ISSN : 0259-1162

Volume 14 / Issue 2 / April-June 2020

Anesthesia: Essays and Researches

www.aeronline.org

Official publication of Pan Arab Federation of Societies of Anesthesiologists

Wolters Kluwer

Medknow

Original Article

Efficacy of New Long-Acting Bupivacaine HTX-011 in Providing Pain Relief for Patients Undergoing Elective Surgery – A Meta-analysis of Prospective Randomized Controlled Trials

Basavana Goudra[1], Navdeep Singh[2], Linag Xue[3], Amandeep Goyal[4], Divakara Gouda[1], Preet Mohinder Singh[5]

[1]Department of Anesthesiology and Critical Care Medicine, Perelman School of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA, [2]Department of Surgery, Division of Abdominal Transplant Surgery, The Ohio State University, Columbus, Ohio, USA, [3]Valley Consortium for Medical Education Family Medicine Program, Modesto, CA, USA, [4]Department of Medicine, Marietta Memorial Hospital, Marietta, Ohio, USA, [5]Department of Anesthesiology, Washington University, Saint Louis, MO, USA

Abstract

Background: The aim of the present meta-analysis is to critically analyze the various prospective randomized controlled trials comparing the safety and efficacy of a new, yet unapproved long-acting local anesthetic HTX-011. This is a combination of bupivacaine and meloxicam, and like its predecessors' liposomal bupivacaine and SABER bupivacaine, the combination slowly releases bupivacaine and provides therapeutic analgesic concentrations at the site of infiltration. **Methods:** We performed a meta-analysis of 7 randomized clinical trials comparing the use of HTX-011 with placebo and/or bupivacaine in patients undergoing abdominoplasty, bunionectomy, and herniorrhaphy. Comparisons were made for the patients who were opioid free at 24 h, pain scores at 24 h, patients likely to be opioid free at 72 h, and reduction of morphine consumption at 72 h. **Results:** While comparing pain scores at 24 h, we found that the use of HTX-011 was associated with a significant decrease in pain score in relation to both bupivacaine and placebo. The overall comparison of 12 groups showed that with HTX-011, patients are 3.25 times more likely to be opioid free at 72 h than either placebo or control. More patients were free of opioid at 24 h in the HTX-011 group when compared to bupivacaine. Finally, the consumption of morphine was less by 10.61 (95% CI: 8.13–13.09) in 14 groups that reported such consumption. **Conclusion:** HTX-011 has a clear advantage in comparison to both placebo and bupivacaine and provides better pain relief and reduces opioid consumption.

Keywords: Bupivacaine, HTX-011, liposomal bupivacaine, meloxicam, SABER bupivacaine

Introduction

The necessity for a long-acting, reliable, and safe local anesthetic has been long felt. Some of the reasons for such a need are increasing number of surgeries,[1] patients desire to get home early, reluctance on the part of both patients and prescribers to prescribe opiates, and the ongoing opioid crisis. Perioperative use of opiates is increasingly seen as an important factor in both initiation and perpetuation of opioid use in the long term. The use of synthetic opioids has been a problem in the USA since 2003, one of which is the drug fentanyl, a very common anesthesia and acute pain medication administered to a majority of patients undergoing surgery.

Majority of the patients undergoing surgical procedures experience moderate-to-severe pain. The pain is especially severe in the first 48–72 h and should be appropriately treated. The many options to treat such pain are opiates, nonsteroidal anti-inflammatory drugs, acetaminophen, acupuncture, and local anesthetics. Effective control of pain is important to prevent an array of side effects such as heightened

Access this article online

Quick Response Code:

Website: www.aeronline.org

DOI: 10.4103/aer.AER_34_20

Address for correspondence: Prof. Basavana Goudra, Department of Anesthesiology and Critical Care Medicine, Perelman School of Medicine, Hospital of the University of Pennsylvania, 680 Dulles, 3400 Spruce Street, Philadelphia, PA 19104, USA.
E-mail: goudrab@uphs.upenn.edu

Submitted: 04-May-2020 **Accepted in Revised Form:** 07-Jun-2020
Published: 12-Oct-2020

How to cite this article: Goudra B, Singh N, Xue L, Goyal A, Gouda D, Singh PM. Efficacy of new long-acting bupivacaine HTX-011 in providing pain relief for patients undergoing elective surgery – A meta-analysis of prospective randomized controlled trials. Anesth Essays Res 2020;14:288-94.

sympathetic activity and chronic pain. The local anesthetic option is attractive as it is nonsedating and devoid of such effects as nausea, vomiting, hyperalgesia, and abuse liability. Nevertheless, limited duration of action is the biggest drawback of this approach. Majority of patients receive bupivacaine (an amide-type local anesthetic), S-bupivacaine, or ropivacaine. All of these suffer from limited duration of action.

