ORIGINAL ARTICLE

INTRA-PERITONEAL BUPIVACAINE INSTILLATION SIGNIFICANTLY REDUCES PAIN FOLLOWING LAPAROSCOPIC CHOLECYSTECTOMY

Ali Mohammad Khatri[1] *,Aruna P Dawani*[1] *,Darayus Percy Gazder*[1]*, Anees Hussain Jaffery*[1]*, Wajahat Hussain Wasty*[1]
[1] *Department of Surgery, Ziauddin University, Clifton Karachi.*

ABSTRACT

Background: Early pain after laparoscopic cholecystectomy is a process which includes different pain components; laparoscopic cholecystectomy is characterized by a short hospital stay, hence, pain control on the day of surgery is increasingly important. This study was designed to observe the analgesic effect of intraperitoneal bupivacaine instillation in early post-operative period following laparoscopic cholecystectomy.

Methods: In this Double-blind Randomized clinical trial, 100 participants were selected. These were divided in two groups: Group-1 received 20 ml of 0.25% bupivacaine solution which was instilled in the sub diaphragmatic, hepatic spaces (10ml at each site) at the end of the operation. Group 2 (Placebo) was instilled with 20ml isotonic saline (0.9%) in a similar manner. Post-operative pain free intervals and duration was observed at the time of analgesia administration for 10 hours.

Results: The mean time of first complaint of pain in group-1 was 5.14 ± 2.89 hours while mean time in group-2 was 1.80 ± 2.01 hours (p- value 0.001). The mean intensity of pain on VAS over 10 hours was higher in the placebo group (mean 6.42) compared to the Bupivacaine group (mean 3.46). All patients, 100%, in placebo group required rescue analgesia within 6 hours after surgery while only 68% in bupivacaine group required analgesia during the same postoperative period.

Conclusion: Patients instilled with intraperitoneal bupivacaine had decreased intensity of pain. Secondly, following surgery complain of pain in Bupivacaine group was after a significant lapse of time compared to placebo group.

KEYWORDS: Pain; Bupivacaine; Cholecystectomy;

Corresponding Author
Dr Ali Mohammad Khatri
Department of Surgery,
Ziauddin University.
Email: khatriali1@hotmail.com

INTRODUCTION

Laparoscopic cholecystectomy (LC) is now the standard technique for gall bladder removal that is mainly due to gall stones.[1] This procedure has significantly reduced the pain compared to caused by open choleystectomy.[2] Although minimal invasive surgery is characterized by reduced pain, yet it is not painless, and controversy still exists about the principle source of pain after laparoscopic procedure.[3]

Pain can prolong hospital stay and lead to increased morbidity; two studies were done to examine the effects of intraperitoneal bupivacaine on length of hospital stay. One study reported that the use of intraperitoneal bupivacaine did not affect duration of hospitalization[4], while the other study reported a significant increase in the proportion of patients who were able to be discharged on the same day of surgery.[5] There were other studies which also assessed the effect of intra operative instillation of analgesia on the respiratory function as

an outcome measure.[6, 7]

Pain that occurs in the early post operative period after Laparoscopic Cholecystectomy, is a process which includes different components secondary to different pain mechanisms, such as peritoneal stretching, diaphragmatic irritation and to a lesser extent abdominal puncture/incisions. The prolonged presence of shoulder tip pain suggests excitation of phrenic nerve.[8] However, the clinical value of infiltration of wound with local anaesthetic, their intraperitoneal instillation, as well as the choice and dosages of LA still remain controversial. Pain may occur in the upper or lower abdomen, shoulder and back. It may be transient or persistent for up to 3-days after laparoscopic cholecystectomy.

