Original Article

Intraperitoneal nebulization of ropivacaine for control of pain after laparoscopic cholecystectomy -A randomized control trial

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Abstract

Background and Aims: Use of high dose opioids following laparoscopic surgery delays discharge from the hospital. Unlike intraperitoneal instillation, nebulization has been reported to provide a homogeneous spread of local anesthetics and provide better analgesia. In our study, we aimed to assess the efficacy of intraperitoneal nebulization of local anesthetic in alleviating postoperative pain in patients undergoing laparoscopic cholecystectomy.

Material and Methods: This randomized control double-blinded study was conducted after obtaining approval from the hospital ethics committee and informed consent from patients undergoing laparoscopic cholecystectomy under general anesthesia. Patients recruited were divided into two equal groups of 20 each. Group B received intraperitoneal nebulization with 4 ml of 0.75% ropivacaine and Group C received intraperitoneal nebulization with 4ml of saline before surgical dissection. Postoperative pain score using a numeric rating scale was monitored until 24 h, the need for rescue analgesics and associated complications were noted. Chi-square test, Student's test, and Mann–Whitney *U* test were used for statistical analysis.

Results: The pain score was significantly less in Group B during rest and deep breathing up to 24 h with a *P* value <0.05. The pain score on movement was also less in Group B and this difference was statistically significant at 6 and 24 h (*P* = 0.004 and 0.005, respectively). Tramadol consumption was less in Group B and was statistically significant at 24 h with *P* value of 0.044. No adverse events were noted.

Conclusion: Intraperitoneal nebulization of ropivacaine is effective and safe in providing postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

Keywords: Analgesia, intraperitoneal nebulization, laparoscopic, local anesthetic, postoperative pain, ropivacaine

Introduction

Minimally invasive surgical approaches have been increasingly used nowadays as they are associated with less pain and faster recovery. But some patients do experience visceral and shoulder pain following laparoscopic surgery, which delays the recovery and discharge from the hospital.[1]Moreover, if postoperative pain is not adequately treated, it may progress to chronic pain.[2]The use of opioids to relieve pain is associated with side effects like nausea, vomiting, pruritis, delayed return of gastrointestinal motility, and sedation, which may further delay the recovery.[3]Intraperitoneal injections of local anesthetic have been previously used to minimize postoperative pain after laparoscopic surgery.[4-6] But the results have been conflicting. Hence not routinely used. Popular techniques for providing postoperative analgesia in laparoscopic procedures is by ultrasound guided transverse abdominus plane block, which

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requires time, skill, and additional cost. Unlike intraperitoneal instillation, nebulization has been reported to provide a homogeneous spread of local anesthetics and provide better analgesia.[7]Thus, we hypothesized that intraperitoneal nebulization of the local anesthetic will alleviate postoperative pain after laparoscopic cholecystectomy. The primary objective of our study was to assess the analgesic efficacy of intraperitoneal nebulization in laparoscopic cholecystectomy. Secondary objectives were to compare the need for rescue analgesics and any adverse effects associated with the block.

Material and Methods

This prospective double-blinded randomized control study was conducted after obtaining approval from the hospital ethics committee (MTH/2013/ANES) and written informed consent from patients undergoing laparoscopic cholecystectomy under general anesthesia in a teaching hospital from December 2013 to December 2015. Patients were informed that the data collected would be used for research and educational purposes. Forty patients belonging to the American Society of Anesthesiologist (ASA) physical classes I and II between the age group 20–65 years were included in the study[Figure 1]. Patients with a diagnosis of acute pancreatitis, acute preoperative pain other than biliary colic, chronic pain treatment, antiepileptic therapy, alcoholic, and allergy to ropivacaine were excluded from the study. In the preoperative room, patients were explained about the grading of numeric rating scale (NRS) pain scores and were divided into two equal Groups B and C by a computer-generated random sequence of numbers in a sealed opaque envelope.

