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CLINICAL EVIDENCE DOES NOT SUPPORT THE USE OF LIPOSOMAL BUPIVACAINE, LEAVING PATIENTS WITHOUT ADEQUATE POST-SURGICAL PAIN CONTROL

A Response to Three Publications in *Anesthesiology* Volume 134, Issue 2, February 2021

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The 72-Hour Window for Post-Surgical Pain

Postoperative pain continues to be inadequately managed in a surprising proportion of patients and is associated with numerous negative clinical, patient-reported, and health economic outcomes.[1-2] Moreover, poorly controlled acute pain after surgery has been consistently shown to be a predictive factor for the development of chronic pain. More effective analgesic/anesthetic perioperative measures may help prevent the adverse consequences of poorly controlled pain, including its transition to persistent pain and the associated dependence upon opioids.

Pain control following surgery is a priority for both the patient and the physician. Post-surgical pain control helps speed the patient's recovery and reduces chances of complications, such as pneumonia, blood clots and opioid addiction. Pain needs to be managed carefully, with the patient and healthcare provider working together to come up with the right plan. Post surgical pain often extends beyond the duration of analgesia from a single administration of a local anesthetic like bupivacaine hydrochloride, both for periarticular and single shot nerve block. Current multimodal techniques generally provide adequate pain control for the first 24 hours or so; however, significant rebound effect can occur when these methods wear off (often when the patient has been rapidly discharged from an ambulatory surgery center).

A long sought-after goal is the ability to extend the duration of analgesia to 72 hours and beyond to prevent the rebound effect. Various adjuvants have been proposed but currently none have been approved to extend analgesia beyond 24 hours.[3-6]

Liposomal bupivacaine was developed with the goal of achieving that sought after 72-hour duration of postsurgical analgesia.[7-8] The manufacturers hoped to accomplish this by encasing standard bupivacaine within a liposomal carrier to achieve a sustained release over time. In theory, this should provide a sustained release of bupivacaine. The pharmacokinetic data demonstrates that slow release of bupivacaine from liposomal carriers can be detected for 48 hours and beyond. However, the analgesic duration cannot be inferred from the time of bupivacaine detectability within the blood. The literature surrounding the supposed benefits of liposomal encapsulation has not supported the hypothesis of extended duration of analgesia.

Multiple reports in the peer-reviewed literature show no clinical difference between liposomal bupivacaine and standard bupivacaine with regard to duration of analgesia- both only achieve approximately 24 hours of postsurgical analgesia.[9-11]

Recent Publications Surrounding Liposomal Bupivacaine

In February of 2021, *Anesthesiology* published three manuscripts discussing the usage of liposomal bupivacaine. These included two review papers by lead authors Nasir Hussain, M.D. and Brian M. Ilfeld, M.D., as well as an editorial by Mary Ellen McCann, M.D. These publications have confirmed what I have seen in real-world evaluations of liposomal bupivacaine- that there is no clinical advantage to using liposomal bupivacaine over standard bupivacaine.

Perineural Liposomal Bupivacaine Is Not Superior to Nonliposomal Bupivacaine for Peripheral Nerve Block Analgesia is a meta-analysis of nine trials (with a total of 619 patients). The study found that while the mean difference in area under the curve (AUC) for pain-at-rest scores was statistically in favor of liposomal bupivacaine, this difference failed to meet the threshold for clinical significance. It is important to note that when the sole industry-sponsored study was excluded, the difference between the two groups was rendered nonsignificant.

This finding is particularly troubling to me, as I have personally been involved with numerous industry-sponsored studies that have had the appropriate controls in place to mitigate any sources of bias. It should be noted that favorable outcomes for liposomal bupivacaine in industry-sponsored studies has also been reported by other investigators.[12-13]

The authors concluded that:

> **"Perineural liposomal bupivacaine provided a statistically significant but clinically unimportant improvement in the AUC of postoperative pain scores compared with plain local anesthetic."**

Clinical Effectiveness of Liposomal Bupivacaine Administered by Infiltration or Peripheral Nerve Block to Treat Postoperative Pain is a systematic review of all randomized, controlled trials (76 trials) involving the clinical administration of liposomal bupivacaine to control postoperative pain. The authors state that 35-40% of randomized controlled trials reviewed had evidence of high risk or some concern for bias. Sources of bias highlighted include comparing a maximum dose of liposomal bupivacaine versus a submaximal dose of bupivacaine.

