Review Article

iMedPub Journals
http://www.imedpub.com

Medical & Clinical Reviews
ISSN 2471-299X

2015
Vol. 1 No. 1: 3

DOI: 10.21767/2471-299X.1000003

Liposomal Bupivacaine: A Promising Post-op Analgesic for the Future

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Abstract

Post-operative period can be very stormy if the patients grapple with intense pain. From time to time various strategies, techniques and drugs have been developed to counter this most feared side effect of surgery but till date no ideal solution lies to this ever predominant problem. In quest of finding an ideal drug, various newer drugs are being developed with wider safety margin and a favourable profile. Liposomal bupivacaine has emerged as one of the newer drugs on this platform of post-op pain relief. However, larger research studies are required before we can really label this promising drug a better post-op analgesic agent.

Keywords: Bupivacaine; Liposomal bupivacaine; Opioids; Post-op pain

Introduction

Ever since the first public demonstration of ether anaesthesia by Sir W.T.G. Morton, anaesthesia fraternity has been making endless search for ideal and improve anaesthetics over the years. However, the last three to four decades have been revolutionary as numerous modern anaesthetic agents have been invented and properties of many older ones have been rediscovered. Regional anaesthesia for post-op pain relief has gained a wider acceptance not only among anaesthesiologists and surgeons but public awareness has also increased to quite an extent over this period. However, an elusive quest to find an ideal regional anaesthetic agent keeps haunting the anaesthesiologist.

Post-operative pain: still a challenging situation

Postoperative pain has always remained a distressing feature and a challenge for anaesthesiologists in perioperative setting. Most of patients experience pain of moderate to severe in intensity during two weeks of postoperative period, especially with major surgeries. The best way to counter such pain syndromes includes but is not limited to use multimodal approach. This is highly essential; particularly in high risk patients as adequate pain relief improves cardiac, respiratory and gastrointestinal functions, thus improving patient survival [1]. Traditionally, opioids have been used for moderate to severe pain but they are associated with various side effects like respiratory depression, drowsiness, nausea, vomiting, pruritis, urinary retention and constipation [2]. Further, the use of commonly available NSAIDs is associated with increased incidence of peptic ulcers, renal, hepatic and platelet dysfunction. Globally, the improved analgesia is mainly achieved with regional anaesthetic techniques such as spinal, epidural and regional blocks. Peri-operatively, such measures help in lowering blood loss, decreased thromboembolism and postoperative catabolism.

Generally speaking, an increased tendency has been seen towards the use of more regional and peripheral nerve blocks, especially with advent of ultrasound guided techniques in operative and critical care arena. Moreover, the tendency to use lower dose and concentration of these local anaesthetic agents also propelled the wider use of various older and newer adjuvants which have got considerable synergistic and additive action with these agents. Recently, the introduction of dexmedetomidine, a drug with lesser side effects as compared to opioids, has spurred a widespread research and usage in anaesthesia practice [3]. However, the concern with local anaesthesia toxicity still remains a major concern even with USG techniques.

Considering these concerns of local anaesthetic toxicity and

essentiality of adequate pain relief post-operatively, numerous researches and studies have been carried out with various LA's and adjuvants but none of them have proved ideal. As such, the quest to develop and use newer and safer anaesthetic agent remains unfulfilled.

Emergence of liposomal bupivacaine

In October 2011, FDA (Food and Drug Administration) approved liposomal bupivacaine for single dose infiltration in to surgical site for postoperative analgesia. It is an amide type of local anaesthetic and has been used in patients undergoing haemorrhoidectomy, inguinal hernia repair, augmentation mammoplasty, bunionectomy and total knee replacements. However, its use has not been studied in patients with age less than 18 years. Also, liposomal bupivacaine is contraindicated in obstetrical paracervical block [4]. Biochemical structure of liposomal bupivacaine is similar to that of bupivacaine hydrochloride but the main merit lies in its preservative free availability. It is manufactured in the form of aqueous suspension of multivesicular liposomes containing bupivacaine in a concentration of 1.33 mg/ml. The availability of free bupivacaine is approximately 3%, which is mainly responsible for providing early onset of analgesia. Drug is incorporated in the form of liposomes either by incorporating them into aqueous space or by intercalating them into lipid bilayer [5]. Liposomal bupivacaine is recommended for use only in adults and further studies and research is required before it can be approved for use in paediatric patients. It is advised that it should be given with needle no smaller than 25 gauges and an opened vial must be used within 4 hours of opening.