Standardized general anesthesia protocol was followed. All patients were kept nil per oral for 6h. They received oral ranitidine 150 mg, metoclopramide10mg, and alprazolam 0.5 mg as premedication on the morning of surgery. In the operating theater, intravenous access was secured and monitoring with the electrocardiogram, noninvasive blood pressure, and pulse-oximeter were done. General anesthesia was induced with intravenous propofol 2–3mg/kg, fentanyl 2 μg/kg, and tracheal intubation was facilitated with atracurium 0.5 mg/kg. After intubation, an end-tidal capnograph, nasogastric tube, and nasopharyngeal temperature probe were placed. Anesthesia was maintained with 33% oxygen in air and sevoflurane titrated to maintain MAC of 1. Intravenous boluses of fentanyl 20μg were used to maintain mean arterial pressure and heart rate to ±20% of basal line values. Ventilation was controlled to maintain end-tidal CO_2 between 30 and 35mmHg.

Intraperitoneal nebulization was performed using the Aeroneb Pro® device (Aerogen, Galway, Ireland) [Figure 2]. The nebulization unit was connected between the insufflator and the insufflation tubing. The nebulizer was connected via

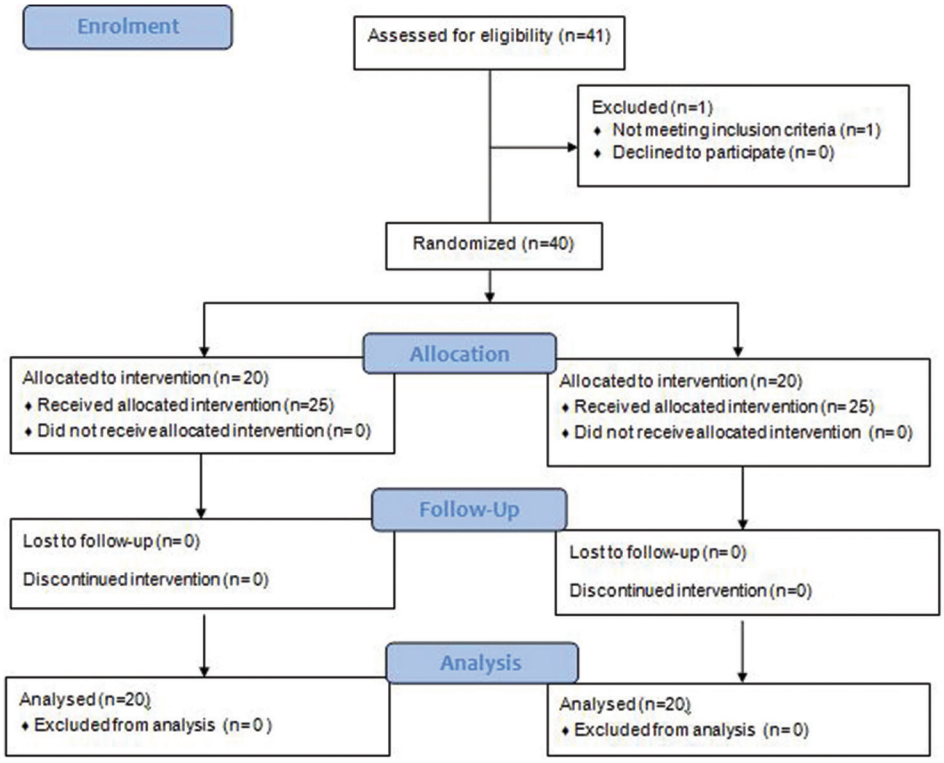

Figure 1: Consort flow diagram

Figure 2: Aeroneb Pro® device

tubing to the umbilical port and was initiated simultaneously with laparoscopic gas insufflations. In Group B, 4ml of 0.75% ropivacaine, and in Group C, nebulization of 4ml saline was performed before surgery. The nebulization takes around 5 min, when the laparoscopic vision is completely blurred. Once the nebulizer is disconnected, the vision clears and surgery can be started without any delay. Laparoscopic cholecystectomy was performed according to the standard surgical protocol. At the end of the surgery, port sites were infiltrated with 3 ml of 0.75% ropivacaine each.

