out rate. This sample size was calculated using G-power 3.1 program.

Data were analyzed using IBM SPSS Statistics version 25. Numerical variables are presented as means with standard deviations and are compared between the two study groups using independent t-test. The interactions

of the pain scores over time with movement status and treatment are assessed by repeated-measures analysis of variance (ANOVA) test. Categorical variables are presented as frequencies with percentages and are compared between the two study groups using Chi-squared test. P < 0.05 is deemed as statistically significant.

3. RESULTS

A total of 56 patients were screened for eligibility and were randomized into either the control group (*n* = 28) or the ketamine group (*n* = 28). Two patients were withdrawn from the study because the duration of surgery exceeded 4 h. Therefore, 54 patients, 27 from the control group and 27 from the ketamine group, were included in the final analysis. The baseline demographic and clinical data for the included patients are

presented in Table 1. The two groups were equivalent at baseline in terms of age, gender, baseline NRS pain score, primary operating team, and timing of surgery (elective or emergency).

The mean postoperative NRS pain score at rest over different time points between the groups

were compared in Table 2. It shows a statistically significant difference at 0 h postoperatively, with a lower NRS pain score at rest in the ketamine group compared to the control group (0.52 ± 1.26 vs 1.56 ± 2.09; P = 0.03). The mean postoperative NRS pain scores at rest between the two groups at 1-, 12-, 24-h were otherwise not statistically significant. Using repeated-measures ANOVA test, there was a significant interaction between the mean NRS pain score at rest and the

Table 1: Comparison of patient characteristics between groups

Parameter	Group D (n = 31)	Group C (n = 31)	P value
Age (years)	30.6 ± 6.9	30.1 ± 5.5	0.792
Weight (kg)	69.9 ± 11.2	73.2 ± 11.6	0.261
Height (cm)	155.8 ± 4.6	157.3 ± 5.2	0.203
BMI	28.8 ± 4.3	29.6 ± 4.7	0.475
Gravida	3.0 ± 2.2	2.9 ± 1.9	0.852
Para	1.7 ± 1.9	1.7 ± 1.6	0.774
Baseline temperature (°C)	36.76 ± 0.37	36.91 ± 0.25	0.070
Duration of operation (min)	49.1 ± 12.6	48.1 ± 16.0	0.799
Duration of drug infusion (min)	34.0 ± 10.1	33.0 ± 12.0	0.707
Baseline SBP (mmHg)	115.6 ± 13.8	111.1 ± 13.3	0.198
Baseline DBP (mmHg)	61.5 ± 8.7	60.2 ± 9.2	0.572
Baseline HR (/min)	90.1 ± 14.0	89.2 ± 13.0	0.794
ASA, n (%)			0.550**
I	12 (38.7)	16 (51.6)	
II	17 (54.8)	14 (45.2)	
III	2 (6.6)	1 (3.2)	

*Data presented as Mean ± SD; P value based on independent-samples t-test; **Pearson chi square*

Table 2: Comparative intraoperative shivering, sedation and need of vasopressors in two groups

Variables	Group D (n = 31)	Group C (n = 31)	P value
Shivering	1 (3.2)	20 (64.5)	< 0.001
Sedation	16 (51.6)	0	< 0.001
Use of vasopressors	4 (12.9%)	8 (25.8%)	0.199

*Data presented as n (%);**Pearson chi-square*

Table 3: Comparison of mean systolic blood pressure between two groups

	Group D (n = 31)	Group C (n = 31)	P value
T0	115.06 (110.41, 119.72)	111.06 (106.40, 115.72)	0.011[a]
T1	110.90 (105.89, 115.92)	111.35 (106.34, 116.37)	
T2	108.74 (104.09, 113.39)	114.39 (109.74, 119.04)	

Data presented as mean systolic BP in mmHg [Adjusted mean (95% CI)]; [a] Repeated Measure ANOVA

	Group D	Group C	P value[a]
T0	115.06 (12.63)	111.06 (13.30)	0.229 [b]
T1	110.90 (11.82)	111.35 (15.82)	0.899 [b]
T2	108.74 (12.38)	114.39 (13.47)	0.091 [b]

