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Liposomal Bupivacaine Infiltration for Knee Arthroplasty

Significant Analgesic Benefits or Just a Bunch of Fat?

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TOTAL knee arthroplasty is among the most common and painful surgical procedures, with more than 700,000 performed annually in the United States alone. Infiltration of the surgical site with local anesthetic is frequently performed by surgeons to provide postoperative analgesia, although the duration of action is limited to that of the longest-acting local anesthetic available, bupivacaine. By encasing standard bupivacaine in liposomes, the duration of local anesthetic release may be prolonged as the liposomes break down and emit the active medication. In 2011, the first (and currently only) liposomal bupivacaine formulation was approved by the U.S. Food and Drug Administration for surgical wound infiltration (Exparel; Pacira Pharmaceuticals, Inc., USA). In the interim, multiple randomized, controlled clinical trials have been published and, while this type of study design has advantages such as determining effectiveness while minimizing confounding, it also has limitations including modest sample size and uncertain generalizability to daily practice.

"…use of liposomal bupivacaine was not associated with a change in billing patterns for opioids… [or] decreased use of naloxone or incidence of opioid-related… complications…"

It is therefore noteworthy that a retrospective cohort study of nearly 90,000 patients appears in this issue of Anesthesiology by Pichler *et al.*, providing the largest, most nationally-representative view to date into the practice patterns of multiple hospitals and practitioners involving liposomal bupivacaine.[1] The authors used the well-known national Premier database to sample patients who underwent total knee arthroplasty with a peripheral nerve block within the United States between 2013 and 2016. A number of significant insights are gleaned from this investigation, including a finding of no clinically meaningful difference in the amount billed for opioids between patients who either did or did not receive liposomal bupivacaine (when accounting for confounding variables). In other words, the use of liposomal bupivacaine was not associated with a change in billing patterns for opioids.

Importantly, the actual opioid consumption was not included in this database, which was designed primarily to capture billing practices in patients undergoing acute care. Unfortunately, the relationship between opioid prescription and consumption is uncertain. For example, bundled payments in which institutions and practitioners are compensated a set amount for performing a total knee arthroplasty may result in an "average" opioid dose being billed, regardless of actual consumption. Similarly, if intravenous patient-controlled analgesia is used, the total amount of opioid in the pump would most likely be billed regardless of the amount consumed. Therefore, we do not have adequate data from this study to definitely address a possible effect of liposomal bupivacaine on decreasing opioid consumption. Conversely, healthcare administrators and policymakers can deduce that the introduction of liposomal

Image: J. P. Rathmell.

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bupivacaine into practices has not decreased opioid charges to a clinically-meaningful degree within the healthcare system.

Highly relevant for both clinicians and policymakers is that the use of liposomal bupivacaine was *not* associated with a decreased use of naloxone or incidence of opioid-related respiratory, genitourinary, central nervous system, or gastrointestinal complications (after accounting for confounding variables). Similarly valuable is the finding that the use of liposomal bupivacaine failed to decrease hospitalization duration or total costs. One might question whether it is realistic to expect the introduction of a single dose of infiltrated liposomal bupivacaine into the surgical wound to decrease either hospitalization duration or costs, but this is precisely what multiple relatively small, retrospective studies—nearly all supported by the manufacturer—have reported for a multitude of surgical procedures, including total knee arthroplasty.[2–5] In contrast, not one of nine randomized, controlled trials comparing joint infiltration/infusion of liposomal bupivacaine and unencapsulated local anesthetic that evaluated length of stay following total knee arthroplasty reported a significant difference.[6–14]

Pichler *et al.* could not determine which patients in their study had received unencapsulated bupivacaine infiltration, so they could not compare the effects of these two formulations. This does not, however, negate their findings of a lack of beneficial effect of liposome bupivacaine in their study, results that stand in stark contrast to smaller retrospective studies that reported decreased hospitalization duration and/or costs by switching from unencapsulated to liposomal bupivacaine or simply adding liposomal bupivacaine (alone or in combination with nonsteroidal antiinflammatory drugs and/or acetaminophen).[2–5,15–18]

A critical caveat is that Pichler *et al.* exclusively included in their analysis patients with a single-injection peripheral nerve block. Of 452,740 total patients within the database, only 88,817—fewer than 20%—received such a block (written personal communication, Stavros Memtsoudis, M.D., Ph.D., F.C.C.P., Hospital for Special Surgery, New York, New York, May 7, 2018). Therefore, their results may not be applicable to more than 80% of patients undergoing total knee arthroplasty nationwide. Although it is conceivable that patients *not* receiving a peripheral nerve block would benefit most from liposome bupivacaine, the preponderance of evidence from the 13 randomized, controlled trials published to date suggests that there are few, if any, benefits in switching from intraoperative infiltration with unencapsulated bupivacaine to liposomal bupivacaine (table 1).