Efforts have been made to lengthen the pain-blocking effects of these local anesthetics. Liposomal bupivacaine, SABER bupivacaine (composed of 12% common local anesthetic bupivacaine, a diluent, benzyl alcohol, and an organic matrix sucrose acetate isobutyrate), and HTX-011 (a bupivacaine and meloxicam combination drug pending approval by the FDA) are three such drugs. Although it is still under investigation, HTX-011, a nonopioid, extended-release dual-acting local anesthetic that combines bupivacaine and low-dose meloxicam, has amassed sufficient data from many scientific studies that a meta-analysis is of potential benefit.

Methods

This meta-analysis has been conducted in accordance with the guidelines for systematic reviews and meta-analyses [Figure 1].[2] The Population, Intervention, Control, and Outcome Study (PICOS) design was used to identify trials that were suitable to be included in this meta-analysis [Table 1]. Trials identified with online database search were summarized into a uniform PICOS arrangement and were evaluated by two independent reviewers to verify their suitability to answer the current analysis question. Studies investigating the use of HTX-011 against bupivacaine, reporting pain intensity at 24 h and/or 72 h, were included as primary end points.

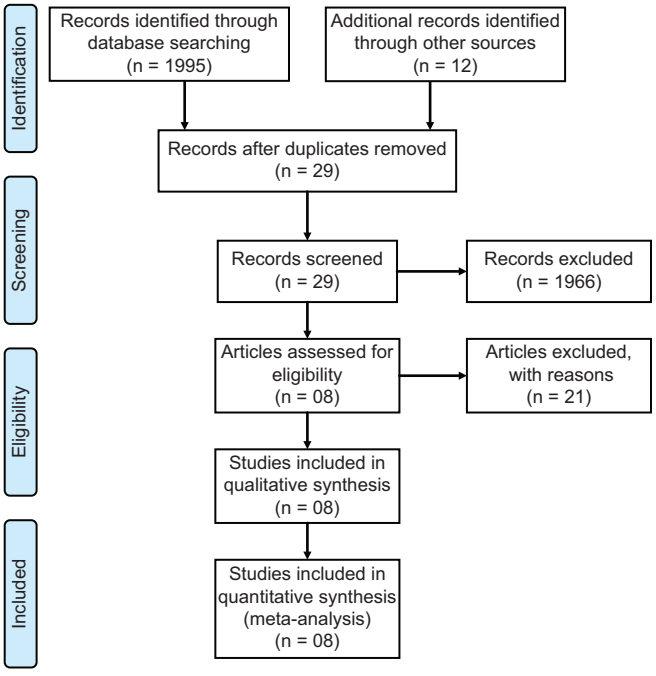

Figure 1: PRISMA flow diagram

Variables being systematically compared and recorded in previous trials were intended to be part of investigative results.

Literature search strategy

The following online medical databases (MEDLINE, Scopus, EMBASE, Cochrane Central Register of Controlled Trials, metaRegister of Controlled Trials for published studies, and Clinical Trials Registry) were searched independently by two separate reviewers. Furthermore, Web of Science (SCI/SSCI) was used to search references from shortlisted publications, systematic reviews, and editorials that included regimens involving HTX-011. The search terms used were HTX-011, bupivacaine, and meloxicam, HTX-011.

The search strategy for this analysis was extended to involve the research articles published as full articles or conferences and meeting abstracts published in peer-reviewed journals. Reference list of similar meta-analysis was also searched for any trials of interest. By extending our search, we also encompassed trials that have been published in English and other languages. When a reviewer deemed an abstract as appropriate for inclusion in the analysis, the complete content of the article was obtained and examined. The ultimate determination to bring a trial for analysis was made by two independent reviewers. Any disagreements among the two reviewers pertaining to inclusion of trials were resolved by a third impartial reviewer. In accordance with the Cochrane Collaboration recommendations, the inculcated trials were assessed by another independent researcher for methodological bias and quality of evidence. The details of the search are illustrated in Tables 1 and 2.

