European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

Pre and Post Incisional Local Infiltration of the Levobupivacaine in Conventional Laparoscopic Cholecystectomy

[1]Naresh Kumar, [2]Shiv Kumar Bunkar, [3]Dinesh Kumar Sharma, [4]Hari Om Dhaker

[1,3,4]Resident, [2]Senior Professor and Unit Head, Department of General Surgery, JLN Medical College, Ajmer, Rajasthan, India

Correspondence:
Hari Om Dhaker
Resident, Department of General Surgery, JLN Medical College, Ajmer, Rajasthan, India
Email: hariomdhaker@gmail.com

ABSTRACT

Background: Laparoscopic cholecystectomy (LC) has become the gold standard for treatment of benign Gall Bladder disease. Pain after laparoscopic surgery though primarily visceral, often affecting the sub diaphragmatic region and often referred to the right shoulder region, also has a parietal component which occurs at the trocar site. The present study was planned to evaluate the effect of combined port site levobupivacaine administration before and after surgery for patients who underwent Laparoscopic cholecystectomy.

Material & Methods: This was a hospital based prospective randomized double blind comparative study done on 100 patients undergoing elective laparoscopic cholecystectomy surgery at Jawahar Lal Nehru Hospital, Ajmer, after approval from ethical committee. The study population were randomly divided into two groups A (Preincisional) and B (Post incisional) with 50 patients in each group using computer generated tables of random numbers. The primary outcome variable was to compare pain (visual analogue scale [VAS]) score. The intensity of post-operative pain was recorded for all the patients using VAS score at 3, 6, 12, 24 h after surgery (mean of all VAS scores).

Results: Our study showed that mean age of patients in group A was 43.20 years and 41.16 years in group B, which was statistical non-significant (P=0.435). There was significant difference in the mean VAS scores between the two groups up to 12th hour postoperatively. There was statistically lower VAS score in group A as compared to group B postoperatively up to 12 hour at 24th postoperative hour there was no significant difference in VAS score in both groups. The mean duration of analgesia was 164.94 ± 27.37 min in group A with a range of 95 to 210 min., while in group B, the mean duration of analgesia was 121.42 ± 14.81 min. with a range of 85 to 145 min, which was statistically longer in Group A as compared to Group B, (p value < 0.0001). Mean number of doses required in group A was 1.70 ± 0.46 and in group B was 2.38 ± 0.49, which was statistically higher in group B (p value <0.0001). In group A total amount of tramadol required in 24 hours was 170.00 ± 46.29 mg in comparison to group B where it was 238.00 ± 49.03 mg (p value <0.0001).

Conclusion: We concluded thatlevobupivacaine can be safely used as local anesthetic infiltration for postoperative pain relief following laparoscopic cholecystectomy surgery.

Keywords: Levobupivacaine, Laparoscopic cholecystectomy, VAS score, Pain

INTRODUCTION

Pain is defined by the international association for study of pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage''.[1]

Laparoscopic cholecystectomy (LC) has become the gold standard for treatment of benign Gall Bladder disease. Though Laparoscopy Surgery has a number of advantages over conventional open surgery, it is not a completely pain free procedure. Pain relief after the cholecystectomy either open or laparoscopic remains a cause of concern. After open cholecystectomy pain is usually because of large incision of surgery, and is of a parietal type. Pain after laparoscopic surgery though primarily visceral, often affecting the sub diaphragmatic region and often referred to the right shoulder region, also has a parietal component which occurs at the trocar site.

Many factors such as humidity and temperature of gas, pressure of pneumo-peritoneum during surgery, residual intra-peritoneal gas at the end of surgery, duration of surgery and length of trocar incision, trauma caused by cholecystectomy itself, individual factors and socio-cultural conditions play an important role in the causation of pain.