On completion of the surgery, all patients received intravenous ondansetron 4 mg as prophylaxis for postoperative nausea and vomiting. Residual muscle relaxation was reversed with intravenous neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and tracheal extubation was performed once clinical signs suggestive of return of muscle power were observed. Patients were then shifted to the post anesthesia care unit (PACU). The intensity of pain on deep breathing, coughing, or movement (rising from supine to sitting position) was assessed using an NRS scale where zero represented no pain and ten represented worst possible pain at 2, 4, 6, and 24h postoperatively by anesthetist in charge of PACU, who was not aware of group allocation. In the first postoperative day, all patients received intravenous paracetamol 1 g eight hourly.Patients were given rescue analgesia for pain score rated three or above with intravenous tramadol 50 mg along with 4-mg ondansetron as antiemetic. The total dose of tramadol given in the first 24 h was noted. Any local complications related to the procedure were also recorded.

Sample Size Calculation

The sample size calculation was based on the results of the mean and standard deviation of the visual analogue score with intraperitoneal nebulization of 3ml of 1% nebulization in the dissection group (24 ± 15) versus the placebo group (38 ± 14) at 6 h.[8] With 80% power and 95% confidence, the minimum sample size was calculated to be 34 with 17 in each group. However, we enrolled 20 patients in each group to take care of any dropouts.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables are expressed using frequency and percentage. Continuous variables are presented using mean and standard deviation. To test the statistical significance of the comparison of categorical variables between groups, Chi-square test was used. To test the statistically significant difference in the mean values of continuous variables, Student's *t*-test/Mann–Whitney *U* test was used. $P < 0.05$ was considered statistically significant.

Results

A total of 40 patients were recruited into this study. The patients in both the groups were comparable in terms of the distribution of age, height, weight, and American Society of Anesthesiologists' physical status [Table 1]. The duration of surgery was comparable between the two groups. The shortest duration of surgery was 80 min and the longest duration was 120 min. The mean and median NRS score at rest was compared between Group B and Group C at 2, 4, 6, and 24h. The mean and median NRS was significantly less in Group B with *P* values of <0.05[Figure 3]. The mean and median NRS on deep breathing was less in Group B and was statistically significant at all time points [Figure 4]. The mean and median NRS on movement was also less in Groups B than C and this difference was statistically significant at 6 and 24 h[Figure 5]. Tramadol consumption was less in Group B compared to Group C, which was statistically significant at 24 h with *P* value of 0.044[Table 2].

Discussion

This randomized controlled trial has demonstrated that pre-emptive nebulization of local anesthetic, ropivacaine is effective in reducing postoperative pain associated with laparoscopic cholecystectomy. None of the patients in this study group had any adverse effects associated with the nebulization of saline or local anesthetic. We did not encounter any symptoms of local anesthetic toxicity in any of the patients in both groups.

Visceral and shoulder pain after laparoscopic cholecystectomy is caused by surgical manipulations, disruption of peritoneum, and dissection of viscera, which result in irritation of peritoneal nerves.[9,10]The use of opioids to relieve this pain is associated

