ANESTHESIOLOGY

Liposomal Bupivacaine for Peripheral Nerve Blockade: A Randomized, Controlled, Crossover, Triple-blinded Pharmacodynamic Study in Volunteers

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ABSTRACT

Background: Little is known about the pharmacodynamic characteristics of liposomal bupivacaine. Hypothesizing that they would not identify pharmacodynamic differences from plain bupivacaine during the initial period after administration, but would find better long-term pharmacodynamic characteristics, the authors designed a randomized, controlled, triple-blinded, single-center study in volunteers.

Methods: Volunteers aged 18 to 55 yr (body mass index, 18 to 35 kg/m^2) received two ulnar nerve blocks under ultrasound guidance. Using a crossover design with a washout phase of 36 days or more, one block was performed with liposomal and one with plain bupivacaine. Which came first was determined by randomization. Sensory data were collected by pinprick testing and motor data by thumb adduction, either way in comparison with the contralateral arm. Endpoints included success, time to onset, and duration of blockade. Residual efficacy was assessed by the volunteers keeping a diary. Statistical analysis included Wilcoxon signed-rank and exact McNemar's tests, as well as a generalized estimation equation model.

Results: Successful sensory blockade was noted in 8 of 25 volunteers (32%) after liposomal and in 25 of 25 (100%) after plain bupivacaine ($P < 0.0001$). Significant differences emerged for time to onset, defined as 0% response to pinpricking in four of five hypothenar supply areas ($P < 0.0001$), and for time from onset to 80% or 20% in one of five areas ($P < 0.001$; $P < 0.001$). Carryover effects due to the randomized sequencing were unlikely (estimate, −0.6286; sequence effect, 0.8772; $P = 0.474$). Self-assessment greater than 3.5 days did reveal, for liposomal bupivacaine only, intermittent but unpredictable episodes of residual sensory blockade.

Conclusions: The results show that liposomal bupivacaine is not a suitable "sole" drug for intraoperative regional anesthesia. Findings of its limited long-term efficacy add to existing evidence that a moderate effect, at best, should be expected on postoperative pain therapy.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Liposomal bupivacaine is a bupivacaine formulation developed with the goal of providing long-lasting regional analgesia
- Because it is recommended that liposomal bupivacaine be used in combination with plain bupivacaine, its intraoperative and immediate postoperative potency when used alone are poorly understood

What This Article Tells Us That Is New

- The hypothesis that the pharmacodynamic characteristics of liposomal bupivacaine do not differ from those of plain bupivacaine during the initial period after administration but are better long term was tested in a randomized, controlled, triple-blinded crossover study in 25 volunteers
- Liposomal bupivacaine produced surgical blockade, defined as no sensory response upon pinprick testing, in 32% of volunteers; plain bupivacaine produced surgical blockade in all volunteers
- Compared to plain bupivacaine, liposomal bupivacaine sensory blockade began later and did not last as long
- Despite being described as an extremely long-acting bupivacaine formulation, liposomal bupivacaine produced unpredictable intermittent patterns of residual blockade

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Techniques of peripheral nerve blockade have an important role in perioperative pain therapy. These procedures of regional anesthesia gained reliability and efficiency with the introduction and advancement of ultrasound, enabling direct visualization of nerve structures, adjacent anatomical structures, and the spread of administered drugs.[1–3] As the technical aspects of peripheral nerve blockade have reached an advanced stage, with little room left for improvement, the focus of research has been shifting to other areas, and particular attention is currently being devoted to pharmacologic factors.