Post operative (PO) pain in turn affects post operative morbidity, hospital stay, increased financial burden on the patient or the state due to increased duration of hospitalization and inability of the patient to return to his/her job in time. A number of studies have been done till date to try to assess the effectiveness of different measures to alleviate the postoperative pain after laparoscopic cholecystectomy.[1-15] postoperative pain management has an important role in preventing the postoperative morbidly and its consequences. Pain management has not been standardized at most medical centers in India and abroad and this is reflected in the number of different pain studies after laparoscopic cholecystectomy available in literature.[1-15]

Till date many different methods have been used with conflicting rates of success, to diminish the intensity of postoperative pain after laparoscopic cholecystectomy.[1-9] They include low pressure pneumo-peritoneum, gasless technique of laparoscopic cholecystectomy, use of warm carbon dioxide, peritoneal wash with saline solution, strict surgical technique, perfect haemostasis, trocar site infiltration of anaesthetic drugs, variable analgesic effects of periportal infiltration of local anesthetics[4], infiltration of the periportal parietal peritoneum[3,5], intraperitoneal spraying above the gallbladder[7,8,14], infiltration into the gallbladder bed parenchyma[6-8], instillation into the subdiaphragmatic space[2,7-14], and into the subhepatic space covering the area of the hepato-duodenal ligament.[7,8,14,15]

Levobupivacaine is an isomerof racemic bupivacaine, equally effective as bupivacaine but is less toxic to the heart and central nervous system[13], Levobupivacaine is a long acting local anesthetic with a half-life of >3.5 hours and has been reported to provide pain control for an average of >6 hours.[16-18] The present study was planned to evaluate the effect of combined port site levobupivacaine administration before or after surgery for patients who underwent Laparoscopic cholecystectomy.

MATERIALS& METHODS

This was a hospital based prospective randomized double blind comparative study done on 100 patients undergoing elective laparoscopic cholecystectomy surgery at Jawahar Lal Nehru Hospital, Ajmer, after approval from ethical committee. 100 eligible gall bladder disease patients needed laparoscopic cholecystectomy surgery were randomly allocated in 2 groups using computerized random number table. The anaesthetist who gave local infiltration was different from the anaesthetist who recorded all the observations.

The study population were randomly divided into two groups **A**(Preincisional) and **B** (Post incisional) with 50 patients in each group using computer generated tables of random

numbers. A person who had not participated in the study kept the computer-generated table of random numbers and prepared medications in syringes.

- **GROUP A (n=50)** – was given preincisional infiltration of levobupivacaine at muscular fascia.
- **GROUP B (n=50)** – was given postincisional infiltration of levobupivacaine at muscular fascia

INCLUSION CRITERIA

- Patients with age >18
- ASA Grade I and II.
- Gall Bladder calculi or polyp with no evidence of acute cholecystitis at the time of surgery.

EXCLUSION CRITERIA

- Patient with known allergy to the study drugs.
- Age < 18 years
- ASA Grade more than 2 (American Society of Anaesthesiology)
- Pregnancy
- Acute Cholecystitis
- Choledocholithiasis
- Conversion of LC to open cholecystectomy.

ANAESTHESIA TECHNIQUE

Thorough preoperative evaluation was done according to standard protocol and relevant demographic data was collected from all the patients before surgery. On arrival to operating room, an 18-gauge intravenous (IV) catheter was inserted and monitoring of electrocardiography, non-invasive blood pressure, oxygen saturation (SpO2) was started and baseline values were recorded.

All patients were premedicated with injection fentanyl 1mg/kg and injection glycopyrrolate 0.004 mg/kg. Pre-oxygenation with 100% oxygen (O2) was done for 3 min. General anaesthesia was induced with injection propofol 2.0 mg/kg followed by succinyl choline 2 mg/kg to facilitate orotracheal intubation. The trachea was intubated with a cuffed orotracheal tube of appropriate size. Anaesthesia was maintained with oxygen and isoflurane. Intermittent boluses of vecuronium bromide were used to achieve muscle relaxation. Minute ventilation was adjusted to maintain normocapnia (end-tidal carbon-dioxide [EtCO2] between 34 and 38 mm Hg) and EtCO2 was monitored.

