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CORR Insights®: No Difference in Early Analgesia Between Liposomal Bupivacaine Injection and Intrathecal Morphine After TKA

Philippe Richebé MD, PhD, Véronique Brulotte MD, MSc

Where Are We Now?

The randomized controlled trial by Barrington and colleagues raises new questions about the utility of using liposomal bupivacaine-based periarticular injection (PAI) (Exparel; Pacira Pharmaceuticals, Parsippany, NJ, USA) to improve pain management after TKA, as the only benefit was a decrease in the postoperative itching from 38% to 15% when

intrathecal morphine was not injected. This randomized controlled trial also shows that interventions such as intraarticular addition of extended-release liposomal bupivacaine or intrathecal morphine do not clearly improve pain profiles or opioid requirements after TKA surgery when compared to a PAI with standard bupivacaine and associated with multimodal analgesia including acetaminophen, Celebrex (G.D. Searle

LLC Division of Pfizer Inc, New York, NY, USA), OxyContin (Purdue Pharma LP, Stamford, CT, USA), and Decadron (Merck & Co Inc, Kenilworth, NJ, USA). This raises the real question: Is there still room for liposomal bupivacaine in TKA surgery?

Administering local anesthetic in combination with multimodal analgesia has been reported to offer better pain relief after TKA [20]. More recently, a meta-analysis [13] reported the same type of positive impact on pain management after TKA when PAI was used. Liposomal bupivacaine (Exparel) was recently approved on the US market and has been used in several studies on TKAs to determine whether it might decrease pain or accelerate recovery after TKA.

Several retrospective studies reported that liposomal bupivacaine did not improve the quality of postoperative pain profiles, nor did it improve the quality of recovery of these patients [11] or was even worse than a cheaper PAI [2]. This also was true in chronic opioid users scheduled for TKA [16]. Nevertheless, a recently published retrospective study on 665 patients [3]

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P. Richebé MD, PhD (✉)
Department of Anesthesiology,
Maisonneuve-Rosemont Hospital,
CIUSSS-de-l'Est-de-l'Ile-de-Montréal,
University of Montreal, 5415, Boulevard
De L'Assomption, Montréal, QC H1T
2M4, Canada
e-mail: philipperichebe@live.com

V. Brulotte MD, MSc
Department of Anesthesiology, Faculty
of Medicine, University of Montreal,
Montréal, QC, Canada

suggested liposomal bupivacaine might be a factor associated with lower VAS scores after TKA. More recently, prospective studies were performed and compared the PAI with standard bupivacaine to the extended-release liposomal bupivacaine. Once again, in this randomized trial, the liposomal bupivacaine did not demonstrate superiority in terms of pain management, but it slightly improved walking distances after TKA [6]. The additional cost of liposomal bupivacaine was not justified [15].

The present study is important because it underlines the fact that exposing patients to intrathecal morphine increases risks without much benefit to postoperative patients who underwent TKA. Additionally, it shows that there is no need to spend more money to use a drug that will not be more efficient than the PAI using standard bupivacaine.

While an important study, Barrington and colleagues did not answer one important question: Is PAI better than femoral nerve block? Indeed, femoral nerve blockade has been the preferred strategy for pain management after TKA surgery in many centers around the world, and has been shown to be superior to morphine patient-controlled analgesia and equivalent to epidural pain management [4, 22]. More recently, it was reported that PAI might be better than continuous

femoral nerve block in terms of pain relief after TKA in retrospective [17, 23] and prospective trials [12, 19], and might even improve the time for discharge from the hospital [9]. One recent meta-analysis of 14 randomized controlled trials confirmed that femoral nerve block was not superior to PAI in terms of opioid consumption, pain scores (at rest or movement), ROM, muscle strength and length of stay [1]. Continuous PAI was also reported to be equivalent to continuous femoral nerve block in terms of analgesic profiles after TKA [21], or even better and allowed for better function and less risk of motor weakness [18].

Where Do We Need To Go?

These recent reports and the current study raise a number of interesting questions. Should we compare liposomal bupivacaine PAI with PAI using standard bupivacaine? Should we compare liposomal bupivacaine to femoral nerve block? How about comparing liposomal bupivacaine to femoral nerve block loaded with liposomal bupivacaine or to the recently developed adductor canal block [7] loaded with extended-release liposomal bupivacaine? One cohort study [5], partly retrospective and partly prospective, evaluated this question and concluded that liposomal

bupivacaine PAI was not superior to femoral nerve block for pain management after TKA [5].

How Do We Get There?

Since femoral nerve block is not superior to PAI and even less superior to continuous PAI, we are left with one strategy that might be of interest for using liposomal bupivacaine: The use of repeated injections of liposomal bupivacaine-based PAI (Exparel) in either femoral nerve block [8] or adductor canal block [7], which was proven to be safe [10]. Another option would be to use an intraarticular catheter with repeated injections of extended release of liposomal bupivacaine to improve pain relief without motor blockade. In the latter case, the number of reinjections would be considerably lower than PAI using administration of standard bupivacaine.

Researchers who study liposomal bupivacaine in combination with periarticular multimodal drug injections should confirm that the mixture used does not disturb the pharmacokinetics or the extended-release liposomal bupivacaine. Indeed, Pacira Pharmaceutical Inc. underlines the fact that nonbupivacaine-based local anesthetics (including lidocaine) may cause an immediate release of bupivacaine from

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liposomal bupivacaine-based PAI (Exparel) if administered together locally [14]. There is little data available on Exparel's stability when mixed with PAI for TKA. As a consequence, in vitro pharmacology studies are warranted prior to using liposomal bupivacaine with periarticular multimodal drug injection in clinical trials in order to avoid any risk of Local Anesthesia Systemic Toxicity.

We still need prospective studies on TKA that will evaluate invasive techniques with the highest efficacy and the lowest risk of side effects and/or toxicity. These studies will have to evaluate multiple objectives such as pain profiles, opioid requirements, opioid side effects, motor function, postoperative rehabilitation, patient satisfaction, time for hospital discharge, incidence of postoperative chronic pain, and cost effectiveness. There is no doubt that these studies will need to be multicenter collaborative efforts in order to enroll sufficient numbers of patients.

Favoring PAI over nerve blocks (especially over adductor canal blocks) remains a controversial choice, and too soon to draw any conclusions. Even though we want to keep our perioperative pain management for TKA simple, we still need to compare repeated administration of liposomal bupivacaine in PAI catheters with the repeated PAI using standard

bupivacaine. We also need to compare these results to a third group—the adductor canal nerve block also loaded with liposomal bupivacaine. Further studies are warranted before we can determine what role, if any, liposomal bupivacaine should play in the analgesic regimen of patients undergoing TKA.

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