Data extraction

Data were individually and independently extracted into a standardized form from all the included 10 studies. The following data are included in the table: Author name, year of abstract presentation, name of surgery, study type, number of groups, dose of HTX-011, dose of bupivacaine, primary end points, adverse events, reported limitations (if any), and any additional comments. While reviewing the trials, if any data was found to be missing, the corresponding author of that particular trial was contacted via E-mail to obtain the missing data. When the data in a trial were expressed as median and interquartile range, we E-mailed the authors of the trial to obtain the mean as well as the standard deviation values. However,

Table 1: Population, Intervention, Control, and Outcome study data extraction framework

Population	Adult patients undergoing abdominoplasty, bunionectomy, herniorrhaphy
Interventions	Local would infiltration of HTX-011
Controls	Local would infiltration of bupivacaine/placebo
Outcomes	Pain scores at 24 h, more likely to be opioid free at 24 h and 72 h, consumption of morphine at 72 h
Study design	Randomized controlled trials

PICOS=Population, Intervention, Control, and Outcome study

Table 2: Characteristics of included studies

Study name	Surgery	Study type	Groups	Dose of HTX-011	Dose of bupivacaine	Primary end points	Adverse events	Limitations reported	Comments
Leiman *et al*., 2017-a[6]	Abdominoplasty	Phase 2, randomized, double-blind, placebo-controlled, multicenter study	2 groups: HTX, placebo	400 mg		SPI through 96 h	Nausea, headache	Low population size (*n*=41)	Demographic is all female
Viscusi *et al*., 2017-a[7]	Bunionectomy	Phase 2, randomized, double-blind, placebo-controlled, multicenter study	4 groups: HTX, bupivacaine, meloxicam, placebo	120 mg	Equipotent equivalent dose	SPI through 24 h	Wound inflammation		
Ottoboni *et al*., 2017a[8]	Bunionectomy	Randomized, blinded, dose-finding trial	4 groups: HTX, bupivacaine, meloxicam, placebo	120 mg	Unknown	SPI through 24 h	None reported		
Viscusi *et al*., 2017-b[9]	Bunionectomy	Randomized, double-blind, placebo-controlled, Phase 2 clinical trial	3 groups: HTX, bupivacaine, placebo	60 mh	50 mg	AUC of numeric rating scale of pain intensity through 72 h	nausea, vomiting, pruritus, headache, constipation		
Viscusi *et al*., 2017-b[9]	Herniorrhaphy	Randomized, double-blind, placebo-controlled, Phase 2 clinical trial	3 groups: HTX, bupivacaine, placebo	300 mg	75 mg	AUC of numeric rating scale of pain intensity through 72 h	nausea, headache, constipation		
Onel *et al*., 2017[10]	Bunionectomy	Randomized, double-blind, placebo-controlled, Phase 2 clinical trial	3 groups: HTX, bupivacaine, placebo	60 mg	50 mg	AUC of numeric rating scale of pain intensity through 72 h	Not reported		
Onel *et al*., 2017[10]	Herniorrhaphy	Randomized, double-blind, placebo-controlled, Phase 2 clinical trial	3 groups: HTX, bupivacaine, placebo	300 mg	75 mg	AUC of numeric rating scale of pain intensity through 72 h	Not reported		
Leiman *et al*., 2017-b[11]	Abdominoplasty	Randomized, multicenter, double-blind, placebo- and active-controlled clinical trial	3 groups: HTX, bupivacaine, placebo	400 mg	100 mg	AUC of numeric rating scale of pain intensity through 72 h	Nausea, vomiting, pruritus, headache, constipation, wound healing, dizziness, hypotension, seroma		
Viscusi *et al*., 2019-c[12]	Bunionectomy	Randomized, double-blind, placebo-controlled, active-controlled Phase 3 study	3 groups: HTX, bupivacaine, placebo	60 mg/1.8 mg	50 mg	AUC of numeric rating scale of pain intensity through 72 h	Nausea, vomiting, dizziness, wound healing		Demographic is all female
Viscusi *et al*., 2019-c[12]	Herniorrhaphy	Randomized, double-blind, placebo-controlled, active-controlled Phase 3 study	3 groups: HTX, bupivacaine, placebo	300 mg/9 mg	75 mg	AUC of numeric rating scale of pain intensity through 72 h			