Study drugs were prepared by an anaesthesiologist not involved in the study. Anaesthesiologist who observed the patient was unaware of the study group until the end of the study.

The patients will be randomly assigned to receive pre incision (pre I) or post incision (post I) local anaesthetic infiltration. In the pre I group local anaesthetic will be administered prior skin incision. Total dose of local anaesthetic will 100 mg in 10 ml of physiologic solution; the total volume will be divided proportionally according to the length of the skin incision (3 ml for the 10 mm trocars and 2 ml for the 5 mm trocars). In the post I group local anaesthetic will be instilled at the end of surgery after trocar removal. The total volume of infiltrated solution in the two groups will be 10 ml divided proportionally according to the length of the skin incisions (3 ml for 10 mm incisions and 2 ml for 5 mm).

The neuro-muscular blockade was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.008 mg/kg and trachea was extubated, and the patient shifted to post-

anaesthesia care unit (PACU). All patients were made to stay in PACU for 2 h after the end of surgery.

Intraoperative hypotension/hypertension was defined as fall/rise in systolic blood pressure of >20% from the baseline values and bradycardia/tachycardia defined as fall/rise in pulse rate of >20% from the baseline values. Haemodynamic fluctuations were to be managed accordingly.

The primary outcome variable was to compare pain (visual analogue scale [VAS]) score. The intensity of post-operative pain was recorded for all the patients using VAS score at 3, 6, 12, 24 h after surgery and over all VAS score (mean of all VAS scores). All the study patients were instructed about the use of the VAS score before induction of anaesthesia (VAS score 0, no pain, VAS score 10, worst possible pain). Patients who reported VAS 3 or ≥3 will be given injection tramadol 100 mg intravenously as rescue analgesia.

Patients were also observed for post-operative nausea and vomiting. Patients who had complain of nausea or vomiting was given injection ondansetron 4 mg IV.

Time to the first request of analgesia (considering the extubation as time 0), total dose of analgesia and adverse or side effects over 24 h postoperatively were noted.

RESULTS

Our study showed that mean age of patients in group A was 43.20 years and 41.16 years in group B, which was statistical non-significant (P=0.435). In Group A there were 13 (26.00%) male and 37 (74.00%) female patients whereas in Group B there was 11 (22.00%) male and 39 (78.00%) female patients, which was not significant (P=0.815). Both groups were comparable according to ASA physical status, weight and height (p value = 0.833, P>0.05 & P>0.05 respectively) (table 1).

Table 1: Characteristics of patients in between groups

Characteristics	Group A (N=50)	Group B (N=50)	P-value
AGE GROUP (YRS)			
20 – 30	12 (24%	11 (22%)	>0.05
31 – 40	14 (28%)	17 (34%)	
41 – 50	8 (16%)	9 (18%)	
51 – 60	10 (20%)	8 (16%)	
61 – 70	6 (12%)	5 (10%)	
Mean ± SD	43.20 ± 13.56	41.16 ± 12.46	0.435 (NS)
GENDER			
Male	13 (26%)	11 (22%)	0.815
Female	37 (74%)	39 (78%)	
ASA STATUS			
I	32 (64%)	34 (68%)	0.833
II	18 (36%)	16 (32%)	
WEIGHT (KG)			
Mean ± SD	75.64 ± 12.98	74.42 ± 10.12	0.601
HEIGHT (FT)			
Mean ± SD	5.60 ± 0.27	5.54 ± 0.29	0.287

The mean duration of surgery in group A was 58.70 ± 7.61 minutes as compared to group B in which it was 60.80 ± 8.23 minutes. The difference in mean duration of surgery was not statistically significant (p = 0.188, NS) (table 2).

