Original Article

Post-operative analgesic effect of intraperitoneal ropivacaine with or without tramadol in laparoscopic cholecystectomy

Address for correspondence:
Dr. Anil Shrestha, Department of Anaesthesiology, T.U. Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu - 44600, Nepal.
E-mail: aanilsh@hotmail.com

Received: 24th July, 2019
Revision: 26th September, 2019
Accepted: 02th December, 2019
Publication: 07th January, 2020

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/ija.IJA_526_19
Quick response code

Anshu Kumari, Binita Acharya[1], Bikal Ghimire[2], Anil Shrestha[1]
Department of Anaesthesiology, Dr. Hedgewar Arogya Sansthan, New Delhi, India, Departments of [1]Anaesthesiology and [2]Surgery, Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal

ABSTRACT

Background and Aims: Intraperitoneal instillation of local anaesthetics has been shown to minimise post-operative pain after laparoscopic surgery. This study was aimed to evaluate the post-operative effect of intraperitoneal ropivacaine with and without tramadol in patients undergoing laparoscopic cholecystectomy. **Methods:** Eighty patients undergoing laparoscopic cholecystectomy were randomised into two groups. Group R received 0.5% ropivacaine 18 mL with normal saline (NS) 2 mL and Group RT received 0.5% ropivacaine 18 mL with tramadol (100 mg, 2 mL) at the end of surgery intraperitoneally through the port. The pain score was monitored using a numerical rating scale (NRS) every 30 min till 4 h post-operatively and then at 6 h, 12 h and 24 h. The primary objective of the study was to compare the severity of pain between the groups. The secondary objectives were to compare the total dose of rescue analgesic and the time to first rescue analgesia between the groups Statistical analysis was performed using statistical package for the social sciences. Chi-square test and Mann Whitney U test were used for analysis. **Results:** The pain score in Group RT was significantly lower than Group R at 2.5 h to 24 h ($P = 0.005$). Only 42.5% in Group RT demanded rescue analgesia as compared to 75% in Group R ($P = 0.003$). Total analgesic consumption of fentanyl was also reduced in the tramadol group (785 μg vs 1800 μg). No significant adverse effects were found. **Conclusion:** Intraperitoneal instillation of ropivacaine with tramadol reduces the post-operative pain and analgesic requirement in laparoscopic cholecystectomy as compared to ropivacaine alone.

Key words: Intraperitoneal, laparoscopic cholecystectomy, post-operative pain, ropivacaine, tramadol

INTRODUCTION

Laparoscopic cholecystectomy (LC) is the treatment of choice for symptomatic cholelithiasis substituting the conventional open method of cholecystectomy.[1] Although post-operative pain is much less severe than that induced by open cholecystectomy, it is still not a pain-free procedure, which is why many patients refrain from early recovery,[2] a major hurdle in enhanced recovery after surgery (ERAS).

Different modalities have been proposed to relieve post-operative pain after laparoscopy, for example, non-steroidal anti-inflammatory drugs (NSAIDS), opioids, intraperitoneal (IP) local anaesthetics, IP saline, removal of insufflations gas or gas drains, low-pressure abdominal insufflations, acetazolamide administration, use of nitrous oxide instead of carbon dioxide, and so on.[3]

Among the various local anaesthetics (LA) techniques, IP use of LA has gained attention and various researches

How to cite this article: Kumari A, Acharya B, Ghimire B, Shrestha A. Post-operative analgesic effect of intraperitoneal ropivacaine with or without tramadol in laparoscopic cholecystectomy. Indian J Anaesth 2020;64:43-8.

have been done to study its efficacy for post-operative analgesia. The rationale to use the IP route is that the peritoneum is exposed to block of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia. Most of the previous studies have shown that local anaesthetic with or without opioids can provide post-operative pain relief when instilled intraperitoneally.[4] Few literatures are available on administration of tramadol alone or in combination with bupivacaine intraperitoneally for post-operative pain relief.[5,6] However, we could not find any literature evaluating the effect of the combination of ropivacaine with tramadol administered intraperitoneally for post-operative analgesia following laparoscopic cholecystectomy.

We thus decided to conduct this study with the aim of evaluating the analgesic efficacy of these two drugs (ropivacaine, tramadol) when used in combination and intraperitoneally for post-operative analgesia. We hypothesised that intraperitoneal instillation of ropivacaine with tramadol improves post-operative analgesia after laparoscopic cholecystectomy without significant side effects compared to intraperitoneal ropivacaine alone.

