EVALUATION OF POSTOPERATIVE ANALGESIC EFFICACY OF INTRAPERITONEAL KETAMINE PLUS BUPIVACAINE IN LAPAROSCOPIC SURGERY

Shailendra Nath Gautam, Anju Poudel, Ankit Agrawal, Jyoti Shah, Srijana Koju

Department of Anesthesia, Nepal Medical College Teaching Hospital, Attarkhel, Gokerneshwor-8, Kathmandu, Nepal

ABSTRACT

Laparoscopic surgery is considered as the gold standard for minimally invasive procedures for abdominal and pelvic surgeries and thought to be less painful compared to open surgeries. Local anesthetic instillation alone addresses parietal pain relief; therefore, the use of adjuvants has been investigated to augment pain relief. To evaluate the change in hemodynamic parameters and analgesic effect of intraperitoneal ketamine plus bupivacaine in patients undergoing laparoscopic general and gynecological surgery, to evaluate pain by using Visual Analog Scale (VAS), time for first rescue analgesia demand, total analgesic consumption in first postoperative day and any drug-related complications during the postoperative period. Fifty seven patients scheduled for laparoscopic general or gynecological surgery were randomly assigned to receive intraperitoneal ketamine 0.5mg/kg plus bupivacaine (0.5% 15ml) diluted in 15 ml of normal saline to make 0.25% bupivacaine. This solution was installed intraperitoneal and infiltrated at incision site at the end of surgery. Then the patients were tilted according to surgeries; Trendelenburg's position to target the hepatodiaphragmatic space in the gall bladder bed and reverse Trendelenburg's position in gynecological surgery to target the pelvic floor. The patients received intraperitoneal ketamine plus bupivacaine reported lower pain scores throughout the postoperative period with VAS scores observed lower on arrival in the postoperative ward, with less demand of supplemental rescue analgesia. No postoperative complications were observed. Intraperitoneal instillation of ketamine plus bupivacaine at the end of laparoscopic surgery was an effective and safe method for pain relief during the postoperative period with less demand for supplemental systemic analgesia, high patient satisfaction and no complications.

KEYWORDS

Intraperitoneal, ketamine, bupivacaine, postoperative pain, laparoscopies surgeries

***Received on**: September 22, 2024*
***Accepted for publication**: November 28, 2024*

CORRESPONDING AUTHOR

Dr. Shailendra Nath Gautam
Associate Professor,
Department of Anesthesia,
Nepal Medical College Teaching Hospital,
Attarkhel, Gokarneshwor-8, Kathmandu, Nepal
Email: shailendragautam@hotmail.com
Orcid No: https://orcid.org/0009-0007-8460-4504
DOI: https://doi.org/10.3126/nmcj.v26i4.74469

INTRODUCTION

Laparoscopic surgery (LS) is considered as gold standard for minimally invasive surgeries and result in less pain compared to open surgery. Although patients may experience visceral, incision site or shoulder tip pain, pain remains a significant factor for delayed hospital discharge.[1] Pain caused by LS draw attention of anesthesiologists for effective pain management using various analgesics with different mechanisms of action that have been suggested as multimodal regimen. The aim of different approaches were to reduce opioid consumption and minimize complications,[2] for which various pharmacological agents that act on different receptor sites have been used including local anesthetics, nonsteroidal anti inflammatory drugs (NSAIDs), opioids, anticonvulsants, alpha-2-adrenergic agonists, N-methyl-D-aspartate (NMDA) receptor antagonists[3] and transversus abdominal plan block among other modalities as a multimodal approach to eliminate nausea, vomiting caused by opioids and to reduce hospital stay.[4,5] Among these approaches, the intra abdominal local anesthetics has been practiced for pain management during LS but local anesthetic alone fails to control pain effectively, therefore, adjuvants plus local anesthetics has been recommended, as a simple and useful approach to control pain. Furthermore, the addition of intra abdominal ketamine is more effective to control pain compared to bupivacaine alone.[6,7] Additionally, combination of newer adjuvants has been explored to enhance pain relief but necessitates to consider the cost of drugs, especially in developing and underdeveloped countries to ensure effective pain management.