Table 2: Comparison of various parameters in between groups

Statistic	Group A (N=50)	Group B (N=50)	P-value
Mean duration of surgery (min.)	58.70±7.61	60.80±8.23	0.188
Mean total duration of analgesia (min.)	164.94±27.37	121.42±14.81	<0.0001 (S)
Mean no. of doses required	1.70 ± 0.46	2.38 ± 0.49	<0.0001 (S)
Mean Amount of recue analgesic used in 24 hours (mg)	170.0±46.29	238.0±49.3	<0.0001 (S)

The mean duration of analgesia was 164.94 ± 27.37 min in group A with a range of 95 to 210 min., while in group B, the mean duration of analgesia was 121.42 ± 14.81 min. with a range of 85 to 145 min, which was statistically longer in Group A as compared to Group B, (p value < 0.0001). Mean number of doses required in group A was 1.70 ± 0.46 and in group B was 2.38 ± 0.49, which was statistically higher in group B (p value <0.0001) (table 2).

In group A total amount of tramadol required in 24 hours was 170.00 ± 46.29 mg in comparison to group B where it was 238.00 ± 49.03 mg (p value <0.0001) (table 2).

There was significant difference in the mean VAS scores between the two groups up to 12th hour postoperatively. There was statistically lower VAS score in group A as compared to group B postoperatively up to 12 hour at 24th postoperative hour there was no significant difference in VAS score in both groups (table 3).

Table 3: Comparison of Post - Operative Mean Vas Score between Study Groups

Time	Group A		Group B		Result (p value)
	Mean	SD	Mean	SD	
3 h	1.38	0.53	1.76	0.98	0.018 (S)
6 h	2.42	0.91	2.86	0.35	0.0019(S)
12 h	2.28	1.03	2.82	0.39	0.0008(S)
24 h	1.64	0.88	1.68	1.13	0.844 (NS)

DISCUSSION

Post-operative pain associated with laparoscopic cholecystectomy is less intense and lasts a shorter time than that seen with open surgery. As there is less functional impairment and pain, patients can be discharged and return to their normal daily activities earlier.[4,5] Pain reaches a peak within the first few hours following the operation but diminishes during the next 2 or 3days.[4.6] Some patients experience a rather painful early post-operative period. Dynamic conditions also such as coughing and mobilization particularly aggravate the pain.

Although Minimal Invasive Surgery is characterized by reduced pain, it is not painless. In a study done by Fredman B et al[1]thirteen patients undergoing Laparoscopic cholecystectomy suffer considerable pain on the day of surgery due to residual pneumoperitoneum, though frequently requires narcotic analgesics.

Controversy exists about the principal source of pain after laparoscopic procedure. Some clinicians mentioned that placement of trocars through the abdominal wall is the primary source; whereas others believe that most pain arises from intra peritoneal dissection and insufflations of CO_2resulting in distension of abdominal wall and prolonged elevation of diaphragm[2]. Early pain after laparoscopic cholecystectomy is a complex process and includes different pain components secondary to different pain mechanisms[16,19], such as surgical trauma to the abdominal wall, intra abdominal trauma secondary to the gall bladder removal, abdominal distention, pneumoperitoneum using carbondioxide etc. Therefore, pain should be treated multimodally[3].

A lot of authors keep into focus the different mechanism of pain after laparoscopic cholecystectomy: in this kind of procedures pain can be divided into three component: visceral, parietal and shoulder tip pain, with different intensity and time courses; visceral and

parietal pain seem to be the most important during the first 24 to 48 h after surgery: in fact, in this period the most common location of the pain is the right upper quadrant and the trocar sites and, at the end, the right shoulder.[7,8] The main sources of pain are: incision sites within the abdominal wall; the pneumoperitoneum in association with both local (peritoneal and diaphragmatic stretching, acidosis and ischemia) and systemic (hypercarbia causing sympathetic nervous system excitation with an amplification of local tissue inflammatory response) changes; and the ‘‘post cholecystectomy wound’’ within the liver (visceral pain). Total abdominal pain after laparoscopic cholecystectomy covers all these aspects: the largest component (50 70%) arising from incisional sites, followed by the pneumoperitoneum (20-30%) and ‘‘cholecystectomy wound’’ (10-20%).[8,9]