Opioid-sparing techniques are a major aspect in today's expectations for perioperative anesthetic management, with long-lasting techniques of regional anesthesia taking center stage.[4] One way to achieve this goal is by catheterization, but these techniques are both complex and potentially compromised by issues of dislocation.[5] The other option, namely pharmaceuticals suitable for use as long-acting local anesthetics, has spurred experimental and clinical interest in combining substances meeting this criterion with specific additive drugs, dexmedetomidine being one example.[6]

In fact, the last time a long-acting local anesthetic was introduced dates back to greater than 25 yr ago.[7] However, even the development of levobupivacaine at the time failed to yield effective levels of sensory blockade greater than 24 h, and what is currently the best combination of a conventional long-lasting local anesthetic and an additive drug is still not capable of providing sufficient postoperative analgesia for more than 24 h.[8]

Liposomal bupivacaine (brand name, Exparel; Pacira BioSciences, USA) was developed with the intention of bridging a gap that existed between limitations in pain control by conventional local anesthetics and subsequent requirements for systemic opioids. The underlying technology, based on bupivacaine encapsulated in a multivesicular liposomal drug-release system, came into existence around 3 decades ago.[9] Human studies began a decade later,[10] with initial applications of site infiltration in hip, knee, or shoulder surgery.[11–13] More recently, liposomal bupivacaine has even been used in blocking the brachial plexus (interscalene approach)[14–16] or the femoral[17,18] or intercostal[19–23] nerve.

However, most of the available research has dealt with infiltration and fascial plane techniques, which cannot truly be considered regional anesthesia.[12,13,24,25] Those very few studies in the literature that do report on liposomal bupivacaine for peripheral nerve blockade have recently been subjected to meta-analysis, the results of which have engendered great controversy.[26]

Despite a good base of citable reports, little is known about the pharmacodynamic characteristics of liposomal bupivacaine, considering that the available clinical studies almost invariably used postoperative opioid requirements as their primary outcome measure. Thus, we hypothesized that the pharmacodynamic characteristics of liposomal bupivacaine would not be found to differ from plain bupivacaine during the initial period of administration while offering better characteristics during an observation period of several days. To test this hypothesis as precisely as possible, we selected a volunteer model in designing a randomized, controlled, triple-blinded, single-center study.

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Materials and Methods

Trial Authorization

As preparatory steps, we obtained approval of the study protocol from the institutional review board (ethics committee) at Medical University of Vienna (ref. 1043/2023; March 24, 2023) and registered the study with the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database on February 27, 2023 (EudraCT No. 2023-000035-74; principal investigator, Markus Zeitlinger, M.D., Ph.D.).

Design and Volunteers

Healthy volunteers aged 18 to 55 yr (body mass index, 18 to 35 kg/m^2) were recruited *via* the Department of Clinical Pharmacology (Medical University of Vienna). Explanation regarding the purpose and risks associated with the study and written informed consent was performed in accordance with the standards of the Department of Clinical Pharmacology (Medical University of Vienna). All of them received payment in line with applicable rules and regulations (420€, approximately $450 USD). Each volunteer received two ulnar nerve blocks, 36 days or more apart, under ultrasound guidance into the nondominant forearm. Using a crossover design, one block was performed with liposomal bupivacaine and the other with plain bupivacaine. Which was administered first was determined by a computer-generated randomization (https://www.randomizer.org/). The aforementioned washout phase (36 days) was more than 30 times the documented biologic half-life of liposomal bupivacaine.[27] Any hypersensitivity or allergy to the study drugs, or poor sonographic visibility of the ulnar nerve at the intended puncture site, resulted in exclusion.

Ulnar Nerve Blockade

A high-resolution ultrasound system (SonoSite X-Porte, Fujifilm SonoSite, USA) was used with a 15-MHz linear probe to visualize the ulnar nerve between the flexor carpi ulnaris, flexor digitorum superficialis (humeroulnar head), and flexor digitorum profundus muscles. Surgical disinfection and sterile preparation of the probe (Safersonic, Austria) were followed by blocking the nerve, using in-plane guidance of a 50-mm facet-tip needle (Polymedic,

Te Me Na SAS, France) to administer the applicable local anesthetic at an injectate volume of 3.0 ml. The study or control solution consisted of liposomal bupivacaine (Exparel) 0.5% (1.0 ml liposomal bupivacaine 1.33% + 2.0 ml NaCl 0.9% = 13.3 mg bupivacaine) or plain bupivacaine 0.5% (15 mg bupivacaine; Aspen Pharma Trading, Ireland), respectively. Since Exparel contains bupivacaine as free base, 1 mg liposomal bupivacaine corresponds to 1.128 mg plain bupivacaine.[28]

Outcome Measures

Success and duration of sensory blockade were defined as the primary endpoints for analysis. As secondary endpoints, we selected time to onset of sensory blockade, time to onset of motor blockade, and duration of motor blockade.

