Journal of Pharmaceutical Research International

19(4): 1-7, 2017; Article no.JPRI.36222
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Postoperative Pain Relief Following Bupivacaine Injection in Sites & Intraperitoneal Spray of Laparoscopic Cholecystectomy

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2017/36222
Editor(s):
(1) Jongwha Chang, University of Texas, College of Pharmacy, USA.
Reviewers:
(1) Hüseyin Ulaş Pınar, Baskent University, Turkey.
(2) Derya Karasu, Health Sciences University, Bursa Yuksek Ihtisas Training and Education Hospital, Turkey.
(3) K. K. Mubarak, Kerala University of Health Sciences, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/21887

Original Research Article

Received 18th August 2017
Accepted 12th September 2017
Published 13th November 2017

ABSTRACT

Background: Postoperative pain management is an important issue to increase the quality of laparoscopic procedures. In this study the effects of Bupivacaine injection in ports of laparoscopic cholecystectomy and adjunction site of liver and gall bladder was determined on postoperative pain and opioid administration.

Materials and Methods: In this randomized clinical trial, 100 patients who underwent elective laparoscopic cholecystectomy between 2013 and 2015 were enrolled in the study. The patients were randomly assigned to receive either intra-peritoneal spray of 15 ml of bupivacaine 0.25% solution over gall bladder bed and infiltration of bupivacaine 0.25% in port 1 to 3 incisions or normal saline in the same manner. The visual analogue scale was used to assess post-operative pain. Also administered opioid dose and side effects were registered and compared between two groups.

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Results: In this study the pain levels of shoulder and ports sites were significantly less in Bupivacaine group compared to control group (P=0.001). Also the vomiting frequency was significantly lower in Bupivacaine group in first and sixth hours (P <0.05) but not after sixth hour (P > 0.05). Additionally the opioid use was significantly lower in intervention group (P < 0.05).
Conclusion: Bupivacaine injection in ports of laparoscopic cholecystectomy and adjunction site of liver and gall bladder is effective on postoperative pain and opioid consumption leading to less pain and lower opioid use.

Keywords: Intraperitoneal injection; bupivacaine; laparoscopic cholecystectomy; postoperative pain.

1. INTRODUCTION

Laparoscopic cholecystectomy has become the treatment of choice for benign gall bladder and biliary tree disorders [1]. Laparoscopic management of abdominal disorders have shown important advantages over conventional surgical methods [1,2]. In this regard, reduced hospital stay which leads to faster return to work is seen in laparoscopic interventions [1-3].

Post-laparoscopic surgery pain is commonly known to be a visceral pain which is due to the stretched intra-abdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity. This pain is considerably different from that of laparotomy which is mostly a parietal pain.

Although previous reports have demonstrated less post laparoscopic surgery pain compared to laparotomy [4,5] but the bothersome pain in abdominal and shoulder regions may be presented in 35-65% of patients reducing in 2-3 days [6,7].

The postoperative pain management is as important as the operation itself. An uncontrolled pain may result in complications such as atelectasia, hypoxia, pneumonia, deep venous thrombosis, tachycardia, hypertension, and occasionally myocardial ischemia [8]. Thus along with lower postoperative complications, pain management would lead to lower health costs, and shorter hospitalization period [8]. Accordingly, analgesics and opioids are the most prescribed medications for postoperative pain relief [1,2,9]. Currently, opioids are the main analgesic for postoperative pain management, but nausea, vomiting, itching, and urinary retention have developed concerns about wide spread application [10,11].

The post-laparoscopic surgery pain is multifactorial including somatic incisional pain, visceral intra-abdominal pain, and visceral shoulder pain [12,13]. In 17-41% of cases, overwhelming pain is the main cause of early readmission [2,3,9,14-21] and would result in longer convalescence period [13,15,16]. Sensory block, intraoperative analgesics use, intra-peritoneal anesthetic administration, and fluid therapy are some proposed therapeutic options [13,15,17,21-26]. In this study the effects of Bupivacaine injection in ports of laparoscopic cholecystectomy and adjunction site of liver and gallbladder was determined on postoperative pain and opioid consumption.