METHODS

This prospective, randomised, double-blinded study was carried out after approval from the institutional review board (Ref. no -269 (6-11-E)^2/074/075, date – 6th December 2017). Written informed consent was obtained from all the patients before surgery. Eighty patients of American Society of Anaesthesiologists physical status (ASA-PS) grade I/II involving patients of both sexes, in the age group of 16–65 years, planned for elective LC were enrolled in the study during 6 months period from January 2018 to June 2018. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The primary objective of the study was to compare the severity of pain between the ropivacaine alone and ropivacaine with tramadol group by numerical rating scale (NRS). The secondary objectives were to compare the total dose of rescue analgesic (fentanyl) in between the groups and to compare the time to first rescue analgesia between the groups.

Pregnant females, patients with a history of hypersensitivity to ropivacaine/local anaesthetics and or tramadol, malignancy, alcohol or drug abuse were excluded. The preanaesthetic evaluation was done 1 day prior to the surgery. Patients were premedicated with oral diazepam 10 mg. Patients were instructed about the NRS preoperatively. Eligible patients were randomised 1:1 using computer-generated series into two groups of 40 each. Allocation concealment was done using a sealed opaque envelope each bearing only the number on the outer side. The study drug was prepared by an anaesthesia assistant not involved in the study. Group R received 18 mL of 0.5% ropivacaine +2 mL of normal saline while Group RT received 18 mL of 0.5% ropivacaine IP with 100 mg (2 mL) tramadol.

Intravenous line with 18G cannula was secured in the preparation area. Noninvasive blood pressure (NIBP), peripheral oxygen saturation (SpO2), end-tidal carbon dioxide (EtCO2), ECG, and heart rate monitoring were done during surgery. All the patients were subjected to the same anaesthetic protocol with intravenous (IV) midazolam 0.02 mg/kg; fentanyl 2 μg/kg and propofol 2 mg/kg IV in titration dose. Orotracheal intubation was facilitated with vecuronium 0.1 mg/kg IV. General anaesthesia (GA) was maintained with isoflurane and oxygen. Minute ventilation was adjusted to keep EtCO2 at 35–45 mmHg. Neuromuscular blockade was maintained by the top-up doses of vecuronium (0.01 mg/kg) IV when required. Intravenous paracetamol 1 gm was given intraoperatively. Intravenous dexamethasone 8 mg at the induction of anaesthesia and ondansetron 4 mg IV during skin closure was administered. At the end of the surgery, before the removal of the trocar, LA was instilled through the laparoscopic irrigation system. The study drug according to the group allocation was instilled over the gall bladder bed, hepato-duodenal ligament and hepatodiaphragmatic space by the operating surgeon who was blinded to the study drug. After instillation, to obtain thorough diffusion of LA, 2 min of trendelenburg position was maintained. The reversal of neuromuscular blockade was done with neostigmine 0.05 mg/kg IV and glycopyrrolate 0.01 mg/kg IV.

NRS score was collected every 30 min till 4 h post-operatively and then at 6 h, 12 h and 24 h, respectively. Duration of analgesia was defined as the time duration from completion of surgery [the time at which the patient reached the post anaesthesia care unit (time 0)] to the time patient requested for first analgesic medication or NRS >3. Intravenous fentanyl 0.5 μg/kg was given as rescue analgesia when required. Intravenous paracetamol 1 g and ketorolac 30 mg

12 hourly in the first 24 h were given to all patients. Cumulative consumption dose of rescue analgesia over 24 h was recorded. Side effects such as nausea, vomiting and shoulder pain were also recorded.

Statistical analysis was performed using statistical package for the social sciences (SPSS) version 16.0 (SPSS Ltd, Chicago, IL, USA). Continuous variables were represented as mean values with standard error or frequency. Nominal categorical data like gender, ASA-PS were analysed using Chi-square test and ordinal data like comparison of the NRS scale and rescue analgesic dose were analysed by Mann Whitney U test. For all determinations, P value < 0.05 (2-tailed) was considered statistically significant.

To calculate the required sample size, mean standard deviation (±11.225) and effect size (the difference between the mean values of visual analogue scale 8.25) at 4 h was taken from a previous study.[7] The sample size was calculated to have power of 80% with an alpha error of 0.05.

RESULTS

The simplified methodology of the conduction of the study is shown as a consort diagram [Figure 1].