Bupivacaine hydrochloride belongs to amide group of local anesthetics and has longer duration of action lasting up to 10 hours. In Pakistan bupivacaine is available in 0.5 and 0.75% strengths. It is used for local infiltration of the wound, nerve block, extradural and spinal block and for intraperitoneal instillation.[9]

One study done in Iraq in 2013 showed that wound infiltration of bupivacaine significantly reduced abdominal pain in the initial postoperative period after LC, and reduced the requirement for analgesia, but intraperitoneal sub-diaphragmatic instillation of a local anesthetic was not significantly effective in reducing shoulder pain, in the early postoperative period.[10] In another study instillation of intraperitoneal bupivacaine with magnesium sulphate showed better pain relief than bupivacaine alone.[11]

A study conducted in Estonia with sample size of 80 patients showed that intra-incisional infiltration of bupivacaine plus phenylephrine significantly reduced post-operative pain while sub diaphragmatic infiltration of diluted lidocaine was not effective in managing overall pain and shoulder pain after laparoscopic cholecytectomy.[12] Previous studies showed diverse and controversial results regarding the effects of intraperitoneal bupivacaine instillation in reducing pain after laparoscopic cholecystectomy. This study was undertaken to evaluate the efficacy of intraperitoneal instillation of bupivacaine in controlling postoperative pain in patients undergoing laparoscopic cholecystectomy.

METHODS

The present study was conducted as a randomized, double blind, controlled clinical trial among patients who underwent laparoscopic cholecystectomy at Dr Ziauddin Hospital Karachi, Department of General Surgery. After approval from the Ziauddin Hospital Ethics committee, a total of 100 patients, with gallstones and classified as American Society of Anesthesiologists I and II (ASA I and II) aging from 18 to 65 years, were recruited and scheduled for elective laparoscopic cholecystectomy under general anesthesia. A written informed consent was signed by all patients before participating in the study. Patients with known allergic reactions to local anesthetics were excluded from the study. Also, excluded were patients who underwent surgery for acute cholecystitis or if the operation had been converted to an open procedure, as well as patients with intra-operative complications or having a history of previous upper abdomen surgeries to avoid adhesions.

Double blinding technique was selected for sampling. Both participants and doctors were blinded, only the anaesthetist who was in charge knew about the solutions and chose the patients randomly by selecting patients using a draw with either of the techniques written on paper. The anaesthetist prepared the appropriate solution and handed over the solution to the surgeon. There was no way to differentiate Bupivacaine and placebo physically since equal amounts were instilled. All the patients were infiltrated with pre-incisional bupivacaine 0.5% in 10ml, as a standard. In Group-1, bupivacaine solution 20 ml of 0.25% was instilled in the sub diaphragmatic and sub hepatic space (10ml at each site) under direct vision at the conclusion of the operation. Group 2 was instilled with 20ml isotonic saline (0.9%) intraperitoneally in a similar manner.

Intraperitoneal instillation of 20 ml of 0.5% bupivacaine provides effective analgesia with plasma concentration below toxic levels (0.92-1.14 µg/ml). In this specific study less than half of this dose was used, hence toxicity was not a concern. Secondly, as it has an effect for about 6-8 hours the patients were monitored over a period of 10 hours. Later on, rescue analgesia was administered, which consisted of a single dose of Injection Toradol (Ketorolac) 30mg IV; it was administered when the patient complained of pain and asked for analgesia.

Data from the selected patients was documented in a pre-approved Performa. The Performa consisted of three parts; demography of patients that included co-morbids, the operative findings and the postoperative findings. Postoperative findings consisted of patient's vitals, when patients complained of pain the first time, the intensity of pain on Visual Analog Scale and the time at which rescue analgesia were administered over a 10 hour period. The visual analog scale [VAS] is a measure of pain intensity. It is a continuous scale comprised of a horizontal (called horizontal visual analogue scale) or, vertical (called vertical visual analog scale) usually 10cm or 100mm length [both gradations were used]. It is anchored by two verbal descriptors,

one for each symptom extreme. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 10). It is a valid and reliable tool for objective assessment of acute pain. Post-operative pain free interval and time at which analgesia was administered, was compared between both the groups for 10 hours.

Data was analyzed using Statistical analysis on SPSS version-23. All data was expressed as means ± standard deviation, with the exception of rescue analgesic treatment which was in percentage. Independent t-test was applied to compare the mean pain score in both groups. Stratification was done to see the effect of age, SBP, DBP, PR and RR on the outcome in both groups. Post-stratification t-test was applied. P-value ≤0.05 was taken as significant.