2. MATERIALS AND METHODS

This study was held as a double-blind randomized clinical trial on 100 patients referring to Shariati hospital, Tehran University of Medical Sciences, Tehran, Iran between 2013 and 2015. The institutional review board and the ethic committee of Tehran University of Medical Sciences approved the study protocol. Patients who were indicated to undergo elective laparoscopic cholecystectomy for acute or chronic cholecystitis and gall bladder stone were evaluated for eligibility. Patients with following criteria were excluded: Age over 70 or under 18 years old, opioid addiction (as any narcotics or drug abuse may confound the results due to tolerance to ordinary dosage of narcotics or anesthetics used for alleviating the pain), illiteracy (as we used VAS (visual analog scale) ruler for pain assessment and illiterate patients are generally unable to express their pain in this scale), American Society of Anesthesiologists (ASA) physical status two or greater and persistent analgesic use. All patients signed written consent after initial explanation of study workflow.

The patients were assigned to receive either bupivacaine (Bupivacaine hydrochloride sterile ampule (Marcaine 0.5% AstraZeneca)) or normal saline (N/S) randomly using sealed envelope method in ports of laparoscopic cholecystectomy and adjunction site of liver and gallbladder. Also the routine anesthetic drugs were similarly used

in both groups. Standard 4 port laparoscopic cholecystectomy was done for all patients by single surgical team and after inserting veress needle in supra-umbilical area insufflation was done with pressure limit about 10 to 15 mmHg according to patients' body habitus. At the end of cholecystectomy and removing gall bladder and hemostasis in bupivacaine group, we sprayed about 15 ml of bupivacaine 25% solution over gall bladder bed and dissection area. After removing all ports, bupivacaine 0.25% was infiltrated in port 1 to 3 incisions (10 ml in supra-umbilical incision in port 1, 10 ml in epigastric incision (port 2) and 5 ml in third port incision).

We did not use bupivacaine in forth port incision as the incision site was very small and there was neither much traction nor manipulation in this area.

The N/S groups received normal saline in the same regimen and in the same ports. Only the chief surgeon was aware of patients' allocation to each group.

Post-laparoscopic pain was scored using the 100 mm visual analogue scale (VAS). In this scale patient will draw their pain from "no pain" end to the point showing their current pain. The longer distance (millimeter) is indicative for more severe pain. Also patients were asked if they felt pain in shoulder, incision site and/or intra-abdomen. These evaluations were made at 1, 6, 18, and 24 hours after operation. Patients complaining pain with VAS score 6 and greater received 25 mg intravenous pethedine q6h. Additional opioid request was administered upon patients' request. Patients with VAS score lower 6 received. The frequency of opioid side effect such as nausea, pruritus and urinary retention was recorded.

Categorical variables were compared using the chi-squared test. An independent student t-test was used to compare means between the two groups. All analyses were performed by the two-sided method using Statistical Package of Social Science software (SPSS version 22; SPSS, Inc., Chicago, IL), and the p-value of <.05 was set as statistically significant.

3. RESULTS

A total number of 100 patients were randomly assigned to two equal size groups. There were no statistically significant difference between age, gender, weight and height of patients in two groups (All p value > 0.05). As age> 40 years is considered to be a cut off point for higher incidence of cholecystitis we evaluated this cut off in two groups. Age > 40 years was seen in 38 (76%) and 35 (70%) patients in Bupivacaine and N/S groups, respectively (P > 0.05). Also female gender was assessed as a demographic characteristic influencing incidence of cholecystitis. 32 (64%) and 33 subjects (66%) were female in Bupivacaine and N/S groups, respectively (P > 0.05). The underlying disease leading to operation is shown in Table 1 and there was no statistically significant difference between two groups (P > 0.05). Vomiting was the most common side effect of opioid application in both groups at any follow up visits also it occurred with significant lower frequency in bupivacaine group at any follow up visits (all P-values <0.05). Other side effects of opioid injection (pruritus and urinary retention) was not significantly different between study groups (p values > 0.05). The mean opioid use was 12.5 mg and 37.5 mg in bupivacaine and N/S groups, respectively (P=0.001). As shown in Tables 3-6, the mean VAS score was significantly lower in all three injected ports of laparoscopic cholecystectomy and shoulder in bupivacaine versus N/S group (all p value = 0.001).