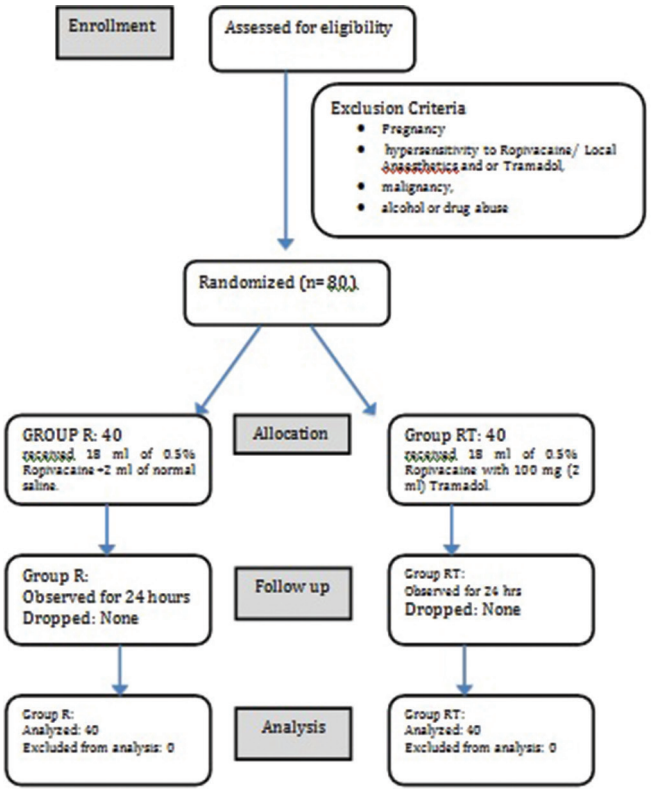

Figure 1: CONSORT Diagram

The two groups were comparable in terms of age, gender, weight, ASA- PS and duration of surgery [Table 1]. The number of female patients (26 and 28) was higher than males (14 and 12) in each group showing no statistically significant difference (P > 0.05). The difference between the severity of pain (mean NRS score with standard deviation) between the two groups is shown in Table 2. The mean NRS score was maximum till 2 h after surgery in both the groups. A significant difference in the mean NRS score was observed among the two groups at 2.5, 3, 3.5, 4, 6, 12, 24h (P < 0.05). There was a single incidence of shoulder pain in Group R after 1 h of surgery which persisted till 24 h.

The requirement of rescue analgesia (fentanyl) was higher in Group R (75% of the patients) compared to Group RT (42.5% of the patients) [Figure 2]. The difference of rescue analgesia requirement between the two groups was statistically significant with P value of 0.003.

Minimum time to receive first rescue analgesia was 5 min in Group R and 10 min in Group RT whereas the maximum time was 210 min in both groups. The comparison of median time (with interquartile range) to receive first rescue analgesia between the two

Table 1: Demographic Profile

	Group R (*n*=40)	Group RT (*n*=40)	*P*
Age (years)	44.83±13.49	46.05±12.63	0.653
Sex (M/F)	14/26	12/28	0.633
Weight (kg)	63.28±10.77	60.15±12.05	0.225
ASA-PS (I/II)	20/20	21/19	1.000
Duration of surgery (min)	73.63±20.22	74.13±19.44	0.911

Data described as (mean±SD); *n*=number, *P*<0.05 is significant.
ASA-PS – American Society of Anesthesiolgists' physical status

Table 2: Comparison of severity of pain between the two groups at different time intervals

NRS at	Group R (*n*=40)		Group RT (*n*=40)		*P*
	Mean	SD	Mean	SD	
30 min	2.53	1.48	2.35	1.31	0.578
1 h	2.43	1.28	2.00	0.82	0.080
1.5 h	2.25	1.01	1.98	0.83	0.187
2 h	1.98	0.83	1.95	0.85	0.894
2.5 h	1.83	0.55	1.78	0.70	0.005
3 h	1.85	0.53	1.45	0.50	0.001
3.5 h	1.88	0.94	1.48	0.75	0.039
4 h	1.68	0.80	1.23	0.42	0.002
6 h	1.38	0.49	1.08	0.27	0.001
12 h	1.10	0.30	0.98	0.16	0.024
NRS_24 h	1.05	0.22	0.93	0.27	0.025

Data described as (mean±SD); *n*=number, *P*<0.05 is significant.
NRS – Numeric rating scale