Liposomal bupivacaine: uses and precautions

Various side effects with its use include nausea, constipation, vomiting. A higher incidence of adverse effects has been seen in geriatric patients and these side effects shows exaggerated incidence in patients with comorbidities. However, the incidence is lower in patients receiving dose lesser than 266 mg, which is the FDA approved dose. Liposomal formulation is not new in anaesthesia practice as liposomal encapsulated morphine was the first drug to be approved by the FDA for postoperative pain management and is in clinical use since 2004.But even liposomal morphine exhibits a greater risk of toxicity in patients with hepatic and renal impairment.

Special considerations of its use include a slower injection into soft tissues of surgical site along with frequent aspiration to check for blood. Its administration should be delayed by 20 minutes after lidocaine use, as it may cause an immediate release of bupivacaine from liposomal bupivacaine. It is also not intended for use via intravenous, Intrathecal and epidural routes. Peak levels are seen after 1 hour and after 12-36 hr after its administration, as seen in a study done by Hu D et al. [6]. During storage, it should preferably be refrigerated, but can be stored at room temperature for up to 30 days in sealed, undiluted vials. Vial should not be re-refrigerated. It can be administered after dilution with preservative-free normal saline (0.9%) in concentration of 0.89 mg/ml. Its vial should be inverted multiple times to re-suspend particles immediately prior to withdrawal from vial. Also the diluted suspension should be used within 4 hr of preparation.

Advantages of single dose of liposomal bupivacaine over infusion include decreased provider time for block placement and infusion management, reduced risk of complications associated with keeping the catheters in situ along with patient inconvenience.

Disadvantages include that it is not clear that if surgical anaesthesia can be attained with any dose of liposomal bupivacaine, inability to titrate down or up the dose in case of dense or inadequate block respectively.

Liposomal bupivacaine: research and comparative evaluation

Liposomal bupivacaine has been compared with other agents in the past (**Table 1**). In a study by Gorfine et al. a placebo controlled trial, done in patients undergoing haemorrhoidectomy, group of patients receiving 300 mg of liposomal bupivacaine had lower pain scores as compared to patients receiving 30 ml of 0.9% normal saline via wound infilteration [7]. In a study by Smoot et al, patients received liposomal bupivacaine (300 mg) as compared to bupivacaine hydrochloride (100 mg) ie. bupivacaine 0.5% with epinephrine 1:200,000 for bilateral breast augmentation,mean cumulative pain score was not different in both groups.Numerical rating pain score was lower in group receiving liposomal bupivacaine at 8 and 12 hr as compared to other group [8]. In a study by Boogaerts et al, 0.5% bupivacaine with 1:200,000 epinephrine was compared with 0.5% liposomal bupivacaine via epidural route. No difference was seen in onset of analgesia, but duration of analgesia increased significantly in liposomal bupivacaine group [9].

In a study by Bagsby et al. [10] a retrospective cohort, done in patients undergoing total knee replacement, concluded that mean pain scores were not significantly different between groups receiving either liposomal bupivacaine (266 mg) or periarticular injection of 400 mg ropivacaine, 0.4 mg epinephrine and morphine 5 mg. In traditional injection group, 47.6% of patients reported pain scores as mild in comparison to 16.9% of patients in liposomal bupivacaine group. Opioids use was not significantly different among both the groups [10].

In a prospective, single-centre study, done by Vogel et al, in patients undergoing ileostomy reversal, mean opioid use in group of patients receiving liposomal bupivacaine along with ketorolac, acetaminophen, ibuprofen for 72 hr was significantly less as compared to patients receiving opioid PCA (patient controlled analgesia) using intravenous morphine. Time to first opioid use was statistically significantly longer with liposomal bupivacaine compared to morphine PCA [11].

In a study by Haas et al, arandomized double-blind study, done in 100 patients undergoing haemorrhoidectomy under general anaesthesia, patients received single dose of bupivacaine HCl 75 mg (0.25% with 1:200,000 epinephrine) or levobupivacaine 66, 199, or 266 mg upon completion ofsurgery. Cumulative pain scores were significantly lower with levobupivacaine at each study dose ($P < 0.05$) compared with bupivacaine HCl 72 hours after surgery [12].