Another source of bias is using AUC as the statistical tool. AUC is known to show significant difference more likely than individual time, giving the impression of extended duration when none exists. In addition, AUCs were not determined exclusively using actual pain scores, but rather with the "windowed worst-observation-carried-forward + last-observation-carried-forward ('wWOCF+LOCF') imputation method" that the FDA states can result in "exaggerated positive effect, biased in favor of treatment."[14] It was also reported that of the 76 randomized, controlled trials, 30 were either unregistered or registered after enrollment. This presents a major risk for Type 1 errors- finding a difference when none truly exists.

The subject of bias in industry sponsored trials was raised in this publication as well- the authors note that liposomal bupivacaine was found to be superior to comparators in 46% of trials that reported funding from industry sources,[12-15] and conclude:

> **"The preponderance of evidence fails to support the routine use of liposomal bupivacaine over standard local anesthetics."**

Finally, an editorial by Dr. McCann, *Liposomal Bupivacaine -Effective, Cost-effective, or (Just) Costly?* summarized the previous two papers and added her unique insight. Dr. McCann was the chair for the FDA's Anesthetic and Analgesic Drug Products Advisory Committee February 14 and 15, 2018, which advised on the NDA application for expanded indication for liposomal bupivacaine for nerve blocks. She stated that she was not surprised by the findings of the other two authors in light of the early studies performed for the regulatory approval of liposomal bupivacaine in 2006.[16-17] At that time, the manufacturer submitted five phase 2 active comparator-controlled studies and three phase 3 active comparator-controlled studies using nonliposomal bupivacaine as the comparator. None of these eight studies showed clinical or statistical difference between the two formulations.

Having failed to demonstrate a benefit over nonliposomal bupivacaine, in 2009, the sponsor submitted two phase 3 placebo-controlled clinical trials

showing efficacy of liposomal bupivacaine against placebo. Despite no greater efficacy of liposomal bupivacaine than nonliposomal bupivacaine, the Food and Drug Administration in 2011 approved liposomal bupivacaine for surgical site infiltration to relieve postoperative pain for hemorrhoidectomy and bunionectomy.[17] It should be noted that a sponsor needs to prove basic safety and efficacy to gain FDA approval, not superiority to existing treatments. Therefore, an FDA approval is not necessarily an indication of better clinical outcomes compared to existing treatments.

Dr. McCann points out the significant and aggressive marketing campaign undertaken by the manufacturer of liposomal bupivacaine shortly after FDA approval. It was posited that marketing efforts, rather than clinical data, may have been the source of widespread adoption of liposomal bupivacaine. Dr. McCann also points out that a single dose of liposomal bupivacaine costs $334, compared to $3 for nonliposomal bupivacaine.[18-20]

The author concludes:

> **"In this era of medical austerity, when the benefits and costs of expensive drugs are being considered, one would hope that newly approved expensive drugs would at least be an improvement over existing, inexpensive drugs."**

Looking to the Future

Long-acting, injectable local anesthetics are of considerable interest to both the medical and scientific community. Researchers have suggested that the inflammatory response following surgery may be responsible for attenuating the efficacy of extended-release local anesthetics. It is well documented that the pH surrounding a surgical site drop considerably following the body's inflammatory response. A lowered pH is believed to cause liposomal bupivacaine to stagnate extracellularly, where it cannot have the desired analgesic effect.[21] Several companies are investing in technologies that modulate the pH around incisional sites so that local anesthetics can have the highest potency.[22] I eagerly await robust clinical trials that can demonstrate safety and efficacy of these products, as any product that helps patients manage their post-operative pain represents an advancement in medicine.

I am particularly excited about new technologies that move away from pharmacological approaches altogether by delivering energy-based therapies to provide even longer durations of analgesia.

Clinically Proven Solutions in Post-Surgical Pain Management

The shortcomings of liposomal bupivacaine have a true human impact- patients suffering from post-surgical pain. Extended analgesia, lasting 72 hours or longer, is key to providing positive patient outcomes and lowering the risk of opioid dependence.

Catheter-based continuous blocks have proven to provide the duration of analgesia for up to five days and beyond and the titratability to provide safe and efficacious post-surgical pain management. As Dr. Hussain stated in his manuscript:

> **"Practitioners seeking prolonged analgesia should consider other proven modalities, including catheter-based continuous blocks and local anesthetic adjuncts"**[20,23]

As medical science continues to advance and discover new, innovative solutions, I will continue to advocate for clinically proven solutions that help patients suffering from post-surgical pain.

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