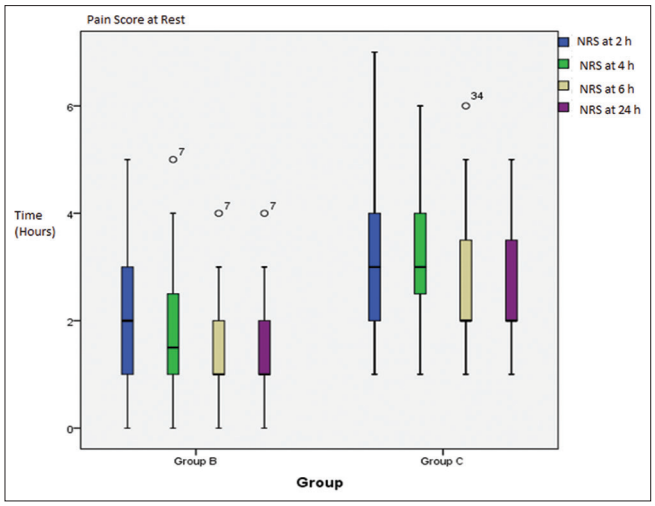

Figure 3: Pain score at rest

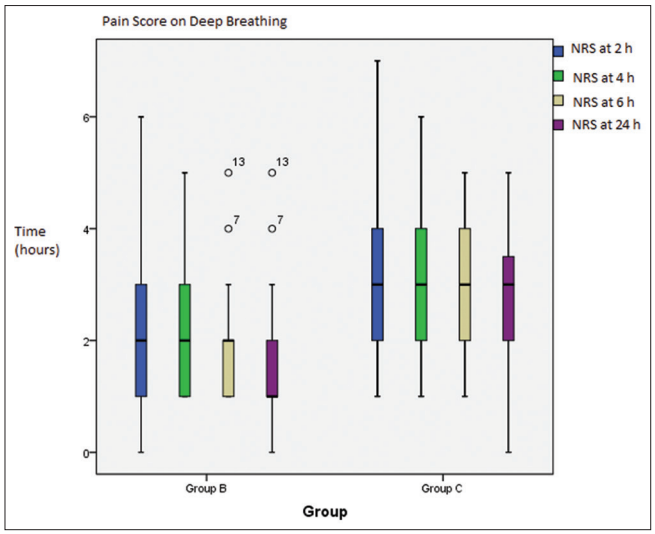

Figure 4: Pain score on deep breathing

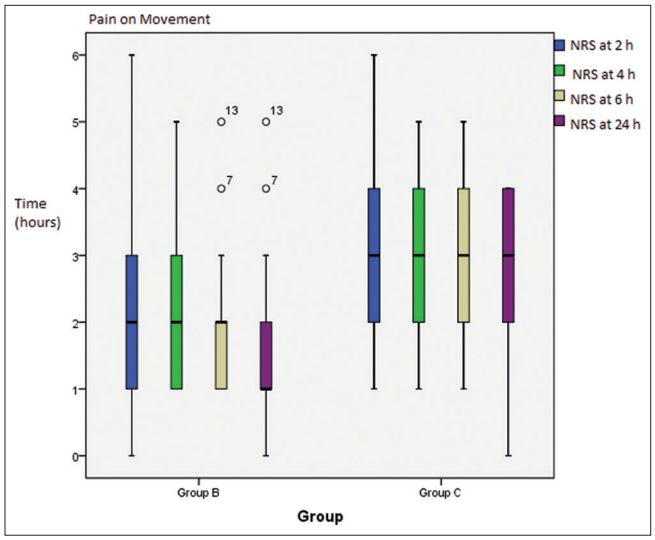

Figure 5: Pain score on movement

Table 1: Demographic data and ASA grade

Variable	Group B *n*=20	Group C *n*=20	*P*
Age in years (mean±SD)	44.15±8.68	41.8±9.47	0.419
Weight in kg (mean±SD)	70.50±11.02	68.01±11.01	0.495
Height in cm (mean±SD)	159.5±4.8	159.6±4.9	0.974
Sex *n* (%)			
Male	9 (45%)	11 (55%)	0.752
Female	11 (55%)	9 (45%)	
ASA Grade *n* (%)			
1	9 (45%)	13 (65%)	0.204
2	11 (55%)	7 (35%)	