Although *Verma et al*[7] say that pain after laparoscopic cholecystectomy is above all a visceral pain, several studies indicates that the parietal pain plays an important role to determinate post-operative pain such as visceral one. Study done by *Cantore F et al*[8] and a lot of others studies, showed the important role of local intrafascial anaesthetic instillation in post-operative pain control reduction.[4,11,12]from these studies it is proved that parietal or somatic pain is important as or more than visceral pain in the first post-operative 24 - 48 hours, so the benefit of local anaesthetics is clear.

However, no consensus has been reached concerning effective post-operative pain mechanism and relief in patient undergoing laparoscopic cholecystectomy, although a number of studies were conducted in an effort to reduce post-operative pain after this kind of surgery.

A lot of study took in exams other local anaesthetics such as ropivacaine or bupivacaine without a univocal results; only few studies analysed the effects of levobupivacaine; according to these studies, levobupivacaine has a better pain reducing effect than ropivacaine and is more potent than bupivacaine; in fact levobupivacaine produces more vasoconstriction at low concentration and has a longer duration of action.[13.14]In study done by *Cantore F et al*[8] they find a significant difference intravenous dose of Ketorolac between the two groups; in the pre I group the consumption of analgesic drug was inferior than in post I group and pain was less intense during the first 24-48 h at rest (VAS) and at cough (IVAS). It is due to a more efficacy of levobupivacaine to control pain and nociception in the post-operative period; and may be the anaesthetic effect of this drug could begin just after the incision of the skin so its effect could conduce to a less inflammatory response of the organism in the incision sites. In this way we could explain the more efficacy of pre-emptive administration of the drug into the trocar sites.

Many researchers have suggested that the combination of somato visceral local anaesthetic treatment reduces incisional, intra-abdominal and shoulder pain in laparoscopic cholecystectomy. These local agents induce antinociception by acting on the nerve membranes. They reversibly decrease the rate of depolarisation and repolarisation of excitable membranes (like nociceptors).[4,6] There are different routes to administrate the local anaesthetic drug; some researchers have shown that local parietal anaesthesia is effective in controlling post-operative pain,[20-22]while others have shown that it is not effective.[23]

In a study by Megahed HA et al[1]used a combination of trocar sites and intraperitoneal local anaesthesia (0.25%levobupivacaine), the administration of local anaesthesia was before surgery in one third of cases, after surgery in the second third of cases, the last third of cases was control cases, all patients received the combined anaesthesia either before or after surgery showed reduced postoperative pain and reduced analgesic requirement, however, before surgery administration of combined anaesthesia was advantageous for less intraoperative fentanyl consumption and after surgery administration of combined anaesthesia was advantageous for less postoperative rescue analgesic requirement.