RESULTS

Mean age of the patients was 42.71 ±13.3 years. 73% of patients were female (Fig-1). In group-1, there were 16 males and 34 females whereas in group-2, 11 were males and 39 were females. The two groups were comparable for age, sex and postoperative vital signs. (Table-1)

It was found that intraperitoneal bupivacaine instillation reduces the intensity and duration of pain in comparison to placebo. The mean time of 1st complaint of pain in group-1 was 5.14 ± 2.89 hours while mean time in group-2 was 1.80±2.01 hours. On applying Independent sample T-test a significant difference was found between both the groups in the onset of 1st complaint of pain, p-value 0.001 at alpha 0.05. (Table-2)

The mean intensity of pain on VAS over 10 hours was higher in the placebo group (mean 6.42, which is rated as dreadful to horrible), compared to the Bupivacaine group (mean 3.46, which is rated as annoying to uncomfortable). On applying independent sample t-test a significant difference was found between both the groups in the VAS score, p-value 0.001 at alpha 0.05 (Table-2), (Figure 1).

Rescue analgesic consisted of a single dose of Injection Toradol (Ketorolac) intra-venous 30mg (maximum dose of 90mg per day), it was administered when the patient first asked for analgesia and the intensity was rated as dreadful to agonizing pain (From 6 to 10) on the Pain visual analogue scale. It was seen that all patients in placebo group had received rescue analgesia within six hours with a maximum of 22 patients requiring at two hours after the operation had ended. On the other hand rescue analgesia spanned over a time of 10 hours in the Bupivacaine group, at 2 hours postoperatively only five patients' required analgesia with a maximum of 13 patients at six hours and 6 patients at 10 hours. It was noted here that the need for analgesia post operatively in both groups did not show any gender discrepancy. We also noted that need for painkillers were similar in different socio economic and educated classes. This proves that Bupivacaine significantly reduces early postoperative pain and increases the duration at which analgesia is provided to the patient over initial 10 postoperative hours.

Table-1: Comparison of demographic data between the groups

	Mean Standard Deviation	
	Group-1(n=50)	Group-2(n=50)
Age (years)	42.2+/- 12.6	43.8+/-13.5
Gender (male/female)	16/34	11/39
Heart rate (beats/minute)	72.61 +/-10.8	73.2+/- 8.0
Respiratory rate(breaths/min)	13+/-2.0	14+/-1.8
Systolic/diastolic pressures(mm of Hg)	123.3+/-11.7 76.3+/-8.2	122.8+/-10.3 77.1+/-7.9

Table-2: Comparison of Visual Analogue Scale and Time Interval between Both Groups When Analgesia Was Required.

	Group	N	Mean ±SD	
Time of 1st c/o pain requiring analgesia.(in hours)	Group 1 (Bupivacaine)	50	5.14 ± 2.89	**p-value** 0.001
	Group 2 (Placebo)	50	1.80 ± 2.01	
VAS SCORE	Group 1 (Bupivacaine)	50	3.46 ± 2.25	**p-value** 0.001
	Group 2 (Placebo)	50	6.42 ± 2.45	

A significant difference between both the groups was seen at p-value 0.001 at alpha 0.05.