Data presented as mean systolic BP (SD); [b] Independent-samples t-test

Table 4: The mean systolic blood pressure differences of time within each group

Comparisons	Group D (n = 31)	P valuea	Group C (n = 31)	P valuea
T0 – T1	4.16 (0.11−8.21)	0.044	−0.29 (−4.94−4.36)	0.899
T0 – T2	6.32 (0.89−11.75)	0.024[b]	−3.32 (−7.76−1.12)	0.137
T1 – T2	2.16 (−1.46−5.78)	0.054	−3.03 (−7.83−1.76)	0.206

Data given as Mean score difference (95% CI); [a] Multiple paired t test; [b] No significant difference after Bonferroni correction

Table 5: Comparison of mean and 95% CI of diastolic blood pressure between groups

	Group D (n = 31)	Group C (n = 31)	F statisticsa (df)	P valuea
T0	61.45 (58.24−64.67)	60.16 (56.95−63.38)	0.174 (2−120)	0.840
T1	61.16 (58.12−64.20)	59.61 (56.58−62.65)		
T2	60.42 (57.58−63.26)	60.03 (57.19−62.87)		

Data given as adjusted mean (95% CI); [a] Repeated Measure ANOVA

two different treatment groups [F (2.35,114.89) = 4.34, P = 0.01], as shown in Table 3.

The mean postoperative NRS pain score on movement showed a statistically significant difference between the two groups at 0-, 1-, and 24-h postoperatively (P < 0.05), with lower NRS pain scores in the ketamine group (1.49 ± 1.7, 2.86 ± 1.52, 3.45 ± 0.9, respectively) compared to the control group (2.93 ± 2.62, 4 ± 2, 4.04 ± 0.71, respectively), as shown in Table 4. Using repeated-measures ANOVA test, there was no significant interaction between the mean NRS pain score on movement and two different treatment groups [F (2.35,114.89) = 2.16, P = 0.115].

Table 5 reveals a significant difference in the total morphine consumption 24 h postoperatively between the two groups. Patients who received RSB with ketamine adjuvant had a lower 24 h postoperative morphine requirement than the control group with bupivacaine alone (P = 0.023). There were no psychomimetic side effects reported in both groups.

4. DISCUSSION

In this randomized controlled trial, we demonstrated that RSB using 0.25% bupivacaine plus ketamine 1 mg/kg produced significantly lower postoperative pain scores

Table 6: Comparative mean heart rates between groups

Time	Group D (n = 31)	Group C (n = 31)	P value
Adjusted mean (95% CI)			
T0	90.10 (85.42−94.77)	88.71 (84.03−93.39)	< 0.001[a]
T1	81.16 (76.69−85.64)	90.35 (85.88−94.83)	
T2	81.00 (76.93−85.07)	90.52 (86.44−94.59)	
Mean score (SD)			
T0	90.10 (14.04)	88.71 (11.90)	0.676 [b]
T1	81.16 (12.74)	90.35 (12.16)	0.005 [b]
T2	81.00 (12.06)	90.52 (10.57)	0.002 [b]

Data presented as Beats/min; [a] Repeated Measure ANOVA; [b] Independent t-test

on movement at most time points postoperatively, in comparison to bupivacaine alone, in adult patients who underwent midline laparotomy surgery under general anesthesia. Patients in the ketamine group also required less morphine consumption in the postoperative period, compared to the control group. There were no ketamine-

Table 7: Comparative differences in mean heart rates of different times in each group

Comparisons	Group D (n = 31)	P valuea	Group C (n = 31)	P valuea
T0 – T1	8.94 (5.67−12.20)	< 0.001[b]	−1.65 (−4.2−0.95)	0.206
T0 – T2	9.10 (5.46−12.73)	< 0.001[b]	−1.81 (−4.59−0.98)	0.195
T1 – T2	0.16 (−2.57−2.89)	0.905	−0.16 (−2.95−2.63)	0.907

Data presented as Mean difference (95% CI) [a] Multiple paired t test; [b] Significant difference after Bonferroni correction

related psychomimetic side effects reported in both study groups.