In this sense, Ketamine is a widely accepted drug due to its affordability and potent analgesic properties, and can be administered through various routes to act on both peripheral (peritoneal), and central receptors. In the periphery (peritoneal) ketamine acts as antagonist on NMDA receptors and opioid receptors producing hypnotic and analgesic effects to reduced analgesic requirement.[8-12.] Ketamine easily crosses tissue membranes for rapid absorption with short duration of onset, and act as immunomodulator as well as anti inflammatory without affecting the local action and prevent central sensitization of nociceptors at subanesthetic doses.[8] In this context, intraperitoneal ketamine plus bupivacaine serves as an alternate analgesic method for pain management and optimizes inflammation to restore homeostasis.[13] Some studies show that intraperitoneal bupivacaine alone effectively reduced visceral, parietal or referred shoulder pain, reduced analgesic requirements and antiemetic effect in some extent,[14-16] while other studies demonstrated that bupivacaine at 7.5 mg and 5.0 mg reduced postoperative visceral and shoulder pain with decreasing analgesic consumption lasting for 4 to 8 hours.[3,17-21]

A research postulated that preincisional subcutaneous infiltration of ketamine decreased Visual Analogue Scale (VAS) scores with increase in duration of analgesia hence decreasing the total analgesic consumption.[12] Borner and colleagues[22] administered intra articular (peripheral) S (+) ketamine to reduce the need for postoperative analgesia. Similarly, Goma and Elhamid[11] compared effectiveness of intraperitoneal ketamine with lidocaine to reduce the analgesic requirement.

Raouf and colleagues 2004[23] stated that intraperitoneal co administration of ketamine 1 mg/kg plus bupivacaine 0.25% was superior analgesic compared to 0.25% bupivacaine alone. Another study by RH Mostafa and colleagues[24] demonstrated that the intraperitoneal ketamine plus bupivacaine significantly reduced postoperative shoulder tip pain and VAS scores in first 24 hours. Shawky's[20] demonstrated that intraperitoneal ketamine 0.5 mg/kg effectively controlled pain without adverse effects. Overall, different studies have highlighted the potential benefits of intraperitoneal ketamine plus bupivacaine to manage postoperative pain without underscore VAS and overuse of opioids to achieve early emergence.[25]

In our study, we have selected bupivacaine due to its prolong duration of action, with a half life of 5 to 16 hours and ketamine as adjuvant to enhance analgesic effects, to reduce hospital stay, decrease morbidity and costs.

MATERIALS AND METHODS

This was a hospital based observational study conducted at Nepal Medical College Teaching Hospital, Kathmandu from February 2024 to July 2024, after obtaining ethical approval from the Institutional Review Committee (Ref no: 51-080/081). Total 57 participants of age 16-65 years of either sex were randomly selected by pickup number to determine eligibility with the American Society of Anesthesiology (ASA) I-II physical status. The exclusion criteria were patients with cardiovascular, pulmonary, psychological, and neurological diseases, obesity (body mass index >35 kg/m^2), coagulation disorders, hypertension, patient`s

refusal to participate in the study and any other comorbidities. The patients were enrolled after a preanesthetic checkup and admitted to the respective department. All eligible patients were trained to use VAS scores during a preanesthetic checkup and written informed consent was obtained.

Routine monitoring including electrocardiography (ECG), noninvasive blood pressure (NIBP), pulse oximetry (SPO_2) and capnography ($ETCO_2$) were attached before induction of anesthesia. The induction of general anesthesia was started after preoxygenation with 100% oxygen for 3 minutes, by the administration of fentanyl 2 µg/kg, midazolam 50µg/kg, propofol 2 mg/kg and rocuronium 0.6 mg/kg for orotracheal intubation. Anesthesia was maintained with isoflurane and oxygen admixture, with intermittent doses of rocuronium for muscle relaxation. Minute ventilation was adjusted to maintain normocapnia with $ETCO_2$ levels between 34 and 40 mmHg.