SPI=Summed pain intensity score, AUR=Area under curve

when no correspondence was received from concerned authors, the mean and standard deviation values were estimated with Hozo's validated formula.[3] Similarly, in the included trials, when means did not have associated variance, efforts were

made to obtain data from the concerned authors, and in case of no response, these variances were calculated according to the Cochrane Collaboration recommendations, which include working with mean from available variances in other trials in the analysis.[4,5] Included trials used a numeric pain scale (NPS) to narrate postoperative pain. All NPS values were carefully adjusted to a scale consisting of 11 points (values 0–10) with the unitary method. On the scale, 0 represents no pain and 1 represents minimal pain which increased to a maximum value of 10 representing the most severe pain. We were able to perform analysis for the following between the studies:

1. Summed pain intensity score – comparisons were possible on postoperative days 1 and 3
2. Opioid free – comparisons were possible on postoperative days 1 and 3
3. Morphine consumption – comparisons were possible on postoperative days 1 and 3.

Statistical analysis

We examined the statistical analysis of the data with the Comprehensive Meta-Analysis software, version 3 (Biostat Inc.). We used the fixed-effects modeling in this meta-analysis and the random-effects modeling when heterogeneity was >40%. Random-effects modeling results were reported whenever heterogeneity was >40%. We used random-effects modeling to perform meta-regression for categorical variable. Heterogeneity between the trials was measured with I^2 statistic. Heterogeneity results were interpreted as: <40% nonsignificant, 40%–60% moderate heterogeneity, and 60%–90% high heterogeneity. Results were disclosed as either or both pooled means and pooled mean difference for continuous variables with a confidence interval of 95%. It was considered statistically significant if $P < 0.05$.

Risk of bias assessment

Two independent reviewers manually assessed all the publications compiled during the literature search. The criteria in the Cochrane Collaboration recommendations[5] were used for evaluation of the risk of bias. Several of these criteria comprise method of randomization; hidden treatment allocation; preoperative, perioperative, and postoperative care blinding; blinded data collection and investigation; blinded adjudication of study end points; and thorough completion of data. The graphical summary of the above assessment was made with the Review Manager 5 software (Cochrane Collaboration). We initially checked studies for potential publication bias with a funnel plot and afterward quantified with the Egger's test.

Results

Opioid free at 24 h

Eight groups compared the opioid-free patients at 24 h. Four groups compared HTX-011 to bupivacaine to assess opioid-free patients at 24 h. A comparison of these eight groups showed that the patients on HTX-011 were 5.53 times more likely to be opioid free at 24 h (95% confidence interval [CI] being 2.6–11.75). The heterogeneity for the aforementioned collective data was 0% ($P = 0.00$).

Another four groups compared HTX-011 to a placebo to assess opioid-free patients at 24 h. Results showed that the HTX-011 group was 9.61 times more likely to be opioid free at 24 h (95% CI being 5.59–16.53). The heterogeneity for the mentioned pooled result was 0% ($P = 0.00$).

The overall pooled result from all these groups showed that the HTX-011 group was 7.96 times more likely to be opioid free at 24 h (95% CI being 5.13–12.36). The heterogeneity for the result was 0% ($P = 0.00$). Comparisons of HTX-011 with bupivacaine and placebo resulted in individual pooled values, as shown in Figure 2.

Pain scores at 24 h

Eighteen groups [Figure 3] have reported the pain scores at 24 h. HTX-011 lowered the pain scores by 1.8 (95% CI: 1.42–2.2) in overall comparison. The heterogeneity for result was 96.94% ($P = 0.00$). The groups providing a comparison of HTX-011 with bupivacaine showed a significant decrease in pain score by 1.81 in the HTX-011 group ($P = 0.00$, CI: 1.44–2.14, $I^2 = 97.8\%$), and similarly, HTX-011 was also superior in pain control in comparison to a placebo in 9 trials, where it decreased pain scores by 1.81 (95% CI: 1.54–2.06, $P = 0.00$, $I^2 = 97.4\%$).