Postoperative pain relief for midline laparotomy remains a challenge due to the vast innervation of the anterior abdominal wall by T6−T12 and L1 spinal nerves.[3] Recent studies have proven the safety and efficacy of ultrasound-guided RSB in the reduction of postoperative pain scores and opioid consumption in gynecological and abdominal midline surgeries.[11,12] RSB with a single injection of 0.25% bupivacaine 20 ml provides a sensory block over the midline of the anterior abdominal wall, lasting about 5 to 7 h.[4] Therefore, the addition of LA adjuvants, such as ketamine, should be considered to enhance analgesic efficacy and duration of RSB with a single injection. However, to our knowledge, current literature scarcely reveals any study describing the addition of ketamine to bupivacaine for RSB in midline laparotomy.

On the other hand, many studies have been done to explore the potential of ketamine as an LA adjuvant in different regional anesthetic techniques, with

inconsistent results. For example, Lashgarinia et al. conducted a study to assess whether coadministration of 2 mg/kg ketamine can prolong the LA effect of lidocaine in the ultrasound-guided supraclavicular brachial plexus block for patients undergoing elective upper extremity surgery. The results showed significantly lower pain scores at all time points during the first 24 h postoperatively in the ketamine group.[13] Correspondingly, our study showed the addition of ketamine to LA in RSB significantly lowered pain score on movement at most time points postoperatively, compared to LA alone. This is possibly due to NMDA receptor antagonism and enhancement of LA effect by sodium channel-blocking action of ketamine at the level of surgical trauma. However, the effect on resting pain score was not significant. We postulate that this may be due to effective somatic analgesia over the anterior abdominal wall by RSB, which reduces pain associated with movement and deep breathing.

Recently, Othman et al. found that the addition of ketamine 1 mg/kg to ultrasound-guided pectoralis nerve block with bupivacaine 0.25% prolonged the time to first request of analgesia and reduced 48 h postoperative morphine requirement in patients who underwent modified radical mastectomy. No significant side effects and psychological complications were reported.[14] This is in keeping with our findings, whereby 24 h postoperative morphine consumption was significantly less in patients receiving RSB with ketamine and bupivacaine compared to bupivacaine alone.

On the contrary, Omar et al. concluded that the addition of ketamine 0.5 mg/kg to bupivacaine 0.5% in a thoracic paravertebral block in radical mastectomy showed no enhancement of analgesic effect, but psychomimetic effects were reported in 19% of the studied subjects. They assumed that this may be related to high systemic uptake of ketamine from the site of injection which is vessel-rich.[15] In our study, there were no such side effects observed. We postulate that the incidence of side effects may be lower when ketamine is deposited in less vascularized rectus sheath compartment, hence lesser systemic absorption, as compared to more vascularized paravertebral space. The variable effects of ketamine in different clinical trials may be due to different concentrations used. Furthermore, it has been observed that the effect of ketamine is more likely to occur locally at the inflamed tissue, compared with normal tissue distant from the surgical site due to its immunomodulating and anti-proinflammatory properties.[8−10]

5. LIMITATIONS

One of the limitations of our study was the small sample size. Potential subjects were recruited over one-year period, during which the COVID-19 pandemic had affected our anesthetic services tremendously with the reduction of elective surgeries. In our center, we had limited PCA dispensers, which affected our capacity of patient recruitment per day. Our patient population was also heterogeneous, involving those who underwent different surgical and gynecological procedures that required midline incisions. The radicalness of the procedure and length of the midline incision were not standardized. We suggest that this drug combination in RSB can be further studied by including a larger sample size in a homogenous patient population, as well as using different dosages of ketamine and LA.

6. CONCLUSION

In conclusion, our findings suggest that addition of ketamine to bupivacaine in rectus sheath block resulted in effective postoperative analgesia by reducing postoperative pain scores on movement. The combination also reduced postoperative morphine requirement in patients who underwent midline laparotomy without ketamine-related psychomimetic side effects.

7. Data availability

8. Acknowledgement

9. Conflict of interest

Authors declare no conflict of interest.