Papadima A et al[17] reported that repeated intraperitoneal instillation of 10 ml of levobupivacaine 0.5% after cholecystectomy results in a lesser visual analog scale score at rest and at movement and a significantly lesser fentanyl consumption in the recovery room.
Studies done by Cantore F et al (2008)[8], Hasaniya NW et al (2001)[3], Papagiannopoulou P et al (2003)[2]and Megahed HA et al (2015)[1] all were also showed the insignificant difference in demographic profile, duration of surgery and preoperative haemodynamic parameters.
In our study we have usedVAS score as a method of pain assessment in patients postoperatively.There was significant difference in the mean VAS scores between the two groups up to 12thhour postoperatively. There was statistically lower VAS score in Group A as compared to Group B postoperatively up to 12 hrs. at 24th postoperative hour there was no significant difference in VAS score in both groups.Results of our study were coinciding with the study conducted by Cantore F et al (2008)[8], Hasaniya NW et al (2001)[3], Papagiannopoulou P et al (2003)[2], Ekinci M et al (2017)[24] and Megahed HA et al (2015)[1]. Hence, we found that the preincisional local infiltration was better in comparison to postincisional in respect to postoperative pain management.
The increase in duration of analgesia after local port site infiltration and intraperitoneal infiltration with levobupivacaine was coincides with study by Cantore F et al (2008)[8], Hasaniya NW et al (2001)[3], Papagiannopoulou P et al (2003)[2], Ekinci M et al (2017)[24] and Megahed HA et al (2015)[1]who found that mean duration of analgesia was significantly higher in pre-incisional Group as compared to post-incisional or intraperitoneal group.Hence, we found that the preincisional levobupivacaine infiltration decreases demand of rescue analgesicas compared to post incisional levobupivacaine infiltration.
In our study, fever, nausea and vomiting were observed more in Group B than Group A but finding are statistically insignificant. None of the patients had hypotension, bradycardia, pruritus, urinary retention or respiratory depression.

CONCLUSION

We concluded that Local anesthetic infiltration is a safe, practical method of pain management following laparoscopic cholecystectomy surgery. Preincisional wound infiltration gives better results in comparison to post incisional wound infiltration. Levobupivacaine can be safely use as local anesthetic infiltration for postoperative pain relief following laparoscopic cholecystectomy surgery.

REFERENCES

1. Megahed HA, Mahmoud IF. Effect of port sites and intraperitoneal levobupivacaine infiltration before or after laparoscopic cholecystectomy on postoperative pain. AL-AZHAR ASSIUT MEDICAL JOURNAL. 2015 Apr;13(2).
2. Papagiannopoulou P, Argiriadou H, Georgiou M, Papaziogas B, Sfyra E, Kanakoudis F. Preincisional local infiltration of levobupivacaine vs ropivacaine for pain control after laparoscopic cholecystectomy. Surgical Endoscopy and Other Interventional Techniques. 2003 Dec;17(12):1961-4.
3. Hasaniya NW, Zayed FF, Faiz H, Severino R. Preinsertion local anesthesia at the trocar site improves perioperative pain and decreases cost of laparoscopic cholecystectomy. Surg Endosc2001;15:962–4.
4. Aps C, Reynolds FE. An intradermal study of the local anaesthetic and vascular effects of the isomers of bupivacaine. British journal of clinical pharmacology. 1978 Jul;6(1):63-8.
5. Bay-Nielsen M, Klarskov B, Bech K, Andersen J, Kehlet H. Levobupivacaine vs bupivacaine as infiltration anaesthesia in inguinal herniorrhaphy. British journal of anaesthesia. 1999 Feb 1;82(2):280-2.