Patients were positioned in 15-20° Trendelenberg's position or reverse Trendelenberg's position with left side tilt or head down position depending on the type of surgery. Intra-abdominal pressure was maintained at 11-15 mmHg during pneumoperitoneum. At the end of the procedure, CO_2 was removed manually by compressing the abdomen with trocar in situ and the patient received intraperitoneal ketamine 0.5 mg/kg with bupivacaine (0.5%15 ml) diluted in 15 ml of normal saline to achieve 0.25% concentration of bupivacaine before the trocar was removed, and infiltration of incisional site with same drug, then the patient was tilted in Trendelenburg's position to target the hepatodiaphragmatic space in the gall bladder bed and reverse Trendelenburg's position in gynecological surgery to target the pelvic floor with continuous monitoring the patient during and at the end of surgery. Subsequently, the neuromuscular blockade was reversed using neostigmine 40µg/kg and glycopyrrolate 10µg/kg. Following the reversal, the patient was extubated and applied 100% oxygen to facilitate recovery. Once patient regained consciousness, patient was transferred to a post-operative ward.

In the postoperative ward, pain assessment was done by an impartial investigator, and data were collected including the level of pain, using a VAS ranging from 0 to 10. A score 0 indicated no pain and score 10 represented the worst pain, assessed at 1, 4, 6, 12 and 24-hour intervals. Additionally, hemodynamic change, time interval to demand for first rescue analgesia, total amount of analgesia administered in the first 24 hours, and any complications during the postoperative period was evaluated. Patients reported VAS scores greater than 3, were received intravenous ketorolac 30 mg and paracetamol 1gm as rescue analgesia, and postoperative nausea and vomiting was dealt with ondansetron 4 mg. The statistical analysis was done by comparing data utilizing the student 't' test. The results were presented as mean ± standard deviation, along with the number and percentage (%) and a P value of 0.05 or less was considered statistically significant.

RESULTS

Among 57 patients, 11 male (19.30%) and 46 (80.70%) female patients, aged 16 to 65 years with a mean age of 44.81±14.52, were eligible and entered the study. None of the patients were excluded from the study. The demographic data illustrating the age, sex, ASA physical status, and mean time of surgery were collected and analyzed (Table 1).

Table 1: Demographic parameters

Variables	Ketamine with bupivacaine
Age in year (Mean S.D)	44.81±14.52
Sex M:F	11/46
ASA I/II PS	39/18
Surgical time min (Mean SD)	90.92±33.09

The change in hemodynamic parameters including heart rate, systolic, and diastolic blood pressure were collected, the mean baseline HR was 80±9.04 beats per minute, and preinduction HR was 76±9.59. The change in mean baseline HR and preinduction HR was insignificant (p >0.05). The mean baseline HR was 80±9.04 and postinduction at 60 minutes was 74±11.93, which was statistically insignificantly (p >0.05). The oxygen saturation change (SPO_2) during baseline and preinduction value was insignificant (p >0.05) (Table 2).

During postoperative pain assessment (Table 3), the VAS was less on arrival at postoperative ward (1.81±1.10), with no pain, and at 1 hours VAS was (2.49±1.18), at 6 hours VAS was 3.22±0.94 with mild to moderate pain, the difference at 1 hour and 6 hours was statistically insignificant (p >0.132). At 12-24 hours VAS was (3.03±0.99 and 2.70±0.96) indicating statistically insignificant

Table 2: Vital parameters

Parameters	Heart rate Mean±SD	Systolic BP Mean±SD	Diastolic BP Mean± SD	SPO_2 Mean±SD
Baseline	80±9.04	122.98±9.96	78.98±8.03	99±7.96
Preinduction	76±9.59	128±12.77	80±9.42	98±1.30
Post induction				
5 mins	75±10.40	130±13.53	82.78±8.7	100±1.06
15 mins	74±11.51	126±18.95	81±9.72	100±4.24
30 mins	78±13.58	117±14.12	76±11.00	100±0.38
45 mins	74±12.07	127±12.76	81±9.81	100±132.48
60 mins	74±11.93	120±18.57	80±16.34	100±0.59