ASA - American Society of Anesthesiologists, SD - Standard deviation

Table 2: Comparison of tramadol consumption

Time (h)	Tramadol consumed (mg)	Group B %	Group C %	*P*
2	0	16 (80.0%)	9 (45.0%)	0.063
	50	4 (20.0%)	10 (50.0%)	
	100	0 (0.0%)	1 (5.0%)	
4	0	17 (85.0%)	11 (55.0%)	0.082
	50	3 (15.0%)	9 (45.0%)	
	100	0 (0%)	0 (0%)	
6	0	18 (90.0%)	12 (60.0%)	0.065
	50	2 (10.0%)	8 (40.0%)	
	100	0 (0%)	0 (0%)	
24	0	19 (95.0%)	13 (65.0%)	0.044
	50	1 (5.0%)	7 (35.0%)	
	100	0 (0%)	0 (0%)	

with adverse effects like sedation, nausea, delayed gastric emptying, and respiratory depression.[11]These side effects can be avoided by epidural infusions, transverse abdominis plane block, or infiltration of port sites with local anesthetics. Studies have shown that instillation and nebulization of local anesthetic into the peritoneal cavity can also be used to relieve pain after laparoscopic surgery. It produces analgesia by blocking the visceral nociceptors.[9]

In our study, we used ropivacaine for intraperitoneal nebulization as it is associated with less toxicity and is equally effective as bupivacaine. In a dose-finding study by Allegri *et al.*[12]50 mg of nebulized ropivacaine was found to be effective in providing adequate analgesia in patients undergoing laparoscopic cholecystectomy. Further increase in the dose of ropivacaine did not provide any additional benefit. In our study, patients had adequate pain relief, with a smaller dose of 30 mg ropivacaine.

Advantages of the nebulization of local anaesthetic are that particle size generated by the nebulizer is small (<5 μm), which helps to uniformly spread the local anesthetic throughout

the peritoneal surface.[8]Sharon *et al.*[13]studied the effects of continuous intra-abdominal nebulization of lignocaine using the insuflow device in gynecological laparoscopic procedures and found that it reduced pain only in the initial postoperative period. The use of short-acting local anesthetic, lignocaine could have resulted in this shorter duration of analgesia. Similar studies by Alkhamesi *et al.*[14]and Ingelmo *et al.*[8]also demonstrated reduced postoperative pain, less opioid consumption, rapid mobilization, and shorter duration of hospitalization. In a study by Catenacci *et al.*,[15]intraperitoneal nebulization and peritoneal instillation of ropivacaine were compared and nebulization was found to be superior to instillation of ropivacaine. Somaini *et al.*[16] and Kumar *et al.*[17]studied the effects of peritoneal ropivacaine nebulization in laparoscopic gynecologic surgery and donor nephrectomy, respectively, and found it to be effective in reducing postoperative pain, which resulted in early ambulation and discharge. Das *et al.*[18] used intraperitoneal nebulization of ropivacaine and found that it reduced pain scores in the early postoperative period making laparoscopic cholecystectomy more amenable to day care surgery.

But some of the studies have shown conflicting results. Zimmer *et al.*[19]used the insuflow device for nebulization of bupivacaine, which was ineffective in producing adequate analgesia. Authors believe that when water soluble bupivacaine in solution was vaporized with insuflow, bupivacaine was left behind, resulting in decreased bioavailability of the drug intraperitoneally, which could have resulted in failure to reduce postoperative analgesic requirement. Similarly, Kaufman *et al.*[20] could not demonstrate any advantage in using ropivacaine nebulization in gynecologic laparoscopic surgery. Authors used infusions of short acting remifentanil intraoperatively, which was discontinued before the end of the procedure. Nebulization of 100 mg of ropivacaine resulted in insufficient amount of local anesthetic to the surgical site. This must have resulted in increased postoperative morphine consumption, masking potential analgesic effects of ropivacaine at later postoperative time intervals. In a study by Baird *et al.*[21]nebulized ropivacaine did not reduce postoperative morphine consumption or pain scores after laparoscopic appendectomy. This study was performed on pediatric patients who underwent emergency appendicectomy for an underlying inflammatory process. Here, the surgeons also complained of poor visibility caused by nebulization of ropivacaine. All the above factors may have contributed to the failure of intraperitoneal nebulization to produce effective results.

