Prolonged Phrenic Nerve Blockade with Liposomal Bupivacaine

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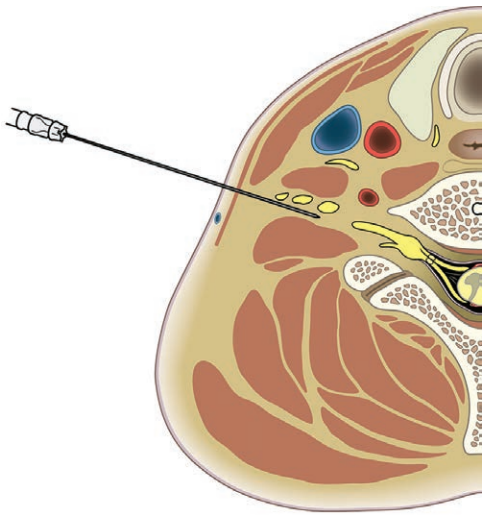
In orthopedic shoulder surgery, obtaining optimal pain control extending beyond the immediate postoperative period is desired for better outcomes second to improved mobilization and analgesia. Interscalene nerve blocks are highly effective and widely used for postoperative pain management after shoulder surgery.[1] However, they can be associated with unwanted side effects, including ipsilateral Horner's syndrome, recurrent laryngeal nerve palsy, and phrenic nerve blockade. Of these complications, the incidence of phrenic nerve blockade approaches 100%. Phrenic nerve palsies are of interest due to the potential to cause hemidiaphragmatic paresis, which can lead to respiratory failure in those at risk.[2,3] Additionally, in pursuit of longer anesthetic control beyond what can be obtained by the short-acting single-injection anesthesia, practitioners have been enticed to place nerve block catheters, add adjuvants to the local anesthetic solutions, or, more recently, use liposomal bupivacaine. Liposomal bupivacaine, a multivesicular drug delivery system, intended to create an extended-release depot of bupivacaine that is marketed as lasting up to 72 h. Its use for interscalene nerve block was approved by the U.S. Food and Drug Administration (Silver Spring, Maryland) in 2018. At first glance, this provides an attractive option given the potential for prolonged analgesia without the maintenance that comes with a continuous nerve block catheter system. Given its potential to provide a lengthened duration of action, it is important to address the safety of liposomal bupivacaine as the extended analgesia may come with a lengthy duration of side effects, such as a prolonged phrenic nerve blockade.



"…at 24 h after [interscalene] nerve block, the liposomal bupivacaine group had sustained reductions in both diaphragm excursion and respiratory function…"

In this issue of Anesthesiology, Berg *et al.*[4] report the results of a clinical trial comparing the effects of interscalene nerve blocks using either plain bupivacaine or liposomal bupivacaine on diaphragmatic excursion. In this blinded study, 26 adult patients were randomized to receive an interscalene nerve block before total shoulder arthroplasty with either 20 ml 0.5% bupivacaine or 20 ml of a mixture of 10 ml liposomal bupivacaine solution with 10 ml 0.5% bupivacaine. Patients had pulmonary function testing and evaluation of diaphragmatic excursion by ultrasound preblock and postblock in the postanesthesia care unit and at 24 h. As would be expected with the high incidence of phrenic nerve blockade from interscalene nerve blocks, patients in both groups had decreased respiratory function (such as forced expiratory volume in 1 s, forced vital capacity, and peak expiratory flow rate) and diaphragm excursion in the postanesthesia care unit. However, the liposomal bupivacaine group had a significantly larger reduction in peak expiratory flow rate and diaphragm movement with the sigh breath. The most intriguing finding of this study, however, was the difference between the two groups at 24 h. Whereas the plain bupivacaine group's respiratory parameters returned to baseline preblock values (except for peak expiratory flow rate) at 24 h after the nerve block, the liposomal bupivacaine group had sustained reductions in both diaphragm excursion and respiratory function (forced expiratory volume in 1 s, forced vital capacity, and peak expiratory flow rate). In contrast to the respiratory data, the investigators found no significant difference in maximum pain scores between the two groups at 24 h postblock. Berg *et al.*[4] reported that despite

Image: G. Nelson/J. P. Rathmell.