Sensory Blockade

Pinprick tests were performed with 22-gauge short-bevel needles applied at a force (indenting the skin without puncture) producing a consistent sensation of pain in nonblocked areas. Five areas of sensory supply were tested in this way: dorsal side of hypothenar muscles, ulnar side of hypothenar area, palmar side of hypothenar muscles, fifth finger, and ulnar side of fourth finger. The sensory responses were rated by scores ranging from 0 (no response) to 100 (equal to contralateral arm), and the tests were performed at baseline, as well as 2, 4, 6, 8, 10, 15, 20, 30, and 60 min after injecting the local anesthetic, followed by repetitions every 30 min until a score of 80 was obtained in one of the five areas.

Success of sensory blockade was defined as four of these five hypothenar supply areas yielding a pinprick score of 0; onset of blockade as the time from injecting the local anesthetic solution to pinprick scores of 0 in four of the five areas; and duration of blockade as the time from onset to a score of 80 in one area (when in-hospital testing was terminated). For evaluation of a simulated surgical block, we also evaluated the time from onset to a score of 20 in one area. In addition, mean pinprick scores were calculated for all five areas to optimize comparability between both groups.

Motor Blockade

A four-point scale was used to rate motor blockade *via* adduction of the thumb, ranging from 0 (volunteer cannot actively adduct; paralysis) through 1 (significant difference from contralateral; can scarcely adduct even against no counterforce) and 2 (slight difference; can adduct against light counterforce) up to 3 (no difference; can adduct against counterforce). Motor onset was defined as the time from performing the block to a score of 0, and duration of motor blockade as the time from onset to a score of 3. In addition, mean motor scores were calculated to optimize comparability between both groups.

Further and Final Assessments

After the first in-hospital session, all volunteers received a journal to keep track of residual blockade at home. They were instructed to enter into this diary their sensory ratings on a scale of 0% (no perception) to 100% (indistinguishable from contralateral) whenever they felt changes in sensory blockade. A telephone interview about ulnar nerve function and the puncture site, performed 7 days after the second in-hospital session, marked the end of the study period.

Statistical Analysis

A power analysis was conducted in the absence of preexisting comparative studies on the pharmacodynamics of liposomal bupivacaine *versus* plain bupivacaine. Hence, two other reports in the literature were selected: a clinical study on surgical infiltration for inguinal hernia repair demonstrating, consistent with the data of this study, mean ± SD apparent half-lives of 15.9 ± 6.7 or 8.5 ± 2.9 h, respectively[29]; and a rat model yielding sensory blockade for median [interquartile range] durations of 240 [208 to 277] min as compared to 158 [139 to 190] min, respectively.[30]

On this basis, we calculated that 25 volunteers were required to attain a target power of 80%, given a significance level of $P = 0.05$ (two-sided), a target power of 80%, a minimum detectable difference of 20 min, an SD (difference of two values for the same subject) of ± 30 min, and a dropout rate of no more than 5 individuals.

All statistical calculations were performed using SPSS Statistics (version 29.0.0.0, IBM, USA). Results are expressed as mean ± SD or as median values with interquartile ranges. Wilcoxon signed-rank tests were used for nonparametric paired samples and exact McNemar's tests to compare the primary endpoint of the study, namely the success of sensory blockade. In order to statistically compare sensory scores and motor scores over time, the area under the receiver operating characteristics curve for the two scores was calculated using the trapezoidal rule. Since the observation period differed between individual subjects, to enable a paired comparison, the last observation carried forward approach up to 600 min was used. To find out whether the crossover sequence of application (*i.e.*, which drug was administered first or second) made a difference to the primary endpoint, we used a generalized estimation equation model. Differences were considered statistically significant at $P < 0.05$ (two-tailed). Descriptive statistics were used to report the outcome measures of motor blockade.