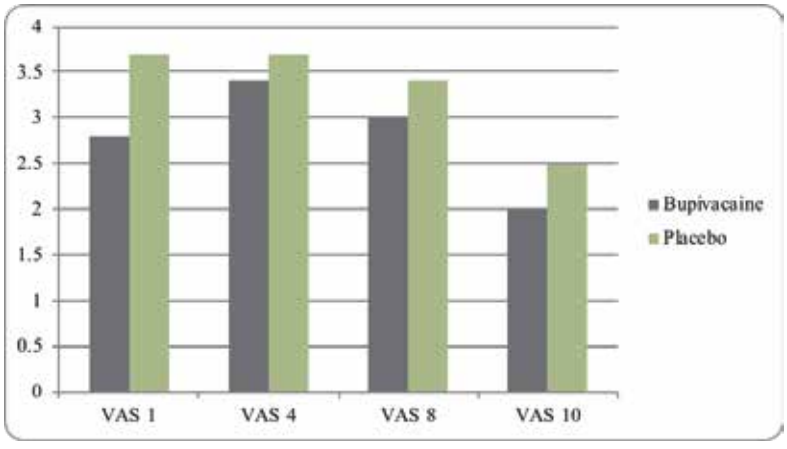

Figure-1: Comparison of Visual Analogue Scale (VAS) between both groups

DISCUSSION

Laparoscopic cholecystectomy results in better surgical outcome in terms of reduced postoperative pain, morbidity and duration of convalescence compared to open cholecystectomy.[13,14] Postoperative pain after laparoscopic cholecystectomy consists of three components; visceral, parietal and referred shoulder pain distinguishable from each other in the intensity, latency and duration.[15] Previous studies[16,17] suggest that predominant cause of pain is parietal but in contrast many other studies emphasized that in early convalescent period, major portion of pain is visceral in origin because compared to small incisions and limited trauma to the abdominal wall, the surgical manipulation and tissue destruction in visceral organs is much more.[18] It is therefore imperative that synergistic methods are applied to combat this pain.

When comparing the results of our study with that of published literature it was found that the age of the patients and gender showed a similar pattern to previously published research.[19] This is explainable by the factors which cause the primary disease of cholelithiasis and the demographic groups it commonly affects. Similarly, different authors internationally have shown a similar distribution for co-morbid disease which affect this specific group of patients who were included in our study.[20,21] This again is understandable as the age group and other determinants of the co-morbid problems have the same factors affecting the general population although regional variations due to genetic and cultural predisposition do occur.

Although not measured in our study it was seen in other studies that the hospital stay was decreased in the intervention group thus it was cost effective as well in the long run. This variable can be measured on the retrospective basis and can prove useful in determining admission and discharge times and hense the cost associated with these surgeries. Also this can in our local context see the availability of such procedures in the day care setting. [22]

In laparoscopic surgeries because of gas insufflations and raised intraperitoneal pressure, there is peritoneal inflammation and neuronal rupture with a linear relationship between abdominal compliance and resultant severity of postoperative pain.[23] Hence, we chose an intraperitoneal instillation as it blocks the visceral afferent signals and modifies visceral nociception. This has been an accepted phenomenon for open surgery for a long time. The local anesthetic agents provide anti-nociception by affecting nerve membrane associated proteins and by inhibiting the release and action of prostaglandins which stimulates the nociceptors and cause inflammation[24], intraperitoneal instillation of 0.25% bupivacaine provide effective analgesia. [25, 26]

In our study, mean Visual Analogue Score (VAS) score of the patients in group 1 with Bupivacaine was 3.46 ± 2.25 and mean VAS score of the patients in group 2 with placebo was 6.42 ± 2.45 (p-value 0.001). This was not only statistically significant but was seen that our results were comparable to Tehniyat et al[27] who did the same study in laparoscopic cholecystectomy and found less VAS score in study group patients. The measurement of this important variable shows a clear difference in the two groups. Thus, patients who were in the intervention group had less pain compared to others and less disturbance of other physiological parameters. In another study by Kim EY and others it was seen that bupivacaine is very effective in pain management. [28]

Despite the best intra-operative measures to control pain it was seen in both groups in previous studies by other authors and patients complained of pain during the post-operative period. This variable was considered important in our study and was measured and recorded for both groups. It was seen that the mean time of first complain of severe pain requiring rescue analgesia during the post-opera-

tive period was 3.47 ± 2.99 hours in the overall study population. These were found to be of significant clinical relevance in our study. This was similar to studies presented in the past.[29,30]Mean time of 1st complain of pain requiring analgesia in the intervention group was 5.14 ± 2.89 hours and mean time of first complain of pain requiring analgesia in placebo group was 1.80 ± 2.01 hours. (P-value-0.001), this is a statistically significant finding and in a clinical setting shows the need for pain relief planning for such procedures. In a trial by Jirantarat et al[29], both visual analogue scale and verbal rating scale were used to assess post-operative pain and analgesia requirements. They report no benefit of using intra-peritoneal bupivacaine for analgesic effects.

The duration of action of intraperitoneal bupivacaine has been found to vary in different studies. Various authors report results ranging from considerable pain reduction for 24-48 hours after surgery[30], to no significant pain reduction.[28, 29] Other authors detected a modest pain reduction that was detectable for only 2 hours after surgery[26,27] or up to 6-8 hours after surgery. This difference can explain the outcome of the various studies that have been quoted as well as the variation.