Table 1 Studies with Liposomal Bupivacaine and their outcome characteristics.

Authors	Type of study	Type of intervention	Results	Conclusion
Boogaerts et al	Open randomized study	0.5% bupivacaine with 1:200,000 epinephrine was compared with 0.5% liposomal bupivacaine via epidural route.	No difference was seen in onset of analgesia, but duration of analgesia increased significantly in liposomal bupivacaine group	Liposomal bupivacaine increased duration of analgesia without adverse side effects or motor block.
Bagsby et al	Retrospective cohort study	Done in patients undergoing total knee replacement. One group of patients received liposomal bupivacaine group (266 mg) and traditional injection group received periarticular injection of ropivacaine (400mg), epinephrine 0.4 mg and morphine (5mg).	Mean pain scores were not significantly different between two groups.	Liposomal bupivacaine group and traditional group showed no difference in pain scores.
Vogel et al	Prospective, single-centre study	Done in patients undergoing ileostomy reversal. One group received liposomal bupivacaine along with ibuprofen, ketorolac, acetaminophen and other group received opioid PCA (patient controlled analgesia) using intravenous morphine.	Mean opioid use for patients who received liposomal bupivacaine group was significantly less as compared to other group.	Decreased opioid consumption seen with liposomal bupivacaine group.
Haas et al	Randomized, double-blind study.	Done in 100 patients undergoing haemorrhoidectomy under general anaesthesia. Patients received single dose of bupivacaine HCl 75 mg (0.25% with 1:200,000 epinephrine) or levobupivacaine 66, 199, or 266 mg upon completion of surgery.	Cumulative pain scores were significantly lower with levobupivacaine at each study dose ($P < 0.05$) compared with bupivacaine HCl 72 hours after surgery.	Local infiltration with levobupivacaine resulted in significantly reduced postsurgical pain compared with bupivacaine HCl.
Bramlett et al	A randomized multi-centre, double-blind study.	Done in 138 patients undergoing total knee replacement under general anaesthesia. Patients were divided into five groups as liposomal bupivacaine in dose of 133mg, 266mg, 399mg, 532 mg and bupivacaine HCl (150mg) with epinephrine (1:200,000).	Pain scores were significantly lower for liposomal bupivacaine 532 mg group as compared to bupivacaine HCl group.	Liposomal bupivacaine in dose of 532 mg appeared to be more effective.
Gorfine et al	Placebo controlled trial	Done in patients undergoing haemorrhoidectomy, 300 mg of liposomal bupivacaine was compared with 30 ml of 0.9% normal saline via wound infilteration.	Patients with liposomal bupivacaine had lower pain scores.	Patients receiving liposomal bupivacaine had less pain.
Smoot et al.	Randomized, double-blind, multi-centre trial	Patients received a single dose of Depo-Foam bupivacaine 600 mg or bupivacaine HCl 200 mg divided into the implant pockets at the end of surgery.	Total amounts of opioid consumed were significantly lower in the Depo-Foam bupivacaine group.	Depo-Foam bupivacaine showed benefit as compared to bupivacaine HCl

In another study by Bramlett et al. [13] a randomized multi-centre, double-blind study had done in 138 patients undergoing total knee replacement under general anaesthesia. Patients were divided into five groups as receiving liposomal bupivacaine in dose of 133 mg, 266 mg, 399 mg and 532 mg and bupivacaine HCl (150 mg) with 1:200,000 epinephrine. Pain scores were significantly lower for the patients receiving liposomal bupivacaine 532 mg as compared to bupivacaine HCl [13].

Other drugs which are available in liposomal form are amphotericin B, Vincristine, morphine, daunorubicin and verteporfin etc. Liposomes modify absorption, decrease metabolism and prolong biological half-life of the drugs, thus enhancing their therapeutic index.

Conclusion

Liposomal bupivacaine thus is an important long acting agent for postoperative pain management despite being a costly drug with acceptable adverse effects profile. However, with availability of more research and studies, its potential use, favourable profile and various merits will hold a greater promise for the future of post-op analgesia.

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