Letter to the Editor

Invited author response to editorials on liposomal bupivacaine in minimally-invasive thoracic surgery: the judge is in favor but the jury is still out

Sora Ely[1,2], Dana A. Dominguez[1,2], Jeffrey B. Velotta[2]

[1]UCSF East Bay Surgery, Oakland, CA, USA; [2]Department of Surgery, Kaiser Permanente – Oakland Medical Center, Oakland, CA, USA

Correspondence to: Sora Ely, MD. 1411 E 31st St, QIC 22134, Oakland, CA 94602, USA. Email: sora.ely@ucsf.edu.

Provenance: This is an invited article commissioned by the Editorial Office, *Journal of Thoracic Disease*.

Response to: Martin LW, Mehran RJ. Intercostal nerve blockade for thoracic surgery with liposomal bupivacaine: the devil is in the details. J Thorac Dis 2019;11:S1202-5.

Caso R, Marshall MB. Liposomal bupivacaine in minimally invasive thoracic surgery: something is rotten in the state of Denmark. J Thorac Dis 2019;11:S1267-9.

Submitted Apr 30, 2019. Accepted for publication May 07, 2019.

doi: 10.21037/jtd.2019.05.28

View this article at: http://dx.doi.org/10.21037/jtd.2019.05.28

We appreciate the insightful editorials by Martin and Mehran (1) and Caso and Marshall (2) regarding our recent manuscript (3), which described a decreased length of stay (LOS) in patients receiving intercostal nerve blocks with liposomal bupivacaine (LB) (Exparel®) compared to standard bupivacaine after video-assisted thoracoscopic surgery (VATS) or minimally-invasive esophagectomy (MIE). Both articles raise a number of interesting points, and we would like to clarify some details of our study and expand on their discussion.

There were several questions regarding technical details from both pairs of authors. We did not feel that these details were critical for a small pilot study and because of the historical cohort study design; nevertheless, it is worthwhile to clarify that the surgical techniques were consistent among the 3 surgeons as well as throughout the study period. Our VATS procedures are performed with a routine 3-port approach from which there is little variation, and our MIEs are performed in a totally minimally-invasive manner, via a 5-port thoracoscopic and 6-port laparoscopic Ivor-Lewis approach. Because we desired to focus on the effect of liposomal versus standard bupivacaine as applied to intercostal nerve blockades (INB), we did not discuss the local analgesia for MIE patients' abdominal port sites, but these incisions were treated with 10–20 mL of standard bupivacaine (0.25%, with epinephrine 1:200,000) intradermal local analgesia as is common for laparoscopic surgery. Caso and Marshall raise a cogent concern about the role of chest tubes in postoperative pain for thoracic surgery patients, but it is rare for this to be a factor in our patient population beyond 24 hours. Both VATS and MIE patients exit surgery with only one rigid chest tube inserted through a port site; MIE patients additionally have a soft round drain placed in the thoracic cavity through a small incision. The MIE patients go home with their small drains, but in the absence of a large air leak or other abnormal findings, chest tubes are removed during morning rounds on the first postoperative day following both VATS and MIE. The chest tube is left in place at that time in only a small minority of patients, and even fewer patients are discharged home with a chest tube in place.

With regards to the specifics of analgesic administration, our INB technique is similar to those described by other publications, including from the authors of these editorials (1,2). We perform the INBs transcutaneously and somewhat posteriorly under direct VATS visualization, injecting all rib spaces—not only the port site intercostal spaces, as mentioned by Martin and Mehran—from one above the most superior incision to one below the most inferior. With our usual port site configuration, a minimum of 6 rib spaces are treated. The "equivalent" or matching dose of standard bupivacaine (SB) that we referred to is based on volume: 30 mL of SB (0.25% bupivacaine with epinephrine 1:200,000), compared to 30 mL of LB solution (manufacturer 20mL diluted with

© Journal of Thoracic Disease. All rights reserved.

10 mL saline), although our study was limited by greater variability in this dose due to less standardization prior to the use of Exparel®. While a majority of the prior studies have administered these blocks at the start of the case, the first study to compare SB-INB and LB-INB in exclusively VATS patients also administered the INB at case end, and the study found a reduction in opiate utilization (4).

Caso and Marshall commented on our operative time and LOS being shorter than expected. We do not have additional explanation for this other than that the numbers in our manuscript were accurate, and our practice has routinely discharged these patients much earlier than national averages. The study period was chosen to exclude the implementation of thoracic surgery regionalization and enhanced recovery after thoracic surgery pathways at our hospital, after which both measures shortened further; a report of that experience is currently being finalized for submission. This overall short LOS influenced our decision to focus on only the first 24 hours postoperatively: the majority of our patients discharge between 24 and 48 hours after surgery and so with this small sample size, there were not enough patients to provide a meaningful comparison past that timepoint. Caso and Marshall also asked the important question of whether there were any pain-related bouncebacks; a manual chart review showed that none of the emergency department visits or readmissions in either study group were pain-related.

We commend Martin's group for their dramatic reduction in morphine equivalent consumption postoperatively (5), but would point out that our postoperative opiate usage is comparable to other reports. The morphine equivalents in our study groups of 29.8 and 31.9 mg are lower than both the experimental group's 44.60 and control group's 117.58 mg described by Kelley *et al.* (6), and are likely similar to the 24-hour usage before enhanced recovery pathway-implementation in the study by Martin *et al.*, given a median total usage of 86 mg over 6.0 days (5).