Greib *et al.*,[6]in an experimental study, evaluated the effectiveness of four types of gas humidifying devices and found that Aeroneb Pro was best to deliver local anesthetics along with CO_2 insufflation during laparoscopy. Aeronob Pro device is high-frequency vibrating nebulizer, which can be reused, sterilized using plasma sterilization and can be easily assembled.[6]Hence in our study, we used the Aeroneb Pro® device for nebulization of ropivacaine. Concern regarding its use is that small droplet formed could create a foggy environment that may interfere with the surgeons'view.[16] Bhatia *et al.*[6]used ingeniously prepared nebulization kit made from the ordinary nebulizer and silicon tubing and achieved adequate analgesia when ropivacaine along with fentanyl was used for intraperitoneal nebulization. Kumar *et al*[22] in their study on donor nephrectomy found that intraperitoneal instillation of ropivacaine reduced postoperative pain. Porika *et al*[23] compared intraperitoneal nebulizations of ropivacaine and bupivacaine and observed that both were equally efficacious in reducing pain.

This study is limited by the fact that we could have assessed the difference in time to ambulation, discharge, and incidence of postoperative nausea and vomiting. We could have also assessed the time to request for the first rescue analgesic. Various additives could be used to prolong the duration of analgesia produced.[24] This should be studied further to see if there is an increased benefit to patients.

Conclusion

Intraperitoneal nebulization of ropivacaine is effective and safe in reducing postoperative pain in patients undergoing laparoscopic cholecystectomy. It improves the pain scores and reduces the use of narcotics in the postoperative period.

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Nil.

Conflicts of Interest
There are no conflicts of interest.

References

1. Ochsner JL. Minimally invasive surgical procedures. Ochsner J 2000;2:135-6.
2. BisgaardT, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: A prospective follow up analysis. Scand J Gastroenterol 2005;40:1358-64.
3. Gibbison B, Kinsella ST. Postoperative analgesia for gynaecological laparoscopy. Saudi J Anaesth 2009;3:70-6.
4. Samimi S, Taheri A, Tanha FD. Comparison between intraperitoneal and intravenous lidocaine for postoperative analgesia after elective abdominal hysterectomy, a double-blind placebo-controlled study. J Fam Plann Reprod Health Care 2015;9:193-8.
5. Govil N, Kumar P. Intraperitone all evobupivacaine with or without clonidine for pain relief after laparoscopic cholecystectomy: A randomized, double-blind, placebo-controlled trial. Anesth Essays Res 2017;11:125-8.