In contrast to infiltration, early trials involving liposomal bupivacaine administered as part of a single-injection peripheral nerve block show promise to significantly extend analgesia and decrease opioid consumption and opioid-related side effects,[19–22] as well as possibly shorten hospitalization

Table 1. Published Randomized, Controlled Clinical Trials Comparing Periarticular Infiltration of Lipo, Bupiv, or Ropiv

Reference	Experimental Group (mg)*	Control Group (mg)*	Primary Pain Endpoint	Opioid Consumption	Manufacturer Contribution
Negative studies					
Alijanipour[6]	Lipo 266	Bupiv 50	Negative	Negative	None
Amundson[7]	Lipo 266 + Bupiv 125	Ropiv 200–400†	Negative	Negative total; Lipo needed more rescue	None‡
Barrington[8]	Lipo 266 + Bupiv 125	Ropiv 250†	Negative	Negative	Funding‡
Bergese[27]	Lipo 532	Bupiv 200	Negative	Not provided	Funding§
Bramlett[28]	Lipo 133–532	Bupiv 150	Negative	Negative	Funding‡,§
Collis[9]	Lipo 266	Ropiv 246	Negative	Negative	None
DeClaire[10]	Lipo 266	Ropiv ?	Negative	Lipo used more total oral opioid	Unclear
Jain[11]	Lipo ?	Bupiv 75†	Negative	Negative	None
Schroer[12]	Lipo 266 + Bupiv 75	Bupiv 150	Negative	Negative	None
Schwarzkopf[13]	Lipo 266 + Bupiv 50	Ropiv 246	Negative	Negative	None
Smith[14]	Lipo 266 + Bupiv ?	Bupiv ? + intraarticular Bupiv infusion	Negative	Negative	None
Positive studies					
Mont[25]	Lipo 266 + Bupiv 100	Bupiv 100 mg	Positive	Positive	Manufacturer provided funding and "participated in the study conception and design; collection, analysis, and interpretation of the data; and review of the manuscript"‡
Snyder[29]	Lipo 266	Ropiv 400	Positive	Positive	None‡

*Indicates only local anesthetics listed (*e.g.,* additives such as epinephrine not listed). †A third treatment group not involving infiltration excluded from chart (*e.g.,* continuous peripheral nerve block). ‡At least one author was a paid consultant to the manufacturer during enrollment year(s). §One author was an employee of the manufacturer during enrollment.

Bupiv = standard bupivacaine; Lipo = liposomal bupivacaine; ? = dosage unknown; Ropiv = ropivacaine.

duration and related costs.[21] Importantly, the U.S. Food and Drug Administration has approved the use of liposomal bupivacaine specifically for transversus abdominis plane and interscalene blocks,[20–22] although other anatomic locations remain off-label at the time of this writing.[19,23] So, the route of administration does, unsurprisingly, appear to influence clinical effects: joint infiltration must be differentiated from use in a peripheral nerve block.

Pichler *et al.* accurately and responsibly state that, "because of the retrospective design, we can only determine associations and not causal relationships. Therefore, associations have to be interpreted taking into account *plausibility* [emphasis added]."[1] As we noted previously, due to the limitations of the Premier database, which was designed to capture billing activity and not opioid consumption, no conclusions may be drawn from the present study regarding the clinical effectiveness of liposomal bupivacaine in decreasing opioid requirements. However, their other findings regarding a lack of change in hospitalization duration/costs and opioid-related complications with the addition of liposomal bupivacaine are more than plausible given the previously published data from multiple well-controlled, randomized clinical trials. In this respect, the investigation by Pichler *et al.* is important because it lends external validity to the findings of the majority of randomized trials.

Medicine is constantly evolving with ongoing research and the application of liposome bupivacaine for analgesia after total knee arthroplasty will certainly be no different. For example, recent industry funded studies theorize that liposome bupivacaine may be superior to plain bupivacaine for knee infiltration using a specific technique involving 94 to 103 separate needle passes/injections, a technique which likely deviates from common practice (based on nearly all other published reports).[24,25] However, given the results of a large majority of published prospective clinical trials, and now a large retrospective cohort study, it seems incumbent on those proposing a switch to liposomal bupivacaine to provide high-quality data conclusively demonstrating results that justify the 100-fold increase in cost.[12,26]

Competing Interests

Dr. Ilfeld's institution has received funding and/or product for his research from Myoscience (Redwood City, California), Epimed (Farmers Branch, Texas), Infutronics (Natick, Massachusetts), Teleflex Medical (Research Triangle Park, North Carolina), SPR Therapeutics (Chapel Hill, North Carolina), Heron Therapeutics (San Diego, California), and Pacira Pharmaceuticals (San Diego, California). In addition, Dr. Ilfeld has directly received funding as a consultant to Pacira Pharmaceuticals (most recently November 2014). Dr. Gabriel's institution has received funding and/or product for his research from Myoscience, Epimed, Infutronics, and SPR Therapeutics. Dr. Eisenach has directly received funding from Adynxx (San Francisco, California) as a consultant in the development of a DNA-based spinal injection to speed recovery after surgery.

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