Another factor which was taken into account to see the difference in perception of severity of pain by the patients enrolled in the two groups was the need for rescue analgesia. Specific parameters were pre-determined for this management modality. Injection Ketorolac [30] mg intravenous was given when the patient complained of severe or agonizing pain during the post-operative period and asked for help in the form of painkiller; this was identified by patient as a VAS of between 6 to 10. The use of this modality was significantly much higher in the placebo group compared to the instillation group; the frequency being 12% in Group 1 compared to 67% in Group 2. Similar finding was seen in the study presented by Donatsky[30] in 2013 where the patients in the placebo group needed earlier intervention with rescue analgesia.

Action of local anesthetic, along with its absorption from the large surface area, could be an added mechanism of action accounting for this phenomenon. The outcome of intra-peritoneal instillation of bupivacaine injection in laparoscopic cholecystectomy in order to reduce postoperative pain and its intensity is significantly better and found effective in large number of cases, and this technique may be promoted for use in routine clinical practice.

CONCLUSION

The present study showed that intraperitoneal instillation of bupivacaine during laparoscopic cholecystectomy significantly reduces pain in the initial postoperative period. Comparison between the two groups show that the patients who received intraperitoneal bupivacaine had better control of pain during the initial postoperative period of ten hours duration. Not only the severity of pain was less but also the need of rescue analgesia in this group was further delayed for few hours after surgery. All patients in placebo group required rescue analgesia within 6 hours after surgery while only 68% required analgesia during the same postoperative period in bupivacaine group.

REFERENCES

1. Romero-Marcos JM, Carbonell-Aliaga MP, Muñoz-Pérez JM, Tejada-Gavela S, Sanchis-Cortés P, Cifuentes-Ródenas JA. Patient preference matters: cholecystectomy for uncomplicated gallbladder diseases should be performed by single port laparoscopy. International Surgery Journal. 2017;4(4):1327-34.
2. Rosenmüller MH, Nilsson E, Lindberg F, Åberg SO, Haapamäki MM. Costs and quality of life of small-incision open cholecystectomy and laparoscopic cholecystectomy-an expertise-based randomised controlled trial. BMC gastroenterology. 2017;17(1):48.
3. Anand LK, Sandhu M, Singh J, Mitra S. Evaluation of analgesic efficacy of pregabalin for postoperative pain relief after laparoscopic cholecystectomy: a double blind study. Anaesthesia, Pain & Intensive Care. 2017;21(2).
4. Khurana S, Garg K, Grewal A, Kaul TK, Bose A. A comparative study on postoperative pain relief in laparoscopic cholecystectomy: intraperitoneal bupivacaine versus combination of bupivacaine and buprenorphine. Anesth Essays Res 2016;10(I):23-8.11.
5. Chakravarty N, Singhai S, Shidhaye RV. Evaluation of intraperitoneal bupivacaine for postoperative analgesia in patients undergoing laparoscopic cholecystectomy: a prospective randomized trial. Anaesth Pain Intens Care 2014;18(4):361-6.
6. Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. Anesthesia & Analgesia. 2006 1;103(3):682-8.
7. Tyagi S. To Evaluate The Analgesic Efficacy Of Intraperitoneal Instillation Of Tramadol Versus Bupivacaine For Post Operative Pain Relief Following Laparoscopic Appendectomy, A Double Blind Randomized Control Trial, Hospital Based Study.2017.
8. Blichfeldt-Eckhardt MR, Ørding H, Andersen C, Licht PB, Toft P. Early visceral pain predicts chronic pain after laparoscopic cholecystectomy. PAIN. 2014;155(11):2400-7.