Results

Volunteers were recruited from May 4, 2023, and the final follow-up was dated November 6, 2023. Of 27 volunteers enrolled in the study, 25 completed both crossover sessions 36 days or more apart in the study ward. Pertinent demographics of these 25 evaluable volunteers are listed in

table 1, and a Consolidated Standards of Reporting Trials (CONSORT)–derived flow chart of the study is provided in figure 1.

Liposomal bupivacaine was found to yield successful sensory blockade in 8 (32%) of these 25 cases, while all blocks (100%) succeeded with plain bupivacaine ($P < 0.0001$).

Table 2 lists our findings for the primary and secondary outcome measures. For better illustration, the mean pinprick and motor scores obtained during the in-hospital sessions greater than 10 h are presented as graphs (figs. 2 and 3).

To compare the durations of sensory blockade against this background of successful blocks in only 32% of the 25 sessions performed with liposomal bupivacaine, block failures were set to infinity in the Wilcoxon signed-rank test. Using this method, highly significant differences between liposomal and plain bupivacaine were found for time to onset ($P < 0.0001$), time to a score of 20 ($P < 0.001$), and time to a score of 80 ($P < 0.001$).

Figure 4 shows the results of self-assessment performed by the volunteers at home over up to 5,000 min (approximately 3.5 days) after having been injected with liposomal bupivacaine for ulnar nerve blockade in the hospital. As no residual sensory effects were reported for plain bupivacaine, only the results for liposomal bupivacaine are shown.

Whether liposomal bupivacaine or plain bupivacaine was administered first or second as part of the randomized crossover design did not make a significant difference to the outcomes of sensory blockade (estimate, −0.6286; SE, 0.8772; Wald, 0.514; $P = 0.474$).

No adverse events were observed throughout the assessments after the blocks. One volunteer (no. 17) reported experiencing muscle pain in the puncture area, which spontaneously resolved within 24 h after administration of liposomal bupivacaine.

Discussion

Exact pharmacodynamic data are essential to the clinical safety and efficacy of local anesthetics. In this study of 25 volunteers, each receiving a single nerve block under ultrasound guidance, liposomal bupivacaine led to successful surgical blockade in merely one third of cases and, despite being described as an extremely long-acting local anesthetic, resulted in unpredictable intermittent patterns of residual blockade.

Regional anesthesia has a key role in minimizing or, indeed, avoiding perioperative pain. Peripheral nerve blocks have come a long way over the past 3 decades, optimization having been achieved mainly by implementing ultrasound guidance.[3,31] Today, as the technical aspects of peripheral regional blocks have reached a stage of being sufficiently well-documented, little room is left for further improvement, so that the focus of research is shifting to pharmacologic considerations of regional anesthesia.

Table 1. Demographics

Volunteers, No.	25
Age, yr	28 [25–32]
Weight, kg	68 [60–81]
Height, cm	173 [167–182]
Body mass index, kg/m^2	22.7 [21.4–24.5]
Sex (female/male)	13/12
Side (left/right)	19/6

Values are number or median [interquartile range].

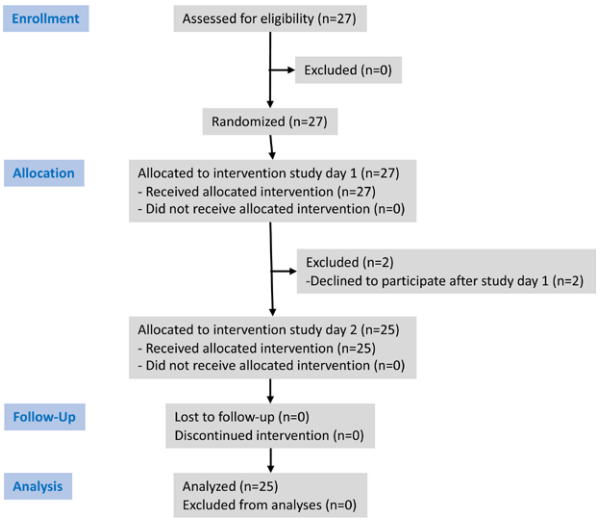

Fig. 1. Flow diagram of the study.