Table 3: VAS (Visual analogue scale)

Time (minute)	VAS (mean±SD)	P value (paired t- test)
On arrival at post op	1.81±1.10	
60 mins	2.49±1.18	00.132
6 hrs	3.22±0.94	
12 hrs	3.03±0.99	P>0.111
24 hrs	2.70±0.96	

Table 4: Total number of analgesic

No. of analgesic	No. of patients	%
0	5	8.6
1	17	29.3
2	19	32.8
3	13	22.4
4	3	5.2

P>0.111, and VAS at 24 hours was 2.70±0.96 indicates that the pain gradually subsides.

The postoperative complications such as nausea, vomiting, bradycardia, hypertension, and hypotension were analyzed and showed no such incidences.

The mean time of surgery was 90.92±33.09 minutes with minimum 60 minutes to maximum 265 minutes. The mean time of first rescue analgesia demanded was 7.52±6.0 hours with minimum 2 hours to maximum 24 hours with better and prolonged pain relief, and total number of analgesia required was 1.85±1.04 with minimum 0 to maximum 4 doses.

During our research, we observed that out of 57 patients, five patients did not request any analgesic with better and longer pain relief lasting up to 24 hours, 17 patients demand a single dose of analgesic, while 19 patients required a combination of ketorolac and paracetamol intravenously. Additionally, 13 patients needed three analgesics, and three patients required combination of four analgesics. Notably, we were able to achieve effective pain control without the use of opioids in postoperative ward.

DISCUSSION

Postoperative pain after LS consists of three components, visceral, parietal, and referred shoulder pain.[2] However; LS has less postoperative pain and reduced analgesic requirement as compared to open surgeries. Different modalities of regimen and technique have been practiced to control pain during the postoperative period. Currently, the standard management for acute post-operative pain is the use of systemic opioids. Unfortunately, opioids are not free from side effects and cause drowsiness, nausea, vomiting, ileus, urinary retention, and pruritus, which may cause longer hospital stay and poor patient outcomes.[9,12] Ketamine used through parenteral routes is known to cause systemic effects such as tachycardia, hypertension, increased intraocular pressure, and hallucination.[26] Local infiltration of ketamine in surgical site effectively reduces postoperative opioid consumption with reduced systemic adverse effects. Thus, instillation of ketamine plus local anesthetics decreases visceral pain, and subscapular referred pain.[27]

Few previous studies have shown the effectiveness of intraperitoneal local anesthetics alone. However, other investigators were unable to show the beneficial analgesic effect of local anesthesia alone in pain management. In this study, ketamine was used as an adjuvant to enhance the analgesic effect as it acts on NMDA receptors antagonism (inhibition), as

well as acts on opioid, nicotinic, muscarinic receptors and has anti inflammatory properties to contribute its efficacy in pain relief.[28,29]

Patient comfort is reflected in vital parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation (SPO_2). An increase in these values indicates a high VAS score. In our study, while comparing the mean HR during preinduction and postinduction, we found a nosignificant change in HR between the preinduction period and at 60 minutes postintubation (p >0.05). However, the difference in SBP and DBP at preinduction and 60 minutes postintubation was insignificant (p>0.05). This finding was consistent with a study by Mostafa and Mekki in 2019[26] which also reported no significant hemodynamic changes.

Specifically, our study found that the mean preinduction HR was 76±9.59 beats per minute, SBP was 128±12.77 mmHg, and DBP was 80±9.42 mmHg, and postinduction at 60 minutes, the HR was 74±11.93 beats per minute, SBP was 120±18.57 mmHg, and DBP was 80±16.34 mmHg. These values remained within normal physiological limits, indicating that the combination of ketamine and bupivacaine effectively controlled pain without causing hypertension, hypotension, or bradycardia. This was consistent with a study done by Kapoor and Dua in 2023[30] even though, they used ropivacaine and ketamine. Furthermore, Goma and Elhamid[11] found that acute hemodynamic changes, such as increased in blood pressure and heart rate, occur during the pneumoperitoneum period in laparoscopic surgery. However, in our study, hemodynamic parameters remained stable during pneumoperitoneum, likely due to effective pain control with the analgesics.