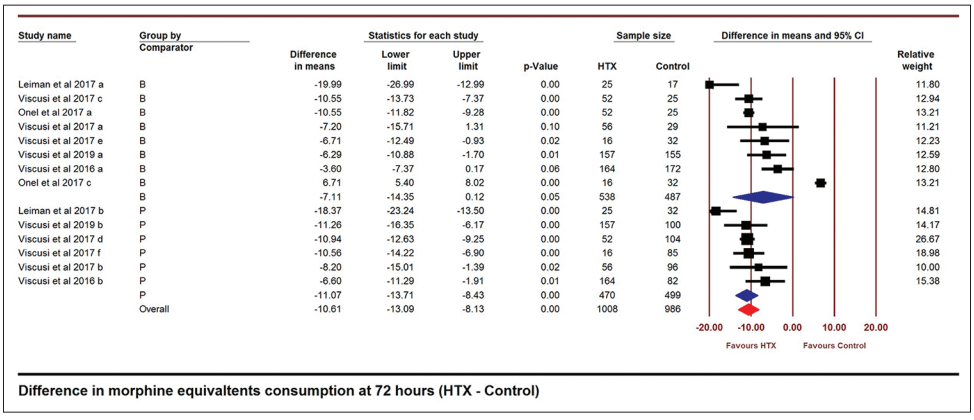

Figure 2: Odds ratio for opioid-free patients at 24 h (HTX vs. control)

Opioid free at 72 h

The overall comparison of 12 groups [Figure 4] showed that with HTX-011, the patients are 3.25 times more likely to be opioid free at 72 h than either placebo or control (95% CI: 2.3–4.58). The heterogeneity for this result was 54.39% ($P = 0.00$). Six of these groups compared HTX-011 to bupivacaine and displayed the benefit of HTX-011, with patients being 2.39 times more likely to be opioid free at 72 h (95% CI: 1.54–3.7, $P = 0.00$, $I^2 = 27.38$). The groups comparing HTX-011 to placebo also showed the benefit of HTX-011 with patients who received HTX-011 being 5.25 times more likely to be opioid free (95% CI: 2.3–4.58, $P = 0.00$, $I^2 = 38.06\%$).

Fourteen groups [Figure 5] have reported the pain scores at 72 h. HTX-011 lowered the pain scores by 0.41 (95% CI: 0.24–0.57) in overall comparison ($P = 0.00$, $I^2 = 88.07\%$). Eight groups compared HTX-011 with bupivacaine and showed a significant decrease in pain score by 0.47 with HTX-011 ($P = 0.01$, CI: 0.12–0.81, $I^2 = 69.35\%$). Six groups compared HTX-011 to a placebo and showed effectiveness of HTX-011 by reduction in pain score by 0.39 (95% CI: 0.20–0.58, $P = 0.00$, $I^2 = 82.76\%$).