6. Gristwood RW. Cardiac and CNS toxicity of levobupivacaine. Drug Safety. 2002 Mar;25(3):153-63.
7. Bisgaard T, Klarskov B, Kristiansen VB, Callesen T, Schulze S, Kehlet H, Rosenberg J. Multi-regional local anesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. Anesthesia & Analgesia. 1999 Oct 1;89(4):1017.
8. Cantore F, Boni L, Di Giuseppe M, Giavarini L, Rovera F, Dionigi G. Pre-incision local infiltration with levobupivacaine reduces pain and analgesic consumption after laparoscopic cholecystectomy: a new device for day-case procedure. International Journal of Surgery. 2008 Jan 1;6:S89-92.
9. Alam MS, Hoque HW, Saifullah M, Ali MO. Port site and intraperitoneal infiltration of local anesthetics in reduction of postoperative pain after laparoscopic cholecystectomy. Medicine today. 2010;22(1):24-8.
10. Raetzell M, Maier C, Schroder D, Wulf H. Intraperitoneal application of bupivacaine during laparoscopic cholecystectomy--risk or benefit?. Anesthesia & Analgesia. 1995 Nov 1;81(5):967-72.
11. Joris J, Thiry E, Paris P, Weerts J, Lamy M. Pain after laparoscopic cholecystectomy: characteristics and effect of intraperitoneal bupivacaine. Anesthesia & Analgesia. 1995 Aug 1;81(2):379-84.
12. Johansson BO, Glise H, Hallerbäck B, Dalman P, Kristoffersson A. Preoperative local infiltration with ropivacaine for postoperative pain relief after cholecystectomy. Anesthesia and analgesia. 1994 Feb 1;78(2):210-4.
13. Johansson B, Hallerbäck B, Stubberöd A, Janbu T, Edwin B, Glise H, Solhaug JH. Preoperative local infiltration with ropivacaine for postoperative pain relief after inguinal hernia repair. A randomised controlled trial. The European journal of surgery= Acta chirurgica. 1997 May 1;163(5):371-8.
14. El-Labban GM, Hokkam EN, El-Labban MA, Morsy K, Saadl S, Heissam KS. Intraincisional vs intraperitoneal infiltration of local anaesthetic for controlling early post-laparoscopic cholecystectomy pain. Journal of minimal access surgery. 2011 Jul;7(3):173.
15. Louizos AA, Hadzilia SJ, Leandros E, Kouroukli IK, Georgiou LG, Bramis JP. Postoperative pain relief after laparoscopic cholecystectomy: a placebo-controlled double-blind randomized trial of preincisional infiltration and intraperitoneal instillation of levobupivacaine 0.25%. Surgical Endoscopy And Other Interventional Techniques. 2005 Nov;19(11):1503-6.
16. Barczyński M, Konturek A, Herman RM. Superiority of preemptive analgesia with intraperitoneal instillation of bupivacaine before rather than after the creation of pneumoperitoneum for laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. Surgical Endoscopy And Other Interventional Techniques. 2006 Jul;20(7):1088-93.
17. Papadima A, Lagoudianakis EE, Antonakis P, Filis K, Makri I, Markogiannakis H, Katergiannakis V, Manouras A. Repeated intraperitoneal instillation of levobupivacaine for the management of pain after laparoscopic cholecystectomy. Surgery. 2009 Sep 1;146(3):475-82.
18. Alexander DJ, Ngoi SS, Lee L, So J, Mak K, Chan S, Goh PM. Randomized trial of periportal peritoneal bupivacaine for pain relief after laparoscopic cholecystectomy. Journal of British Surgery. 1996 Sep;83(9):1223-5.
19. Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. Anesthesia & Analgesia. 2006 Sep 1;103(3):682-8.

20. Gupta A, Thörn SE, Axelsson K, Larsson LG, Ågren G, Holmström B, Rawal N. Postoperative pain relief using intermittent injections of 0.5% ropivacaine through a catheter after laparoscopic cholecystectomy. Anesthesia & Analgesia. 2002 Aug 1;95(2):450-6.
21. Bourget JL, Clark J, Joy N. Comparing preincisional with postincisional bupivacaine infiltration in the management of postoperative pain. Archives of surgery. 1997 Jul 1;132(7):766-9.
22. Turner GA, Chalkiadis G. Comparison of preoperative with postoperative lignocaine infiltration on postoperative analgesic requirements. BJA: British Journal of Anaesthesia. 1994 May 1;72(5):541-3.
23. Lee IO, Kim SH, Kong MH, Lee MK, Kim NS, Choi YS, Lim SH. Pain after laparoscopic cholecystectomy: the effect and timing of incisional and intraperitoneal bupivacaine. Canadian journal of anesthesia. 2001 Jun;48(6):545-50.
24. Ekinci M, Golboyu B, Yeksan A, Dulgeroglu O, Aksun M, Baysal P. Comparison of preincisional and postincisional 0.25% levobupivacaine infiltration in thyroid surgery. JOURNAL OF CLINICAL AND ANALYTICAL MEDICINE. 2017;8(1).