The article published by Mraovic and Jurisic 1997[25] showed that the intensity of postoperative pain at the first hour was maximum, requiring systemic opioids. Whereas, our study showed that intraperitoneal ketamine plus bupivacaine was sufficient to control postoperative pain, and systemic requirement of analgesic was less at 1, 6, 12, and 24 hours with lower mean VAS score 2.49±1.18, 3.22±0.94, 3.03±0.99, 2.70±0.96 respectively. Similarly, the study done by Maryam and colleague 2022[29] stated that the intraperitoneal ketamine plus bupivacaine has longer duration of pain relief and less systemic analgesic requirement and effective pain control modality rather than using systemic opioids in postoperative period. In our study, we did not have to use opioid as rescue analgesic. Regarding needs for postoperative supplemental analgesia, patients with intraperitoneal ketamine plus bupivacaine required less systemic analgesia within first 24 hours. The number of postoperative supplemental analgesia given was shown in Table 4. Most patients asked for postoperative supplemental analgesia at first 6-12 hours with VAS 3.22±0.94 and 3.03±0.99.

The study conducted by Kamali and colleague 2019[31] to compare and control postoperative pain by intraperitoneal ketamine, dexmedetomidine, and bupivacaine alone, and showed that ketamine was more effective than dexmedetomidine and bupivacaine alone which was comparable with our study. The results of our study were similar with report published by Goma and Abd Elhamid 2015[11] Another study stated that peripheral (peritoneal) S (+) ketamine block NMDA receptors to reduced postoperative pain and analgesic requirement.[25] On other studied by Moharari *et al*[9] reported that intraperitoneal 0.5 mg/kg ketamine in LS significantly reduces the postoperative pain and the analgesic requirement.

In our study, the mean time for first rescue analgesia in the postoperative ward was 7.52±6.0 hours. This was managed by using non steroidal anti inflammatory (NSAID) drugs for the effective and prolonged pain relief without opioids requirement. Additionally, none of the patients in the study reported experiencing nausea or vomiting. These findings suggest that NSAID drugs may offer a promising alternative for pain management following surgery. Whereas in a study conducted by Oza *et al* 2019[28] reported 62.85% of patients experienced nausea and vomiting as a side effect when using intraperitoneal ropivacaine in combination with ketamine. The results of our study demonstrate that intraperitoneal ketamine plus bupivacaine could be a better alternate and effective approach to control postoperative pain in laparoscopic surgeries without complications.

Conclusion: The present study concluded that intraperitoneal ketamine plus bupivacaine at the end of LS is effective and safe alternate for reducing postoperative opioid use with better pain management, decreased analgesic consumption, higher patient satisfaction, and minimal adverse effects.

Limitations: There were some limitations in our study that should be addressed in future research. First, we have used the intravenous analgesic dose of ketamine for the intraperitoneal instillation, thus further research is needed to determine the appropriate intraperitoneal dose. Second, relatively smaller

sample size of our study. Finally, we have not evaluated the extubation and recovery times affected by the study drugs.