10. Authors' contribution

WAAWMA: Concept, conduction of the study work

WMNWH: Concept, Interpretation of data for the work

PS: Drafting the work and revising it critically for important intellectual content, Manuscript Editing

SCO: Drafting the work and revising it critically for important intellectual content

NANM: Acquisition, analysis, or interpretation of data for the work, Manuscript Editing

11. REFERENCES

1. Subramanian P, Ramasamy S, Ng KH, Chinna K, Rosli R. Pain experience and satisfaction with postoperative pain control among surgical patients. Int J Nurs Pract. 2016 Jun;22(3):232−8. [PubMed] DOI: 10.1111/ijn.12363

2. Wu CL, Cohen SR, Richman JM, Rowlingson AJ, Courpas GE, Cheung K, et al. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a meta-analysis. Anesthesiology. 2005 Nov;103(5):1079−88; quiz 1109−10. [PubMed] DOI: 10.1097/00000542-200511000-00023

3. Chin KJ, McDonnell JG, Carvalho B, Sharkey A, Pawa A, Gadsden J. Essentials of Our Current Understanding: Abdominal Wall Blocks. Reg Anesth Pain Med. 2017 Mar/Apr;42(2):133−183. [PubMed] DOI: 10.1097/AAP.0000000000000545

4. Webster K. Ultrasound guided rectus sheath block - analgesia for abdominal surgery. Updat Anaesth. 2010;26:12–7. Available from: https://www.e-safe-anaesthesia.org/e_library/09/ultrasound_guided_rectus-sheath_block_update_2010.pdf

5. De Kock M, Lavand'homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? Pain. 2001 Jun;92(3):373−380. [PubMed] DOI: 10.1016/S0304-3959(01)00278-0

6. Schnoebel R, Wolff M, Peters SC, Bräu ME, Scholz A, Hempelmann G, et al. Ketamine impairs excitability in superficial dorsal horn neurones by blocking sodium and voltage-gated potassium currents. Br J Pharmacol. 2005 Nov;146(6):826−33. [PubMed] PMCID: PMC1751212 DOI: 10.1038/sj.bjp.0706385

7. Hayashi Y, Kawaji K, Sun L, Zhang X, Koyano K, Yokoyama T, et al. Microglial Ca (2+)-activated K(+) channels are possible molecular targets for the analgesic effects of S-ketamine on neuropathic pain. J Neurosci. 2011 Nov 30;31(48):17370−82. [PubMed] PMCID: PMC6623803 DOI: 10.1523/JNEUROSCI.4152-11.2011

8. Loix S, De Kock M, Henin P. The anti-inflammatory effects of ketamine: state of the art. Acta Anaesthesiol Belg. 2011;62(1):47−58. [PubMed]

9. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg. 2012 Oct;115(4):934−43. [PubMed] DOI:10.1213/ANE.0b013e3182662e30.

10. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. CNS Neurosci Ther. 2013 Jun;19(6):403−10. [PubMed] PMCID: PMC6493703 DOI: 10.1111/cns.12104

11. Marret E, Remy C, Bonnet F. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. Br J Surg. 2007 Jun;94(6):665−73. [PubMed] DOI: 10.1002/bjs.5825

12. Bakshi SG, Mapari A, Shylasree TS. REctus Sheath block for postoperative analgesia in gynecological ONcology Surgery (RESONS): a randomized-controlled trial. Can J Anaesth. 2016 Dec;63(12):1335−1344. English. [PubMed] DOI: 10.1007/s12630-016-0732-9

13. Lashgarinia M, Naghibi K, Honarmand A, Safavi M, Khazaei M. Effect of ketamine as an adjuvant in ultrasound-guided supraclavicular brachial plexus block: A double-blind randomized clinical trial study. Adv Biomed Res. 2014 Nov 29;3:232. [PubMed] PMCID: PMC4260270 DOI: 10.4103/2277-9175.145730

14. Othman AH, El-Rahman AM, El Sherif F. Efficacy and Safety of Ketamine Added to Local Anesthetic in Modified Pectoral Block for Management of Postoperative Pain in Patients Undergoing Modified Radical Mastectomy. Pain Physician. 2016 Sep-Oct;19(7):485−94. [PubMed] PMID: 27676665.

15. Omar AM, Mansour MA, Abdelwahab HH, Aboushanab OH. Role of ketamine and tramadol as adjuncts to bupivacaine 0.5% in paravertebral block for breast surgery: A randomized double-blind study, Egyptian Journal of Anaesthesia, 2011; 27:2, 101−105 DOI: 10.1016/j.egja.2011.04.002