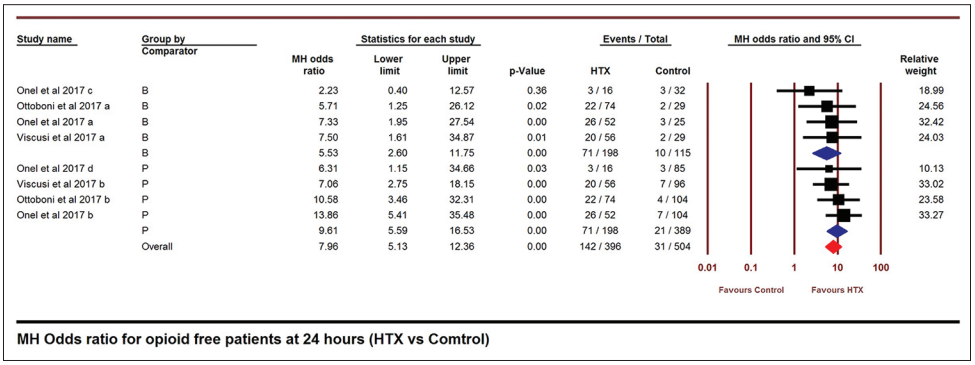

Figure 3: Mean differences in visual analog scale scores

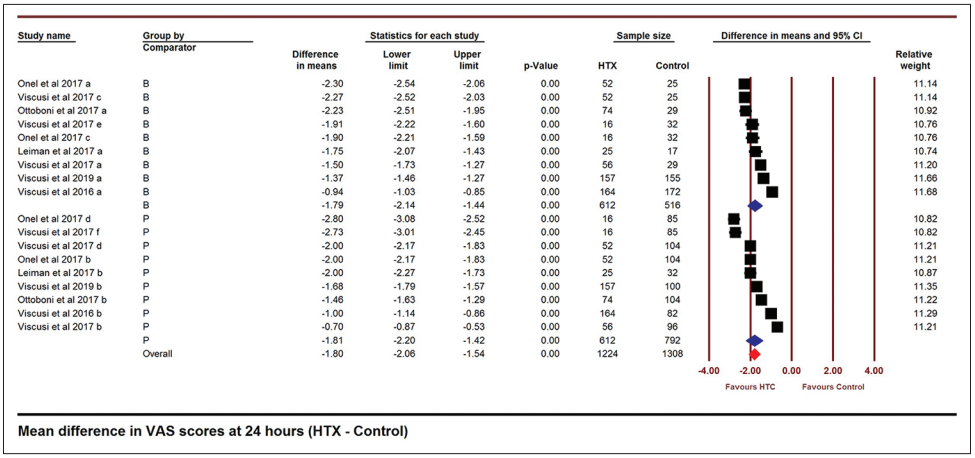

Figure 4: Odds ratio for opioid-free patients at 72 h (HTX vs. control)

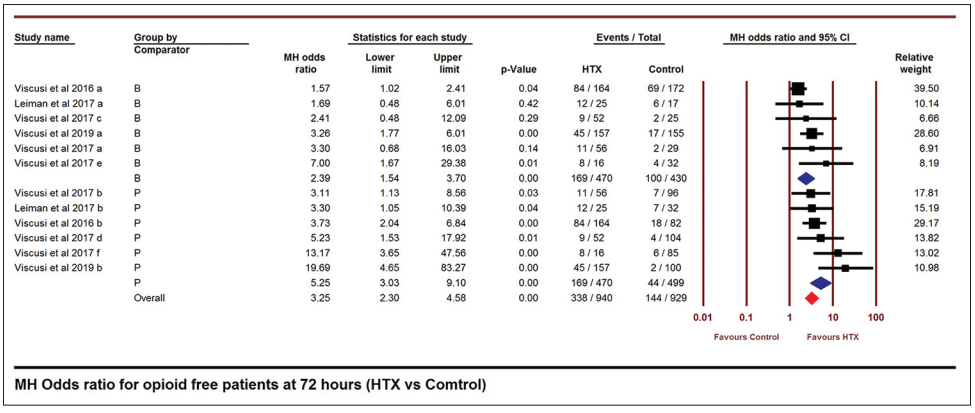

Figure 5: Mean differences in visual analog scale scores at 72 h (HTX vs. control)

Morphine consumption at 72 h

The overall comparison of 14 groups that reported morphine consumption [Figure 6] showed the superiority of HTX-011 in reducing morphine consumption by 10.61 (95% CI: 8.13–13.09). The heterogeneity for the result was 97.40% ($P = 0.00$). The groups comparing HTX-011 with bupivacaine showed a 7.11 reduction in morphine equivalents, but the results were not statistically significant (95% CI: 0.12–14.35, $P = 0.05$, $I^2 = 97.22\%$). Groups comparing HTX-011 to placebo showed a statistically significant reduction in morphine consumption in the HTX-011 group of 11.07 (95% CI: 8.43–13.71, $P = 0.00$, $I^2 = 61.19\%$).

Discussion

HTX-011 is an extended-release, dual-acting local anesthetic consisting of bupivacaine and meloxicam combination in Biochronomer polymer technology.[12] Biochronomer technology allows delivery of therapeutic levels of normally short-acting pharmacological agents over a much longer course of days and up to weeks with a singular subcutaneous application.[13] Like other long-acting local anesthetics such as Exparel (bupivacaine liposome injectable suspension) and SABER bupivacaine, it is designed to diminish postoperative use of opiates and reduce the postoperative pain for periods longer than that can be achieved with the standard local anesthetic solutions.