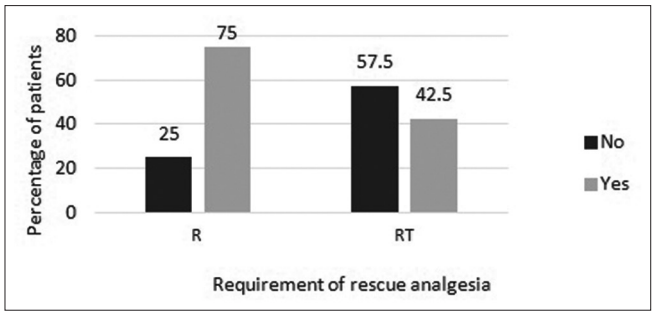

Figure 2: Comparison of patients needing rescue analgesia (Fentanyl) between the two groups

groups is shown in Table 3 which is not statistically significant. Total analgesic consumption (TAC) of fentanyl ranged from 0 to 120 μg individually and mean TAC was found to be 32.31 μg in the total study population. The median TAC in Group R was 40 μg and Group RT was 0 μg [Table 4].The difference of median TAC between the groups was statistically significant with *P* value of 0.002. Total analgesic consumption summated in Group R was 1800 μg and Group RT was 785 μg [Figure 3].

Total of 36 patients in Group R (90%) and 31 patients in Group RT (77.5%) had nausea over 24 h period. Comparing the severity of nausea between the groups with time, the maximum percentage of the population in each study group complained of no nausea till 1 h. The incidence of nausea started after 1 h of surgery. At this time interval, 40% of the population of Group R and 30% population of Group RT experienced nausea. Nausea with retching was experienced mainly in 1.5 h in both the group with 22.5% in Group R and 15% in Group RT. Combining nausea and nausea with retching, the incidence was 50% in Group R while 32% in Group RT in 1.5 h. Vomiting was experienced by a single patient in Group R at 3 h. None of these values were statistically significant ($P > 0.05$). Patients who suffered from nausea with retching and vomiting were treated with ondansetron 4 mg IV.

DISCUSSION

Our study demonstrates that the IP instillation of ropivacaine with tramadol reduces the intensity of abdominal pain significantly after LC. The NRS score for abdominal pain in Group RT was significantly less compared to Group R 2.5 h onward till 24 h. A similar decrease in pain score till 24 h was also found by Pratap *et al.*[8] when intraperitoneal tramadol was used during laparoscopic appendectomy. Our results are also in concordance with the studies by Labaille *et al.*,[9] Gupta

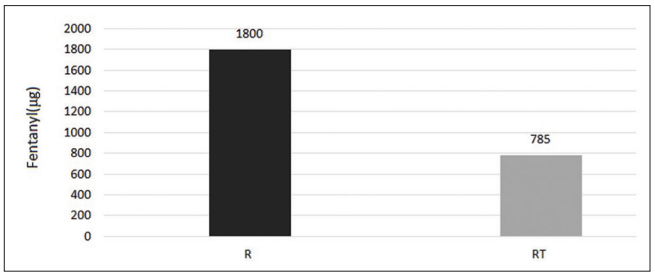

Figure 3: Total Fentanyl (in μg) consumption between two groups in 24 h

Table 3: Comparison of time to receive the first rescue analgesia (Fentanyl)

Group	Median (Q1, Q3)	*P*
R	47.5 (27.5, 90)	0.679
RT	30 (15, 90)	

Data described as median, *P*<0.05 is significant. Q=Interquartile range

Table 4: Comparison of total analgesic consumption

Total analgesic consumption (Fentanyl in μg)	Median (Q1, Q3)		*P*
	R (*n*=40)	RT (*n*=40)	
	40 (0, 70)	0 (0,38.75)	0.002

Data described as median, *P*<0.05 is significant. Q=Interquartile range

et al.,[10] Trikoupi *et al.*,[11] Kucuk *et al.*,[12] Memedov *et al.*,[13] Pavlidis *et al.*,[14] Park *et al.*[15] However, studies conducted by Bisgaard *et al.*[16] and Scheinin B *et al.*[17] failed to show any decrease in the visceral pain after intraperitoneal instillation of ropivacaine. This could be due to reduced concentration (0.2% of 38 mL of ropivacaine by Bisgaard and 0.15% of bupivacaine in 100 mL NS by Scheinin) used for intraperitoneal instillation.