Conflict of interest: None

Source of research fund: None

REFERENCES

1. Esmat ME, Elsebae MM, Nasr MM, Elsebaie SB. Combined low-pressure pneumo peritoneum, and intra-peritoneal infusion of normal saline for reducing shoulder tip pain following laparoscopic cholecystectomy. *World J Surg* 2006; 30: 1969-73. doi: 10.1007/s00268-005-0752-z.
2. Manworren RC. Multimodal pain management and the future of a personalized medicine approach to pain. *AORN J* 2015; 101: 308-18. DOI: 10.1016/j.aorn.2014.12.009.
3. El-Labban GM, Hokkam EN, El-Labban MA *et al*. Intra-incisional vs intra-peritoneal infiltration of local anesthetic for controlling early post-laparoscopic cholecystectomy pain. *J Minim Access Surg* 2011; 7: 173-7. doi: 10.4103/0972-9941.83508.
4. Upadhya M, Pushpavathi SH, Seetharam KR. Comparison of intra-peritoneal bupivacaine and intravenous paracetamol for postoperative pain relief after laparoscopic cholecystectomy. *Aneth Essays Res* 2015; 9: 39-3. doi: 10.4103/0259-1162.150154
5. Hayashi H, Dikkes P, Soriano SG. Repeated administration of ketamine may lead to neuronal degeneration in the developing rat brain. *Paediatr Anaesth* 2002; 19:770-74. doi: 10.1046/j.1460-9592.2002.00883.x.
6. Choi GJ, Kang H, Baek CW, Jung YH, Kim DR. Effect of intraperitoneal local anesthetic on pain characteristics after laparoscopic cholecystectomy. *World J Gastroenterol* 2015; 21:13386-13395. doi: 10.3748/wjg.v21.i47.13386
7. Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. *Curr Opin Anaesth* 2010; 23: 697-03. doi: 10.1097/ACO.0b013e32833fad0a.
8. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. *Can J Anaesth* 2011; 58:911-23. doi: 10.1007/s12630-011-9560-0.
9. Moharari RS, Hodavi M, Pourfakhr P, Najafi A, Etezadi F, Khajavi MR. Evaluation of the postoperative analgesic efficacy of intraperitoneal ketamine compared with bupivacaine in laparoscopic cholecystectomy. *Arch Anesthesiol Crit Care* 2016; 2: 146–9. eISSN: 2423-5849.
10. Mc Cartehy C, Shinha A, Katz J. A qualitative systemic review of the role of N-methyl aspartate receptors antagonists in preventive analgesia. *Anesth Analg* 2004; 98: 1385-00. doi: 10.1213/01.ane.0000108501.57073.38.
11. Goma HM, Elhamid BA. Intra peritoneal S ketamine reduces postoperative analgesic requirements in morbidly obese patients: a controlled study. *J Anesthesiol Crit Care Med* 2015; 2: 1-4. doi:10.18650/2374-4448.25015.
12. Safavi M, Honarmand A, Nematollahy Z. Pre-incisional analgesia with intravenous or subcutaneous infiltration of ketamine reduces postoperative pain in patients after open cholecystectomy: a randomized, double-blind, placebo-controlled study. *Pain Med* 2011; 12:1418-26. doi: 10.1111/j.1526-4637.2011.01205.x.
13. El-Gaby SS and Mohamed SS. Intraperitoneal ketamine attenuates the inflammatory reactivity associated with pneumoperitoneum. *Res Opinion Anesth Intensive Care* 2017; 4: 149-55. doi: 10.4103/roaic.roaic-121-6.
14. Joris J, Thiry E, Paris P, Weerts J, Lamy M. Pain after laparoscopic cholecystectomy: characteristics and effect of intra-peritoneal bupivacaine. *Anesth Analg* 1995; 81: 379-84. doi: 10.1097/00000539-199508000-00029.
15. Golubovic S, Golubovic V, Cindric Stancin M, Tokmadzic VS. Intra-peritoneal analgesia for laparoscopic cholecystectomy: bupivacaine versus bupivacaine with tramadol. *Coll Antropol* 2009; 33: 299-02.
16. Mc Roberts JA, Coutinho SV, Marvizon JC *et al*. Role of peripheral N-methyl-D-aspartate (NMDA) receptors in visceral nociception in rats. *Gastroenterol* 2001; 120: 1737-48. doi: 10.1053/gast.2001.24848.
17. Hernandez-Palazon J, Tortosa JA, Nuno de la *et al*. Intra-peritoneal application of bupivacaine plus morphine for pain relief after laparoscopic cholecystectomy. *Eur J Anaesth* 2003; 20: 891-6. doi: 10.1017/s0265021503001431
18. Malhotra N, Chanana C, Roy KK *et al*. To compare the efficacy of two doses of intra-peritoneal bupivacaine for pain relief after operative laparoscopy in gynecology. *Arch Gynecol Obstet* 2007; 276: 323-6. doi: 10.1007/s00404-007-0337-1.
19. Chundrigar T, Hedges AR, Morris R, Stamatakis JD. Intraperitoneal bupivacaine for effective pain relief after laparoscopic cholecystectomy. *Ann R Coll Surg Engl* 1993; 75: 437-9.
20. Shawky AM, Essa A, Emam A. Effect of intra-peritoneal ketamine as postoperative analgesia in laparoscopic cholecystectomy. *Egypt J Hosp Med* 2018; 72: 224-9. doi: 10.21608/EJHM.2018.9142
21. Marks JL, Ata B, Tulandi T. Systematic review, and meta-analysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. *J Minim Invasive Gynecol* 2012; 19: 545-53. doi: 10.1016/j.jmig.2012.04.002
22. Borner M, Bürkle H, Trojan S, Horoshun G, Riewendt HD, Wappler F. Intra-articular ketamine after arthroscopic knee surgery. Optimization of postoperative analgesia.