Table 2. Primary and Secondary Outcomes

	Liposomal Bupivacaine	Plain Bupivacaine	*P* Value
Success of sensory blockade, No. (%)	**8/25 (32)**	**25/25 (100)**	**< 0.0001***
Duration of sensory blockade, score of 80, min†	**375 [345–435]**	**562 [450–610]**	**< 0.001‡**
Duration of sensory blockade, score of 20, min†	210 [150–270]	360 [240–480]	< 0.001‡
Onset of sensory blockade, min†	105 [60–150]	15 [10–30]	< 0.0001‡
Success of motor blockade, No. (%)	0/25 (0)	6/25 (24)	
Onset of motor blockade, min†	—	15 [10–28]	
Duration of motor blockade, min†	—	292 [193–434]	

Data are No. (%) or median [interquartile range]. Median values are based on cases of successful blockade exclusively. Primary outcome parameters are in bold.

*Exact McNemar's test. †See text under the subheading "Sensory Blockade" in the Materials and Methods section for explanations. ‡Wilcoxon signed-rank test.

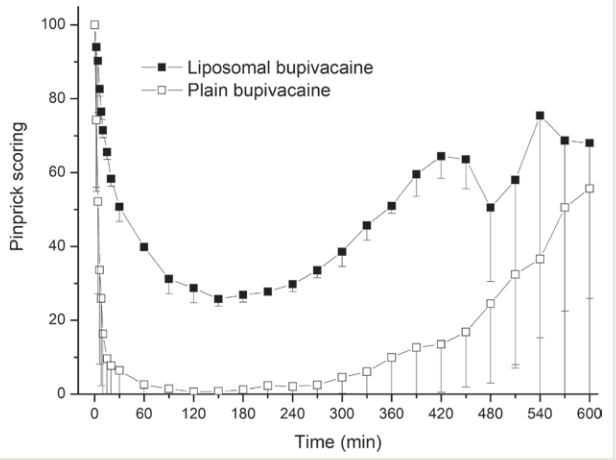

Fig. 2. Mean ± SD sensory scores (obtained by pinprick testing during the in-hospital sessions. Mean ± SD area under the curve (Wilcoxon signed-rank test); $P < 0.0001$.

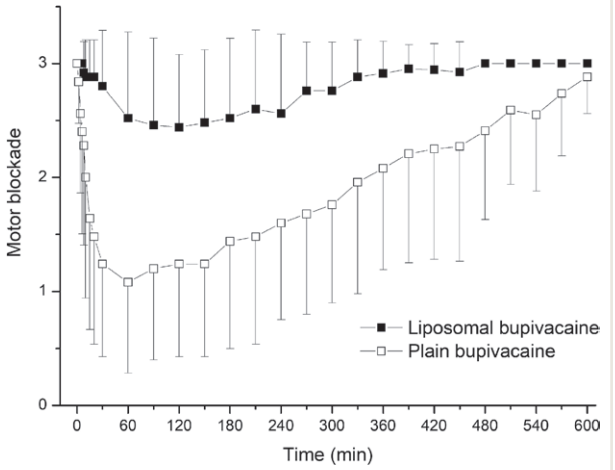

Fig. 3. Mean ± SD motor scores obtained by thumb adduction during the in-hospital sessions. Mean ± SD area under the curve (Wilcoxon signed-rank test); $P < 0.0001$.

Given the current knowledge and techniques of peripheral regional anesthesia, it has become possible to manage patients in opioid-free settings intraoperatively, whereas limitations do remain with regard to postoperative pain control not involving opioids. Even the best-documented combinations of long-lasting local anesthetics and additive drugs fail to control postoperative pain for longer than 24 to 36 h.[32–34] To improve this situation, it is essential to develop novel pharmaceuticals for regional anesthesia.

In recent years, a number of scientific efforts have been made to investigate possible alternatives to conventional local anesthetics, with experimental approaches including the use of neosaxitoxin or capsaicin, to name but two examples.[35–38] Liposomal bupivacaine, as investigated in the current study, was initially used for surgical infiltration with the main focus on postoperative pain therapy.[11–13,24,25,29] Only then was the spectrum of applications expanded to interscalene brachial plexus,[15,16] femoral nerve,[18,39] intercostal nerve,[19–23,40] and fascial plane block[41] techniques.