Shoulder tip pain after laparoscopic cholecystectomy was found to be 30–50% of the patients in a study conducted by Sarli *et al.*[18] We observed a single incidence of shoulder pain in Group R which is not comparable; this could have been due to the absorption of gas at the end of surgery as well as subhepatic surface instillation with ropivacaine and maintenance of trendelenburg position for at least 2 min.

In our study 57.5% of patients in the Group RT didn't demand any rescue analgesia compared to 25% patients in Group R. Thus, there was a statistically significant difference in demand for rescue analgesia between the groups ($P = 0.003$). This finding is similar to the study done by Pratap *et al.*[8] where 56.67% of patient in the tramadol group did not demand rescue analgesia compared to 6.67% in the placebo group. The number of patients demanding rescue analgesia was higher in the placebo group in the study compared to our study

maybe because they used only normal saline in the placebo group while we used ropivacaine 0.5%.

The total analgesic consumption was also decreased in Group RT (785 μg vs 1800 μg, $P = 0.002$). In the study by Shukla *et al.*,[5] a similar decrease in rescue analgesic dose was also noted in tramadol group (85 ± 35 mg diclofenac) than bupivacaine alone group (175 ± 75 mg). A similar finding was also found by Jairath *et al.*[19] where rescue analgesic dose of diclofenac was significantly lower at 1 h and 24 h post-surgery (0 and 84 ± 59.92 mg) in tramadol group compared to placebo (76.47 ± 10.39 and 213 ± 41.11 mg).

While comparing the time of first rescue analgesia in our study, it was not found significant in between groups ($P = 0.679$). The minimum time to receive first rescue analgesia was 5 min in Group R and 10 min in Group RT while the maximum time was 210 min in both the groups. Thus, in both the groups the duration of analgesia was widely distributed giving insignificant results. Moreover, in our study, there is a large difference in the number of patients demanding rescue analgesia between the groups (17 vs 30). So, the analysis of a heterogeneous sample with data not following normal distribution resulted in unexpected contradictory finding with the study by Golubovic *et al.*,[20] however they had used larger volume (50 mL) compared to our study.

Comparing side effects, the incidence of nausea and vomiting was less in Group RT, 31 compared to 36 patients in Group R but not significant. Though the results were not significant at any time interval, it revealed that the incidence started only after half an hour of surgery and was maximum at 1.5 h and went on decreasing with time in both the groups.

Another side effects of local anaesthetics like LA toxicity were not seen in our study as we never crossed the standard dose. However, we did not measure the plasma concentrations of ropivacaine in our study patients as we believed our concentration was safe and below toxic levels (4 mg/kg of ropivacaine), as per the study by Kayani *et al.*[21]

Peripheral antinociceptive effect of opioids occurs due to interaction of opioids with opioid receptor located on peripheral intact perineurium that prevents the entry of hydrophilic opioid molecule, such as morphine while lipophilic opioids, such as tramadol, buprenorphine can diffuse across the intact perineural barrier, which results in better analgesia on intraperitoneal administration. Secondly, as the duration of action of parenterally administered tramadol is 6 to 8 h, so this explains low NRS scores and less need for rescue analgesia in the early post-operative period.

Our study had a few limitations. Visceral pain is affected and increased by movement but we did not assess pain scores at rest and on movement from a supine position to sitting. Patients in both groups also received paracetamol and ketorolac as standard practice for analgesia in our study, hence the NRS scores in both groups may have decreased because of these medications. We did not compare the influence of the timing of ropivacaine treatment (preoperative vs end of the surgery) on post-operative pain relief. We did not record the duration of hospital stay and did not compare them among the groups which is a key variable to measure here in terms of health economics.

CONCLUSION

Intraperitoneal instillation of ropivacaine in combination with tramadol in elective laparoscopic cholecystectomy significantly reduces the post-operative pain and analgesic requirement in post-operative period as compared to ropivacaine without tramadol combination.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. De U. Evolution of cholecystectomy: A tribute to Carl August Langenbuch. Indian J Surg 2004;66:97-100.
2. McGinn FP, Miles AJ, Uglow M, Ozmen M, Terzi C, Humby M. Randomized trial of laparoscopic cholecystectomy and mini-cholecystectomy. Br J Surg 1995;82:1374-7.
3. Singla S, Mittal G, Raghav, Mittal RK. Pain management after laparoscopic cholecystectomy-a randomized prospective trial of low pressure and standard pressure pneumoperitoneum. J Clin Diagnostic Res 2014;8:92-4.