4. DISCUSSION

In this study the effects of Bupivacaine injection in ports of laparoscopic cholecystectomy and adjunction site of liver and gall bladder were determined on postoperative pain and opioid consumption. It was seen that the pain severity, opioid use and vomiting rate was significantly lower in bupivacaine versus N/S group. Alper et al. [27] compared the efficacy of levobupivacaine and normal saline for reduction of postoperative pain in laparoscopic cholecystectomy. They infiltrated 15 mL levobupivacaine 0.25% prior to skin incisions for trocar insertion and then applicated either 40 mL of 0.25% levobupivacaine or N/S intra-peritonealy. They found lower pain score, higher patients' satisfaction and lower vomiting frequency in operation site in intervention group. They also similarly reported no adverse effects. But in contrast to our study, the shoulder pain was not significantly reduced in intervention group. Vieira and colleagues [28] used 0.5% bupivacaine (100 mg) with epinephrine via intercostal or interpleural route and found that mean analgesia duration was 505 minutes for interpleural and 620 minutes for intercostal results groups,

Table 1. The underlying disease leading to operation

	Acute cholecystitis	Chronic cholecystitis	Gall bladder stone	P value
Bupivacaine group	2 (4%)	34 (68%)	14 (28%)	> 0.05
N/S group	2 (4%)	25 (50%)	23 (46%)	> 0.05
Total	4 (4%)	59 (59%)	37 (37%)	

Table 2. Vomiting frequency in patients of both groups

	Bupivacaine group	N/S group	P value
1 hour after surger	6 (12%)	16 (32%)	0.016
6 hour after surgery	7 (14%)	16 (32%)	0.032
18 hour after surgery	14 (28%)	22 (44%)	0.05 <
24 hour after surgery	15 (30%)	24 (48%)	0.05 <

Table 3. Reported VAS score in shoulder region in both groups

	Groups	Mean±SD	P value
1 hour after surgery	Bupivacaine group	2.32 ± 0.89	0.001
	N/S group	3.22 ± 0.86	
6 hour after surgery	Bupivacaine group	3.38 ± 0.92	0.001
	N/S group	4.14 ± 1.21	
18 hour after surgery	Bupivacaine group	4.20 ± 0.75	0.001
	N/S group	5.04 ± 0.90	
24 hour after surgery	Bupivacaine group	4.98 ± 1.07	0.001
	N/S group	6.56 ± 0.86	

Table 4. Reported VAS score in port one of laparoscopic cholecystectomy regions in both groups

	Groups	Mean ± SD	P value
1 hour after surgery	Bupivacaine group	2.34 ± 0.93	0.001
	N/S group	3.22 ± 0.86	
6 hour after surgery	Bupivacaine group	3.04 ± 1.04	0.001
	N/S group	4.34 ± 1.08	
18 hour after surgery	Bupivacaine group	4.04 ± 0.69	0.001
	N/S group	5.54 ± 0.78	
24 hour after surgery	Bupivacaine group	5.06 ± 1.03	0.001
	N/S group	6.26 ± 0.63	

Table 5. Reported VAS score in port two of laparoscopic cholecystectomy regions in both groups

	Groups	Mean ± SD	P value
1 hour after surgery	Bupivacaine group	1.82 ± 1.00	0.001
	N/S group	3.84 ± 1.20	
6 hour after surgery	Bupivacaine group	2.92 ± 1.06	0.001
	N/S group	4.34 ± 1.40	
18 hour after surgery	Bupivacaine group	3.62 ± 0.69	0.001
	N/S group	5.24 ± 1.08	
24 hour after surgery	Bupivacaine group	4.54 ± 1.05	0.001
	N/S group	6.86 ± 0.99	

Table 6. Reported VAS score in port three of laparoscopic cholecystectomy regions in both groups

	Groups	Mean ± SD	P value
1 hour after surgery	Bupivacaine group	1.90 ± 0.70	0.001
	N/S group	3.34 ± 0.77	
6 hour after surgery	Bupivacaine group	3.08 ± 0.82	0.001
	N/S group	4.40 ± 1.08	
18 hour after surgery	Bupivacaine group	4.06 ± 0.91	0.001
	N/S group	5.48 ± 0.86	
24 hour after surgery	Bupivacaine group	5.16 ± 1.36	0.001
	N/S group	7.34 ± 0.79	

respectively which considered to be satisfactory but without significant difference. Along with our study, nausea, vomiting and mild abdominal pain were the most frequent postoperative complaints and there was no postoperative complication related to bupivacaine blockade.