We thank the editorial authors for identifying these technical points needing clarification, and would like to add to their broader discussion about the interpretation of the current literature and practice of LB use for INB. Each editorial cites different studies from within the LB-INB thoracic literature that nonetheless all report disparate findings. It is difficult to reach a decisive verdict on the precise impact of LB-INB analgesia on thoracic surgery outcomes from studies that are so variable in both their design and results, but all studies have reported one or more positive effects. Perhaps the most consistent finding has been a decreased LOS, as in our study, a study by Mehran *et al.*, and others (3,7-9). Our study was the first to examine ambulation as an outcome, an endpoint that may have implications for short- and long-term morbidity (3). Additionally, of the 3 LB-INB studies focused on VATS cases (3,4,6), ours was the first to evaluate pain scores.

We agree with both editorials that the limited available data does not yet demonstrate a consistent trend, although compelling firsthand clinical experience is evident in the conclusions of both articles. We must respectfully disagree with the conclusion by Martin and Mehran that our study "reports no benefit to LB compared to bupivacaine PINB for VATS surgery" (2), as we felt that the reduction in LOS and increase in early ambulation were clinically significant, particularly in the absence of an increased need for opiate analgesia supplementation (3). We are, in fact, seemingly in agreement with the other authors that our patient care experience has clearly manifested positive clinical changes since integration of LB-INB into our analgesic regimen, despite the vagaries in the published data. As such, we have been conducting additional research that may address some areas of concern through several modifications to our original study design. While we felt that our initial study on a small, mixed VATS-MIE patient population was valid as a first step, we agree with the other authors that a more homogeneous study population could make interpretation of results simpler and cleaner. Due to the more promising findings among our VATS lobectomy sub-group, and given that these patients may theoretically derive greater benefit from the LB-INB than VATS wedge resection patients, we have undertaken a larger study of only VATS lobectomy patients. We were also surprised in our pilot study that 24-hour pain scores were slightly but statistically significantly higher in the experimental group. Though the other VATS studies did not evaluate pain scores, this odd finding may be reflected in Martin *et al.*'s supplementation of LB-INBs with a subarachnoid spinal morphine injection for their VATS lobectomy patients (5). We speculated that a potential pitfall of existing LB studies may be that the longer interval to onset results in a lower level of analgesia in the immediate/early postoperative period, and so we added a second experimental group to our study. Our hospital recently approved, as is described for other applications in the Exparel® prescribing information (10), the use of an SB-LB mixture, and we are now using this solution for our INBs. Ultimately, Caso and Marshall are correct in pointing out that a large, randomized, controlled trial is needed, but we believe that this forthcoming study from a large sample of VATS lobectomy

© Journal of Thoracic Disease. All rights reserved.

patients receiving INB with either SB, LB, or SB+LB, may be one more step toward a final ruling on the effects of Exparel® use in INB for VATS analgesia.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Martin LW, Mehran RJ. Intercostal nerve blockade for thoracic surgery with liposomal bupivacaine: the devil is in the details. J Thorac Dis 2019;11:S1202-5.
2. Caso R, Marshall MB. Liposomal bupivacaine in minimally invasive thoracic surgery: something is rotten in the state of Denmark. J Thorac Dis 2019;11:S1267-9.
3. Dominguez DA, Ely S, Bach C, et al. Impact of intercostal nerve blocks using liposomal versus standard bupivacaine on length of stay in minimally invasive thoracic surgery patients. J Thorac Dis 2018;10:6873-9.
4. Parascandola SA, Ibañez J, Keir G, et al. Liposomal bupivacaine versus bupivacaine/epinephrine after video-assisted thoracoscopic wedge resection. Interact Cardiovasc Thorac Surg 2017;24:925-30.
5. Martin LW, Sarosiek BM, Harrison MA, et al. Implementing a thoracic enhanced recovery program: lessons learned in the first year. Ann Thorac Surg 2018;105:1597-604.
6. Kelley TM Jr, Bailey DW, Sparks P, et al. Intercostal nerve blockade with Exparel® results in lower opioid usage during the first 24 hours after video-assisted thoracoscopic surgery. Am Surg 2018;84:1433-8.
7. Rice DC, Cata JP, Mena GE, et al. Posterior intercostal nerve block with liposomal bupivacaine: an alternative to thoracic epidural analgesia. Ann Thorac Surg 2015;99:1953-60.
8. Khalil KG, Boutrous ML, Irani AD, et al. Operative intercostal nerve blocks with long-acting bupivacaine liposome for pain control after thoracotomy. Ann Thorac Surg 2015;100:2013-8.
9. Mehran RJ, Walsh GL, Zalpour A, et al. Intercostal nerve blocks with liposomal bupivacaine: demonstration of safety, and potential benefits. Semin Thorac Cardiovasc Surg 2017;29:531-7.
10. Exparel® (bupivacaine liposome injectable suspension) [package insert]. San Diego, CA: Pacira Pharmaceuticals, Inc.; 2018.

Cite this article as: Ely S, Dominguez DA, Velotta JB. Invited author response to editorials on liposomal bupivacaine in minimally-invasive thoracic surgery: the judge is in favor but the jury is still out. J Thorac Dis 2019;11(5):E71-E73. doi: 10.21037/jtd.2019.05.28

© Journal of Thoracic Disease. All rights reserved.