Anaesth 2007; 56: 1120-27. doi: 10.1007/s00101-007-1249-y.

23. Abdel-Raouf M and Amer H. Postoperative analgesic effects of intra-peritoneal NMDA receptor antagonists (ketamine and magnesium) in patients undergoing laparoscopic cholecystectomy. *Egypt J Anaesth* 2004; 20:107-71. (Without quotes)
24. Raham HM, Yehia M, Hassan M. Comparative evaluation of intra-peritoneal bupivacaine and bupivacaine ketamine combined with lung recruitment for reducing postoperative shoulder pain in laparoscopic cholecystectomy. *Egypt J Anaesthe* 2018; 34: 159-64. doi.org/10.1016/j.egja.2018.10.001
25. Mraovic B, Jurisic T, Kogler-Majeric V, Sustic A. Intraperitoneal bupivacaine for analgesia after laparoscopic cholecystectomy. *Acta Anesthesia Scand* 1997; 41: 193-6. doi: 10.1111/j.1399-6576.1997.tb04664.x
26. Mostafa RH and Mekki YMH. Comparative evaluation of intraperitoneal bupivacaine and bupivacaine ketamine combined with lung recruitment for reducing postoperative shoulder pain in laparoscopic cholecystectomy. *Egypt J Anaesth* 2018; 34: 159-64. doi.org/10.1016/j.egja.2018.10.001
27. Abd El-Rahman AM, El Sherif FA. Efficacy of postoperative analgesia of local ketamine wound instillation following total thyroidectomy: A Randomized, Double-blind, Controlled Clinical Trial. *Clin J Pain* 2018; 34: 53-8. doi: 10.1097/AJP.0000000000000521.
28. Oza V, Patel S, Parmar V, Sarathy S, Adhiya P. A comparative study of intra peritoneal instillation of ketamine and magnesium sulphate for intraoperative and postoperative pain relief in patients undergoing laparoscopic cholecystectomy. *Med Pulse Int J Anesth* 2019: 12: 279-84. doi.org/10.26611/1015121313
29. Maryam S, A Melika, P Shirin, K Alireza. The effect of intraperitoneal ketamine, dexmedetomidine, and bupivacaine on postoperative pain control in patients undergoing abdominal hysterectomy. *Med Sci* 2022; 26: 2-7. doi.org/10.54905/disssi/v26i120/ms47e1835
30. Kapoor R, Dua S, Saxena AK, Narayan S. Evaluation of the efficacy of intraperitoneal installation of ropivacaine with dexmedetomidine versus ropivacaine with ketamine for post-operative pain relief following laparoscopic cholecystectomy: a randomized controlled study. *Arche Anesthesiol criti Care* (Supple) 2023; 9: 411-7. https://doi.org/10.18502/aacc.v9i5.13960
31. Kamali A, Zarepour Z, Shokrpour M, Pazuki S. Comparison of intradermal dexmedmotidine and subcutaneous ketamine for post-surgical pain management in patients with abdominal hysterectomy. *Eur J Transl Myol* 2019; 29. doi: 10.4081/ejtm.2019.7873