Most clinical reports that are currently available on liposomal bupivacaine for regional anesthesia have used postoperative opioid consumption or pain as primary outcome measures. Intraoperative pain control can be provided even with conventional local anesthetics for regional anesthesia without opioids.[42,43] As to liposomal bupivacaine, its intraoperative effect remains inconclusive, since all pertinent studies have used it, as recommended, in combination with plain bupivacaine and general anesthesia.[14,15] The current study supports the understanding of the true perioperative clinical potency of liposomal bupivacaine since we avoided a mixture with plain bupivacaine, where a differentiation of pharmacodynamic characteristics between liposomal and plain bupivacaine is not possible. Subsequent studies need to show the (mainly intraoperative) clinical potency of liposomal bupivacaine plus plain bupivacaine in a similar study setting as compared with the current study.

Challenges to evaluating the clinical usefulness of liposomal bupivacaine also arise from a significant bias in publications. Depending on the declaration of funding (industrial *vs.* departmental), liposomal bupivacaine came out as superior to comparators in almost 50% *versus* only around 10% of available studies, respectively.[44] In this context, heterogeneity, equipoise, publication bias, and clinical relevance are essential to high-quality and translational science or, in other words, for scientific results to be directly transferred to clinical practice.

The volunteer model used for our pharmacodynamic evaluation is well established.[33,34] Even if not explicitly mentioned in the spectrum of indications for Exparel, ulnar nerve blockade is an adequate regional anesthetic technique for the current investigation. According to the published manufacturers guidelines, safety and efficacy of Exparel are established only for interscalene brachial plexus nerve block, sciatic nerve block in the popliteal fossa, and adductor canal blockade.[45] Nevertheless, the ulnar nerve is a distal approach for blockade of the brachial plexus compared with the more proximal interscalene approach, and therefore, no specific pharmacodynamic differences between a proximal and distal approach to the ulnar nerves should be expected.

Applying strict criteria to the pharmacodynamic characteristics of nerve blocks, we found liposomal bupivacaine to yield surgical blockade, defined as no sensory response upon pinprick testing, in merely one third of cases. Compared to plain bupivacaine, sensory blockade began significantly later and did not last as long. As we had been expecting block durations of up to 96 h with liposomal bupivacaine,[10] each volunteer received a diary for self-assessment at home after his or her first in-hospital