6. Bhatia N, Mehta S, Saini V, Ghai B, Kaman L. Comparison of intraperitoneal nebulization of ropivacaine with ropivacaine-fentanyl combination for pain control following laparoscopic cholecystectomy: A randomized, double-blind, placebo-controlled trial. J Laparoendosc Adv Surg Tech A2018;28:839-44.
7. Greib N, Schlotterbeck H, Dow WA, Joshi GP, Geny B, Diemunsch PA. An evaluation of gas humidifying devices as a means of intraperitoneal local anaesthetic administration for laparoscopic surgery.AnesthAnalg 2008;107:549-51.
8. Ingelmo PM, Bucciero M, Somaini M, Sahillioglu E, Garbagnati A, Charton A, *et al.* Intraperitoneal nebulization of ropivacaine for pain control after laparoscopic cholecystectomy: A double-blind, randomized, placebo-controlled trial. Br J Anaesth 2013;110:800-6.
9. Kahokehr A, Sammour T, Soop M, Hill AG. Intraperitoneal use of local anesthetic in laparoscopic cholecystectomy: A systematic review and meta-analysis of randomized controlled trials. J Hepatobiliary Pancreat Sci 2010;17:637-56.
10. Tobias JD. Pain management following laparoscopy: Can we do better? Saudi J Anaesth 2013;7:3-4.
11. Lee LA, Caplan RA, Stephens LS, Posner KL, Terman GW, Voepel-Lewis T, *et al.* Postoperative opioid-induced respiratory depression–A closed claims analysis. Anaesthesiology 2015;122:659-65.
12. Allegri M, Ornaghi M, Ferland CE, Bugada D, Meghani Y, Calcinati S, *et al.* Peritoneal nebulization of ropivacaine during laparoscopic cholecystectomy: Dose-finding and pharmacokinetic study.Pain Res Manag 2017;2017:4260702.
13. Sharon A, Hirsh I, Kaufman Y, Ostrovski L, Brandes-Klein O, Spiegelet D, *et al.*The effect of continuous intra abdominal nebulization of lidocaine during gynecological laparoscopic procedures- a pilot study. Gynecol Surg 2008;5:221-5.
14. Alkhamesi NA, Peck DH, Lomax D, Darzi AW. Intraperiton ealaerosolization of bupivacaine reduces postoperative pain in laparoscopic surgery: A randomized prospective controlled double-blinded clinical trial.SurgEndosc 2007;21:602-6.
15. Catenacci SS, Lovisari F, Peng S, Allegri M, Somani M, Ghislanzoni L, *et al.* Postoperative analgesia after laparoscopic ovarian cyst resection: Double-blind multicenter randomized control trial comparing intraperitoneal nebulization and peritoneal instillation of ropivacaine.J Minim Invasive Gynecol2015;22:759-66.
16. Somaini M, Brambillasca P, Ingelmo PM, Lovisari F, Catenacci SS, Rossini V, *et al.* Effects of peritoneal ropivacaine nebulization for pain control after laparoscopic gynecologic surgery.J Minim Invasive Gynecol2014;21:863-9.
17. Kumar R, Nath SS, Agarwal A. Intraperitoneal nebulisation versus intraperitoneal instillation of ropivacaine for postoperativepain management following laparoscopic donor nephrectomy. Korean J Anesthesiol 2019;72:357-65.
18. Das NT, Deshpande C. Effects of intraperitoneal local anaesthetics bupivacaine and ropivacaine versus placebo on postoperative pain after laparoscopic cholecystectomy: A randomised double blind study. J Clin Diagn Res 2017;11:UC08-12.
19. Zimmer PW, McCann MJ, MO'Brien M. Bupivacaine use in the Insuflow device during laparoscopic cholecystectomy: Results of a prospective randomized double-blind controlled trial. Surg Endosc 2010;24:1524-9.
20. Kaufman Y, Hirsch I, Ostrovsky L, Klein O, Shnaider I, Khoury E, *et al*.Pain relief by continuous intraperitoneal nebulization of ropivacaine during gynecologic laparoscopic surgery--a randomized study and review of the literature. J Minim Invasive Gynecol 2008;15:554-8.
21. Baird R, Ingelmo P, Wei A, Meghani Y, Perez EV, Pelletier H, *et al.* Nebulized analgesia during laparoscopic appendectomy: A randomized triple-blind placebo controlled trial. J Pediatr Surg 2019;54:33-8.
22. Kumar R,NATH SS,Agarwal A. Intraperitoneal nebulization versus intraperitoneal instillation of ropivacaine for postoperative pain management following laparoscopic donor nephrectomy. Korean j anesthesiol.2019;72:357-365.
23. Porika S, Lakshmi VN. Intraperitoneal nebulization of ropivacaine 0.75%vsintraperitoneal nebulization of bupivacaine 0.5%for post-operativeanalgesia in laparoscopic surgeries:Prospective double blinded randomized controlled trial.IAIM.2018;5:105-117.
24. Elnabtity AM, Ibrahim M. Intraperitoneal dexmedetomidine as an adjuvant to bupivacaine for postoperative pain management in children undergoing laparoscopic appendectomy: A prospective randomized trial. Saudi J Anaesth 2018;12:399-405.