9.Wasim M, Shafqatullah S. Role Of Intraperitoneal Bupivacaine In Laparoscopic Cholecystectomy. The Official Journal of The International Hepato Pancreato Biliary Association. 2015;17:32-3.
10. Hasson S, Chalabi FA. Postoperative Pain Reduction with Bupivacaine Instillation After Laparoscopic Cholecystectomy. Iraqi Postgraduate Medical Journal. 2013;12(2).
11.Maharjan SK, Shrestha S. Intraperitoneal magnesium sulphate plus bupivacaine for pain relief after laparoscopic cholecystectomy. Journal of Kathmandu Medical College. 2012 18;1(1):21-5.
12. Loizides S, Gurusamy KS, Nagendran M, Rossi M, Guerrini GP, Davidson BR. Wound infiltration with local anaesthetic agents for laparoscopic cholecystectomy. The Cochrane Library. 2014.
13. Wills VL, Hunt DR. Pain after laparoscopic cholecystectomy. British Journal of surgery. 2000;87(3):273-84.
14. Pappas-Gogos G, Tsimogiannis KE, Zikos N, Nikas K, Manataki A, Tsimoyiannis EC. Preincisional and intraperitonealropivacaine plus normal saline infusion for postoperative pain relief after laparoscopic cholecystectomy: A randomized double-blind controlled trial. SurgEndosc. 2008;22:2036–45.
15. Papadima A, Lagoudianakis EE, Antonakis P, Filis K, Makri I, Markogiannakis H, et al. Repeated intraperitoneal instillation of levobupivacaine for the management of pain after laparoscopic cholecystectomy.Surgery. 2009;146:475–82.
16. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology. 2000;93:1345–9.
17. Kahokehr A, Sammour T, Soop M, Hill AG. Intraperitoneal local anaesthetic in abdominal surgery-A systematic review. ANZ J Surg. 2011;81:237–45.
18. 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 journal of anaesthesia. 2015;59(4):234.
19. Tobias JD. Pain management following laparoscopy: Can we do better? Saudi J Anaesth. 2013;7:3–4.
20. Schulte-Steinberg H, Weninger E, Jokisch D et al. – Intraperitoneal versus interpleural morphine or bupivacaine for pain after laparoscopic cholecystectomy. Anesthesiology, 1995; 82:634-640.
21. Liu SS, Hodgson PS. Local anaesthetics. In: Barash PG, Cullen BF, Stoelting RK, editors. Clinical Anaesthesia. 4th ed. Philadelphia: Lippicott Williams and Wilkins; 2001:449–69.
22. Khurana S, Garg K, Grewal A, Kaul TK, Bose A. A comparative study on postoperative pain relief in laparoscopic cholecystectomy: Intraperitoneal bupivacaine versus combination of bupivacaine and buprenorphine. Anesthesia, essays and researches. 2016;10(1):23.
23. Campbell JN, Michaelis AF, inventors; Centrexion Therapeutics Corporation, assignee. High concentration local anesthetic formulations. United States patent US 9,370,500. 2016
24. Feroci F, Kröning KC, Scatizzi M. Effectiveness for pain after laparoscopic cholecystectomy of 0.5% bupivacaine-soaked Tabotamp® placed in the gallbladder bed: a prospective, randomized, clinical trial. Surgical endoscopy. 2009;23(10):2214-20.
25. Mitra S, Khandelwal P, Roberts K, Kumar S, Vadivelu N. Pain relief in laparoscopic cholecystectomy—a review of the current options. Pain Practice. 2012 1;12(6):485-96.
26. Pandove PK, Arora N, Garg A, Pandove L, Kumar A. Intraperitoneal instillation of bupivacaine in gallbladder fossa and at trocar sites in reduction of postoperative pain after laparoscopic cholecystectomy: a prospective randomized controlled double blind trial. International Surgery Journal. 2017;4(4):1204-8.
27. Tehniyat W, Fahim M, Khatoon A, Khan JS, Khan MM, Hasan H. Effect of Injection Bupivacaine Instillation in Gall Bladder Fossa on Post-op Pain Relief after Laparoscopic Cholecystectomy. Journal of Rawalpindi Medical College (JRMC). 2014;18(2):230-3.
28. Kim EY, You YK, Kim DG, Hong TH. The Simple and Multidimensional Method of Pain Reduction After Laparoscopic Cholecystectomy: A Randomized Prospective Controlled Trial. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2017 ;27(3):229-33.
29. Jirantarat V, Rushatakukayanut W, Lert-akyamenee N et al. Analgesic effect of intraperitoneal instillation of bupivacaine for postoperative laparoscopic cholecystectomy. J Med AssocThai.Sep 2002;85:S897-903.
30. Donatsky AM, Bjerrum F, Gögenur I. Intraperitoneal instillation of saline and local anesthesia for prevention of shoulder pain after laparoscopic cholecystectomy: a systematic review. Surgical endoscopy. 2013 ;27(7):2283-92.