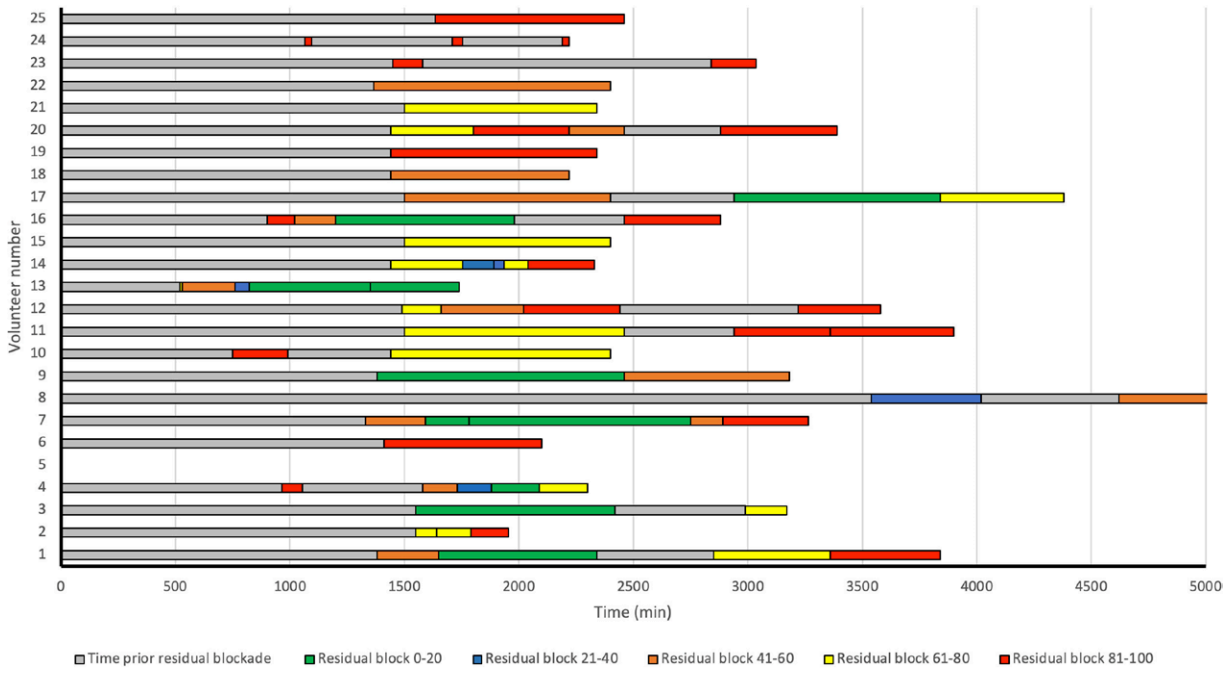

Fig. 4. Diary entries (self-evaluations) by all 25 volunteers over up to 5,000 min (around 3.5 days) after having received liposomal bupivacaine in the hospital. The different residual-block values along the *x*-axis are explained under the subheading "Sensory Blockade" in the Materials and Methods section. The intensity of residual blockade is quantified in five different values (0 to 20, 21 to 40, 41 to 60, 61 to 80, 81 to 100) according to sensory ratings *via* pinprick scoring on a scale of 0% (no perception) to 100% (indistinguishable from contralateral) whenever the volunteers felt changes in sensory blockade.

session. Such diaries, while obviously not on par with clinical assessments, are well documented and used routinely in clinical studies for longer-term evaluations.[46] Table 2 provides the details regarding primary and secondary outcomes, and it should be considered that the median values in this table are confined to sessions that resulted in successful blockade, thus greatly underestimating the true difference between both drugs.

All volunteers complied as required, and while invariably not noticing residual blockade after plain bupivacaine, they did report periods of sensation loss alternating with normal sensation after liposomal bupivacaine. Yet these episodes did not seem to follow any kind of predictable pattern (fig. 4). In a previous volunteer study of liposomal bupivacaine, Ilfeld *et al.*[39] used the drug in various low-dose but large-volume regimens for bilateral blockade of the femoral nerve. They, too, reported less-than-complete successes of sensory and motor blockade, which also is consistent with clinical findings of only minor reductions in postoperative opioid use after administration of liposomal bupivacaine as compared with other techniques of pain control.[26]

Problems in assessing clinical studies of liposomal bupivacaine arise from heterogeneity, both regarding groups for comparison and outcome parameters, as well as from the clinical settings of evaluating the subjects. Because placebo control is a less-than-ideal choice in perioperative settings, it is more useful to compare liposomal bupivacaine with an equipotent formulation of plain bupivacaine, and volunteers do optimize comparability by eliminating any distracting factors related to surgery, anesthesia management, pain, casts, or other confounders. Obviously, studies not involving surgery also have their drawbacks, and studies comparing sensory testing methods in volunteers with the clinical setting of postsurgical analgesia are needed. Therefore, it has been suggested that studies in volunteers require verification from well-designed clinical trials.[47] On balance, however, motivated volunteers not exposed to perioperative stressors may fairly be regarded as conducive to exact data collection.[48,49]

In summary, given complete sensory blockade in merely 32% of cases, as compared to 100% with plain bupivacaine, liposomal bupivacaine does not emerge from our study as a suitable "sole" local anesthetic for intraoperative regional anesthesia. As for its postoperative efficacy, liposomal bupivacaine did produce patterns of residual sensory blockade up to 3.5 days, but these patterns were unpredictable in terms of intermittence, quality, and quantity. Our findings add to existing evidence from clinical and scientific reports that a moderate effect, at best, should be expected of liposomal bupivacaine with regard to postoperative pain reduction and subsequent opioid use.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: markus.zeitlinger@meduniwien.ac.at. Raw data available at: markus.zeitlinger@meduniwien.ac.at.

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