Combination therapy to achive maximum post laparoscopic pain relief had been investigated by Jabbour-Khoury et al. [29]. They investigated four different regimens as follows: 1) intraperitoneal spray of 40 mL bupivacaine 0.25%, 2) intraperitoneal spray of 40 mL bupivacaine 0.25% mixed with 200 mg ketoprofen, 3) intraperitoneal spray of 40 mL bupivacaine 0.25% and intravenous injection of 200 mg ketoprofen and 4) injection of 200 mg ketoprofen intravenously. In this study the fifth group was control group who received intrapetoneal spray of 40 mL normal saline. Authors claimed that in patients undergoing elective laparoscopic cholecystectomy, the combination of intraperitoneal spray of 40 mL bupivacaine 0.25% and 200 mg intravenous ketoprofen is the best regimen to achieve lower postoperative pain and postoperative vomiting.

The duration of post operative efficacy of pain relief may vary between different studies as Castillo-Garza and colleagues [30] compared analgesic effects of 20cc of 0.5% bupivacaine and 20cc normal saline installed into the gallbladder in patients undergoing laparoscopic cholecystectomy. They proposed that only at 6 hours after laparoscopy, the difference between pain levels was significant. Although we reported that pain score would be lower in all post-operation follow ups and more extended efficacy was reported, but the fact that bupivacaine pharmaceutical dynamic and kinetic alternate between different studies may answer the observed difference.

National studies about the analgesic efficacy of bupivacaine was along with our study. In the study by Zare Joshaghani M et al. [31] the efficacy of intra-pleural bupivacaine and opioids was compared and authors found better effects in bupivacaine group. Also Hashemi and colleagues [32] compared the efficacy of intra-peritoneal bupivacaine versus placebo for reduction of post laparoscopic cholecystectomy pain. They reported significantly lower morphine use in intervention group as well as our study.

5. CONCLUSION

Totally, it may be concluded that bupivacaine injection in ports of laparoscopic cholecystectomy and adjunction site of liver and gall bladder is effective on postoperative pain and opioid consumption leading to lower pain and less opioid use. Regardless of these appreciable effects, future researches should be dedicated to studies with larger sample size comparing the analgesic effects of other drugs both in combination and without bupivacaine. Also finding the most effective dosage to achieve analgesia and safety profile of prescribed medications both in short and long term is mandatory.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Downs S, Black N, Devlin H, et al. Systematic review of the effectiveness and safety of laparoscopic cholecystectomy. Ann R Coll Surg Engl. 1996;78:241-323.
2. Dabbagh N, Soroosh A, Khorgami Z, Shojaeifard A, Jafari M, Abdehgah AG, Mahmudzade H. Single-incision laparoscopic cholecystectomy versus mini-laparoscopic cholecystectomy: A randomized clinical trial study. Journal of research in medical sciences: The official journal of Isfahan University of Medical Sciences. 2015;20(12):1153.
3. Fiorillo M, Davidson P, Fiorillo M, et al. 149 ambulatory laparoscopic cholecystectomies. Surg Endosc. 1996; 10:52-6.
4. Kum C, Wong C, Goh M, Ti T. Comparative study of pain level and analgesic requirement after laparoscopic and open cholecystectomy. Surg Laparosc Endosc. 1994;4:139-41.
5. Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. Anesth Analg. 1996;82:44-51.
6. Ure B, Troidl H, Spangenberger W, et al. Pain after laparoscopic cholecystectomy. Intensity and localization of pain and analysis of predictors in preoperative symptoms and intraoperative events. Surg Endosc. 1994;8:90-6.
7. Joris J, Thiry E, Paris P, et al. Pain after laparoscopic cholecystectomy: characteristics and effect of intraperitoneal bupivacaine. Anesth Analg. 1995;81:379-84.
8. Miller RD, Fleisher LA, Johns RA, Suvares JJ, Wiener-kronis PJ, Young LW. Miller's Anesthesia. Sixth ed., Elsevier, Curtis Centre. 2005;2:2729-51.
9. Callesen T, Klarskov B, Mogensen, et al. Day case laparoscopic cholecystectomy: Feasibility and convalescence. Ugeskr Laeger. 1998;160:2095-100.
10. Strömskag K, Reiestad F, Holmqvist E. Intrapleural administration of 0.25%, 0.375% and 0,5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg. 1988;67:430-4.
11. Kastrissios H, Mogg G, Triggs E, et al. Interpleural bupivacaine infusion compared with intravenous pethidine infusion after cholecystectomy. Anaesth Intensive Care. 1991;19:539-45.
12. Bisgaard T, Klarskov B, Rosenberg J, et al. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain. 2001;90:261-9.
13. David C. Analgesic treatment after laparoscopic cholecystectomy. Anesthesiology. 2006;104:835-46.
14. Molavi B, Shojaiefard A, Jafari M, Ghorbani-Abdehgah A, Nasiri S, Yaghoobi-Notash A, Mir A, Soroush A. The effect of ticlopidine on early arteriovenous fistula thrombosis: A randomized clinical trial. Academic Journal of Surgery. 2017;4(1):9-12.
15. Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. Ann R Coll Surg Engl. 2001;167:84-96.
16. Bisgaard T, Klarskov B, Rosenberg J, et al. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. Arch Surg. 2001;136:917-21.
17. Wills V, Hunt D. Pain after laparoscopic cholecystectomy. Br J Surg. 2000;87:273-84.
18. Narchi P. Intraperitoneal local anaesthetic for shoulder pain after day case laparoscopic cholecystectomy. Lancet. 1991;338:1569-73.
19. Pascalucci A. Preemptive analgesia: Intraperitoneal local anesthetic cholecystectomy. A randomized double blind, placebo controlled study. Anesthesiology. 1996;85:11-20.
20. Gordon S. Intraperitoneal ropivacaine and saline were similar in preventing pain after extensive laparoscopic excision of endometriosis. J Am Assoc Gynecol Laparosc. 2002;9:29-34.
21. Barnes P, Belvisi M, Rogers D. Modulation of neurogenic inflammation: Novel approaches to inflammatory disease. Trend Pharmacol Sci. 1990;11:185-9.
22. Sadat-Safavi SA, Nasiri S, Shojaiefard A, Jafari M, Abdehgah AG, Notash Jr AY, Soroush A. Comparison the effect of stump closure by endoclips versus endoloop on the duration of surgery and complications in patients under laparoscopic appendectomy: A