4. Singh A, Mathur SK, Shukla VS. Postoperative analgesia with intraperitoneal ropivacaine with and without fentanyl after laparoscopic cholecystectomy: A randomized double-blind controlled trial. OA Anaesthetics 2013;1:1-9.
5. Shukla U, Prabhakar T, Malhotra K, Srivastava D, Malhotra K. Intraperitoneal bupivacaine alone or with dexmedetomidine or tramadol for post-operative analgesia following laparoscopic cholecystectomy: A comparative evaluation. Indian J Anaesth 2015;59:234-9.
6. Yadava A, Rajput SK, Katiyar S, Jain RK. A comparison of intraperitoneal bupivacaine-tramadol with bupivacaine-magnesium sulphate for pain relief after laparoscopic cholecystectomy: A prospective, randomised study. Indian J Anaesth 2016;60:757-62.
7. Kim TH, Hyun K, Park JS, Chang IT, Park SG. Intraperitoneal ropivacaine instillation for postoperative pain relief after laparoscopic cholecystectomy. J Korean Surg Soc 2010;79:130-6.
8. Pratap V, Parappa Bellad A. Analgesic efficacy of intraperitoneal tramadol vs. placebo for postoperative pain relief following laparoscopic appendicectomy: A double-blinded 1-year randomized control trial: Single centric, hospital based study. J Evol Med Dent Sci 2016;5:2390-7.
9. Labaille T, Mazoit JX, Paqueron X, Franco D, Benhamou D. The clinical efficacy and pharmacokinetics of intraperitoneal ropivacaine for laparoscopic cholecystectomy. Anesth Analg 2002;94:100-5.
10. Gupta A, Thörn SE, Axelsson K, Larsson LG, Agren G, Holmstrom B, *et al.* Postoperative pain relief using intermittent injections of 0.5% ropivacaine through a catheter after laparoscopic cholecystectomy. Anesth Analg 2002;95:450-6.
11. Trikoupi A, Papavramidis T, Kyurdzhieva E, Kesisoglou I, Vasilakos D. Intraperitoneal administration of ropivacaine during laparoscopic cholecystectomy. Eur J Anaesthesiol 2010;27:222.
12. Kucuk C, Kadiogullari N, Canoler O, Savli S. A placebo-controlled comparison of bupivacaine and ropivacaine instillation for preventing postoperative pain after laparoscopic cholecystectomy. Surg Today 2007;37:396-400.
13. Memedov C, Mentes O, Simsek A, Kece C, Yagci G, Harlak A, *et al.* Comparison of analgesic effects of intraperitoneal lornoxicam and ropivacaine administration in laparoscopic cholecystectomy. Trak Univ Tip Fak Derg 2010;27:142-9.
14. Pavlidis TE, Atmatzidis KS, Papaziogas BT, Makris JG, Lazaridis CN, Papaziogas TB. The effect of preincisional periportal infiltration with ropivacaine in pain relief after laparoscopic procedures: A prospective, randomized controlled trial. JSLS 2003;7:305-10.
15. Park YH, Kang H, Woo YC, Park SG, Baek CW, Jung YH, *et al.* The effect of intraperitoneal ropivacaine on pain after laparoscopic colectomy: A prospective randomized controlled trial. J Surg Res 2011;171:94-100.
16. Bisgaard T, Klarskov B, Kristiansen VB, Callesen T, Schulze S, Kelhet H, *et al.* Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: A randomized, double-blinded, placebo-controlled study. Anesth Analg 1999;89:1017.
17. Scheinin B, Kellokumpu I, Lindgren L, Haglund C, Rosenberg PH. Effect of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. Acta Anaesthesiol Scand 1995;39:195-8.
18. Sarli L, Costi R, Sansebastiano G, Trivelli M, Roncoroni L. Prospective randomized trial of low pressure pneumoperitoneum for the reduction of shoulder tip pain following laparoscopy. Br J Surg 2000;87:1161-5.
19. Jairath A, Gupta S, Singh K, Katyal S. Can intraperitoneal tramadol decrease pain in patients undergoing laparoscopic cholecystectomy in the postoperative period? A randomized controlled trial. World J Laparosc Surg 2016;9:5-8.
20. Golubovic S, Golubovic V, Cindric-Stancin M, Tokmadzic VS. Intraperitoneal analgesia for laparoscopic cholecystectomy: Bupivacaine versus bupivacaine with tramadol. Coll Antropol 2009;33:299-302.
21. Kayani M, Azad A. Maximum recommended dose of ropivacaine. Br J Anaesth 2013;110:482.