Our results of HTX-011 are comparable to both Exparel and SABER bupivacaine.

SABER bupivacaine also reduced opioid requirements and was more efficacious than placebo and possibly longer acting than bupivacaine hydrochloride. A randomized, parallel-group, double-blind, active- and placebo-controlled Phase 2 trial looked at the effects of different local anesthetics on 107 adult patients greater than the age of 18 who underwent elective shoulder arthroscopy. SABER bupivacaine greatly decreased the level of pain compared to SABER-placebo for 72 h postsurgery ($P = 0.0003$) as well as diminished use of rescue opioid and lengthened median time to first rescue opioid medication during the same time period.[14] Patients undergoing inguinal hernia repair under general anesthesia when operated on with the tension-free Lichtenstein technique also reported similar benefits.[15] There were no signs of systemic bupivacaine toxicity when instilling 5 mL (660 mg) of HTX-011 into various abdominal surgical sites as evidenced by adverse events, laboratory tests, and strict Holter monitoring.[16]

Patients who underwent total knee arthroplasty experienced significantly improved postsurgical pain, decreased opioid usage, and prolonged time to first opioid rescue with liposomal bupivacaine infiltration.[17] The aforementioned study included adult males and nonpregnant females undergoing primary, unilateral, tricompartmental total knee arthroplasty with spinal anesthesia administered. The study was a randomized, Phase 4, double-blind, active-controlled, parallel-group study performed between April 25, 2016, and January 19, 2017, at 16 different US locations. Within a 4-h window before the surgery, patients were also administered oral pregabalin 300 mg, celecoxib 200 mg, acetaminophen 1000 mg, and intravenous (i.v.) tranexamic acid 1 g.

Exparel usage decreased both postoperative pain and length of stay in implant-based breast reconstruction. In this retrospective review of 90 immediate implant-based breast reconstruction procedures, the use of liposomal bupivacaine was associated with reduced patient visual analog pain scale pain scores right after the surgical procedure versus pain management using bupivacaine infusion pain pumps as well as oral and IV narcotic.[18] A reduction in length of hospital stay was also noted.

A meta-analysis that included 16 trials involving periarticular infiltration of liposomal bupivacaine for total knee arthroplasty concluded the solution to have ambiguous clinical improvements. There was only an insignificant decrease in patients' inpatient stay compared to patients receiving femoral nerve block for pain. High heterogeneity was a shortcoming of this study.[19]

Although plasma levels with all long-acting anesthetics are below toxic levels at therapeutic doses due to slow absorption, the concern of accidental i.v. injection remains. It is unclear if the ensuing cardiac and neurotoxicity responds to traditional treatments such as Intralipid.

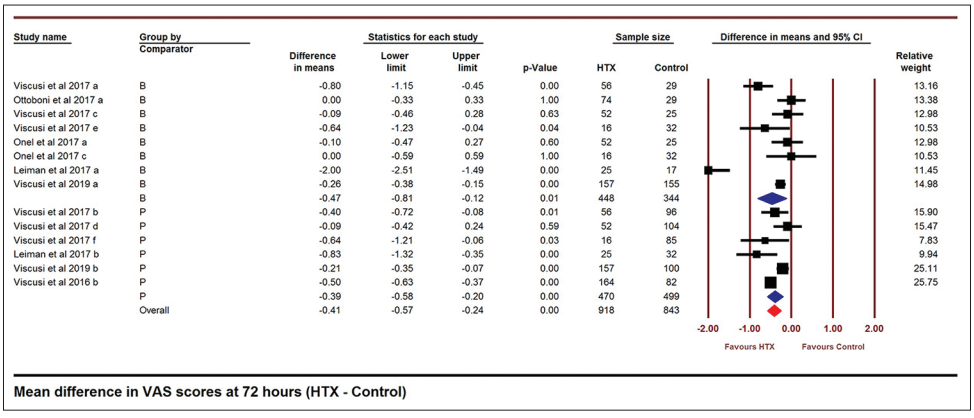

Figure 6: Difference in morphine equivalents at 72 h (HTX vs. control)