randomized clinical trial. Journal of research in medical sciences: The official journal of Isfahan University of Medical Sciences. 2016;21.
23. Gupta A, Thorn S, Axelsson K, et al. Postoperative pain relief using intermittent injections 0.5% ropivacaine through a catheter after laparoscopic cholecystectomy. Anesth Analg. 2002;95:450-6.
24. Ahmed BH, Ahmed A, Tan D, et al. Post-laparoscopic cholecystectomy pain: Effects of intraperitoneal local anesthetics on pain control--a randomized prospective double-blinded placebo-controlled trial. Am Surg. 2008;74(3):201-9.
25. Lepner U, Goroshina J, Samarutel J. Postoperative pain relief after laparoscopic cholecystectomy: A randomised prospective double-blind clinical trial. Scand J Surg. 2003;92:121-4.
26. Kim T, Kang H, Park J, et al. Intraperitoneal ropivacaine instillation for postoperative pain relief after laparoscopic cholecystectomy. J Korean Surg Soc. 2010;79:130-6.
27. Alper I, Ulukaya S, Ertugrul V, Makay O, Uyar M, Balcioglu T. Effects of intraperitoneal levobupivacaine on pain after laparoscopic cholecystectomy: A prospective, randomized, double-blinded study. Agri. 2009;21(4):141-5.
28. Vieira AM, Schnaider TB, Brandao AC, Campos Neto JP. Comparative study of intercostal and interpleural block for post-cholecystectomy analgesia. Rev Bras Anestesiol. 2003;53(3):346-50.
29. Jabbour-Khoury SI, Dabbous AS, Gerges FJ, Azar MS, Ayoub CM, Khoury GS. Intraperitoneal and intravenous routes for pain relief in laparoscopic cholecystectomy. JSLS. 2005;9(3):316-21.
30. Castillo-Garza G, Diaz-Elizondo JA, Cuello-Garcia CA, Villegas-Cabello O. Irrigation with bupivacaine at the surgical bed for postoperative pain relief after laparoscopic cholecystectomy. JSLS. 2012;16(1):105-11.
31. Zare Joshaghani M, Mirhosseini S, Hosseininasab S, HajiEsmaili M. Pain reduction amount after intra-pleural injection of bupivacaine versus opiums in upperabdominal surgeries. Shahid-Sadooghi Med Univ J. 2005;13(4):26-9.
32. Hasehmi S, Naghibi KH, Rahimi M, Raei M, Nasirian B. Effect of intra-peritoneal administration of bupivacaine on morphine use after cholecystectomy. Gilan Med Univ J. 2002;11(43):5-10.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/21887