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the significant reduction in respiratory parameters noted in the postoperative period, no major adverse events were noted, and no patients in either group developed subjective dyspnea or oxygen desaturation.

More detailed information on how the patients were evaluated for subjective dyspnea or how often oxygen saturation was checked would be helpful as it has been shown that postoperative hypoxemia is common and often unnoticed in the postsurgical population, regardless of brachial plexus blockade, when pulse oximetry is intermittent instead of continuous.[5] Furthermore, postoperative supplemental oxygen use can mask hypoxemia, and unfortunately, there was no account for supplemental oxygen use between the two groups. Finally, despite blinding of the patients, there was inconsistent blinding of the investigators of outcome assessments, which could be a source of detection bias. What we ascertain from this study is that while critical respiratory failure was not observed, possibly due to the power of the study, an observable and quantifiable decrease in respiratory capacity was evidenced in liposomal bupivacaine at 24 h after interscalene nerve block. Since this study only evaluated up to 24 h after the interscalene nerve block, the actual duration of this effect on the diaphragm is unknown.

In general, no study has shown a clear relationship between decreased diaphragmatic function and clinically significant respiratory complications. Previous studies examining the effect of interscalene nerve blocks on phrenic nerve blockade have used diaphragm movement and/or pulmonary function tests as the primary outcome rather than respiratory complications. Respiratory distress from phrenic nerve blockade is fortunately a rarer outcome and thus needs to be studied with a larger sample size to understand how certain interventions impact it. However, as with any intervention, it is desirable to be able to have a reversal or contingency strategy at hand. A small body of evidence including case studies have described that the effect of nonliposomal local anesthetics on phrenic nerve paralysis can be improved and reversed with normal saline washout through a catheter while maintaining adequate analgesia.[6] On the other hand, the effectiveness of the washout technique to reverse phrenic nerve blockade by liposomal bupivacaine is unknown.

Berg *et al*.[4] did not find a difference in pain scores at 24 h between the liposomal bupivacaine and plain bupivacaine groups, but worst pain score was a secondary outcome. Multiple previous clinical trials have compared liposomal bupivacaine to nonliposomal local anesthetics and examined pain score as a primary outcome. One meta-analysis comparing the use of liposomal bupivacaine to plain bupivacaine for peripheral nerve blocks included nine randomized clinical trials. The meta-analysis found a statistically significant difference in the area under the curve pain scores for the 24- to 72-h period of 1.0 cm · h (95% CI, 0.5 to 1.6; $P = 0.003$) in favor of liposomal bupivacaine. This small difference was thought to be clinically unimportant as total opioid consumption (up to 72 h postblock) and time to first analgesic request were not different between patients who had received liposomal bupivacaine and those who had received plain bupivacaine for the peripheral nerve block.[7]

Aside from liposomal bupivacaine, prolonged perineural blockade can be achieved with local anesthetic adjuvants and continuous peripheral nerve blocks through perineural catheters. The addition of adjuvants (such as dexamethasone or clonidine) in nerve blocks can prolong the effect of single injections, but the practice is off label and therefore a potential liability. Continuous nerve blocks through peripheral nerve catheters have been shown to be superior to single injections in prolonging analgesia and demonstrate lower postoperative pain scores, decreased postoperative opioid consumption, decreased postoperative nausea vomiting, and increased patient satisfaction.[8,9] Unfortunately, not all institutions have the resources to facilitate the deployment of continuous peripheral nerve blocks.

Regardless of the potential limitations of the study of Berg *et al*.,[4] it is a meaningful contribution to the field of regional anesthesia. This study, on a small group of patients, clearly demonstrates that liposomal bupivacaine will significantly decrease phrenic nerve function at 24 h postinjection and possibly much longer. Therefore, caution is warranted if using liposomal bupivacaine for interscalene nerve blocks in patients with any pulmonary compromise. In addition to informed consent regarding phrenic nerve risks, we suggest that the practitioner consider having in place a robust observation capacity to monitor for hemidiaphragm paresis before considering liposomal bupivacaine, given the stakes involved and the lack of proven reversal strategies.

Competing Interests

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