Conclusion

Like its predecessors, HTX-011 holds a significant promise. We hope that it will provide yet another valuable option in the field of local infiltration anesthesia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Hall MJ, Schwartzman A, Zhang J, Liu X. Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. Natl Health Stat Report 2017;(102):1-5.
2. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
3. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
4. Chowdhry AK, Dworkin RH, McDermott MP. Meta-analysis with missing study-level sample variance data. Stat Med 2016;35:3021-32.
5. Lundh A, Gøtzsche PC. Recommendations by Cochrane Review Groups for assessment of the risk of bias in studies. BMC Med Res Methodol 2008;8:22.
6. Leiman D, Minkowitz HS, Patel SS, Boccia G, Chu A, Heiner L, *et al*. Reduced pain intensity and opioid consumption for 96 hours after abdominoplasty after administration of HTX-011, a proprietary, extended-release combination of bupivacaine and meloxicam. J Am Coll Surg 2017;225:e147.
7. Viscusi E, Deleon-Casasola O, Gan TJ, Onel E, Boccia G, Chu A, *et al*. HTX-011, a proprietary, extended-release synergistic combination of bupivacaine and meloxicam for the relief of acute postoperative pain. J American College of Surg 2017;225:e37.
8. Ottoboni T, Quart B, Pawasauskas J, Dasta JF, Pollak RA, Viscusi ER. Response to the letter to the editor by Hafer and Johnson concerning 'Mechanism of action of HTX-011: A novel, extended-release, dual-acting local anesthetic formulation for postoperative pain'. Reg Anesth Pain Med 2020;rapm-2020-101488.
9. Viscusi E, Onel E, Boccia G, Chu A, Keller M, Ottoboni T, *et al*. HTX-011, a locally administered analgesic, reduces postoperative pain intensity and opioid use through 72 hours across bony and soft tissue surgical models. Reg Anesth Pain Med 2017;42:e74-5.
10. Onel E, Chu A, Patel S, Ottoboni T, Wilker C, Quart B. Synergistic effect of bupivacaine and meloxicam in HTX-011 across multiple doses and surgeries. In Anesthesia and Analgesia 2017;124:1031.
11. Leiman D, Minkowitz H, Patel S, Boccia G, Chu A, Heiner L, *et al*. HTX-011, a proprietary, unique, long-acting local anesthetic, reduces acute postoperative pain intensity and opioid consumption following abdominoplasty. J American College of Surg 2017;225:e147.
12. Viscusi E, Gimbel JS, Pollack RA, Hu J, Lee GC. HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: Phase III results from the randomized EPOCH 1 study. Reg Anesth Pain Med 2019;44:700-6.
13. Our Technologies Heron Therapeutics. Available from: https://www.herontx.com/our-technologies. [Last accessed on 2020 Apr 11].
14. Ekelund A, Peredistijs A, Grohs J, Verity N, Rasmussen S. Treatment of Postoperative Pain in Shoulder Surgery with SABER®-Bupivacaine. Poster Presented at 39th Annual Regional Anesthesiology and Acute Pain Medicine Meeting, Chicago: United States; 2014.
15. Watts R, Wulf H, Verity N, Yang A, Ekelund A. SABER-Bupivacaine Concurrently Reduces Postoperative Pain Intensity and Opioid Use for 72 Hours: Evaluation of CROPIRS Scores, Abstract, American Society of Anesthesiologists; 2014.
16. Gan TJ, Papaconstantinou H, Durieux M, Singla N, Johna S, Lissin D, *et al*. Treatment of postoperative pain in major abdominal surgery with SABER®-Bupivacaine: Results of the BESST trial. Chicago, IL: Poster presented at: 39th Annual American Society of Regional Anesthetic and Pain Medicine Meeting; 2014.
17. Mont MA, Beaver WB, Dysart SH, Barrington JW, Gaizo DJ. Local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty: Results of a randomized controlled trial. J Arthroplasty 2018;33:90-6.
18. Butz DR, Shenaq DS, Rundell VLM, Kepler B, Liederbach E, Thiel J, *et al*. Postoperative pain and length of stay lowered by use of exparel in immediate, implant-based breast reconstruction. Plast Reconstr Surg Glob Open 2015;3:e391.
19. Singh PM, Borle A, Trikha A, Michos L, Sinha A, Goudra B. Role of periarticular liposomal bupivacaine infiltration in patients undergoing total knee arthroplasty-A meta-analysis of comparative trials. J Arthroplasty 2017;32:675-880.