Original Article

Interscalene nerve block with plain bupivacaine versus liposomal bupivacaine for arthroscopic rotator cuff repair: A randomized controlled trial

ABSTRACT

Background: Although single injections with anesthetics are commonly administered given their safety, their short-acting nature limits pain control. Liposomal bupivacaine represents a promising alternative to plain bupivacaine in interscalene nerve blocks. The goal of our study was to determine whether an interscalene block with liposomal bupivacaine provides superior analgesia and reduces opioid requirements compared to plain bupivacaine in patients undergoing arthroscopic rotator cuff repair (ARCR).

Methods and Materials: A single-center, double-blinded, randomized controlled trial of patients undergoing ARCR was performed. Patients received a single-shot interscalene nerve block with plain bupivacaine or liposomal bupivacaine. Visual analog scale pain scores at rest and with activity, as well as morphine milligram equivalents, were recorded in postoperative recovery and on postoperative days 1, 2, 3, and 7. Comparisons between groups were made using descriptive statistics; the significance level was set at $P < 0.05$.

Results: A total of 41 patients were randomized into the liposomal bupivacaine (n = 18 patients) and plain bupivacaine (n = 23 patients) groups. The differences in visual analog scale and morphine milligram equivalents between the two groups were not significant, with or without movement, on all postoperative days assessed.

Conclusion: There was no difference in the visual analog scale or morphine milligram equivalents after arthroscopic rotator cuff repair with interscalene blocks using liposomal bupivacaine versus plain bupivacaine. Given the increased cost associated with liposomal bupivacaine use and the variation in multimodal pain regimens worldwide, multicenter clinical trials are necessary to examine the clinical benefit and cost-effectiveness of liposomal bupivacaine in patients undergoing rotator cuff repair.

Key words: Arthroscopic rotator cuff repair, interscalene nerve block, liposomal bupivacaine

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Introduction

With over 250,000 arthroscopic rotator cuff repairs (ARCR) performed annually in the United States, ARCR is a common treatment for rotator cuff pathology.[1] Despite its minimally invasive nature, ARCR is a painful procedure, with severe postoperative pain impacting postoperative rehabilitation, patient satisfaction, and hospital recovery.[2,3] While patients are often provided with multimodal pain management after ARCR, the literature suggests that improved pain control can be achieved through regional nerve blocks in conjunction with multimodal pain regimens.[4,5]

Given its opioid-sparing nature and effective reduction of postoperative pain, interscalene brachial plexus blocks (ISBs) have grown to become the standard of care for pain control for ARCR.[1,6] As such, single-injection blocks with local anesthetics like bupivacaine are commonly used due to their efficacy, safety, and ease of administration.[7] However, because of the short-acting nature of a single injection of bupivacaine, rebound pain may occur after 12–24 hours,[8,9] indicating that better alternatives are needed; an ideal intervention would be one that could be administered as a single injection but provides longer-lasting analgesic effects.[10]

Liposomal bupivacaine (LB) is an effective intervention that provides extended-release delivery of the analgesic bupivacaine with a prolonged half-life.[11,12] Through its outer phospholipid bilayer structure that encapsulates the anesthetic within the liposome, LB can prolong drug delivery for up to 72 hours.[13,14] In fact, one pharmacokinetic study demonstrated that while the terminal half-life of plain bupivacaine (PB) administered via subcutaneous infiltration was 131 ± 58 min, that of LB was 1294 ± 860 min.[15] Accordingly, ISBs with LB have been shown to be associated with reduced opioid use compared to placebo,[7,16] decreased opioid use compared to PB plus dexamethasone,[10] and improved quality of recovery when compared to peripheral nerve catheters.[17] However, with varied research comparing PB versus LB in ARCR patients, controversy exists regarding whether the increased cost of LB justifies its supposed benefit compared to PB.

In this randomized controlled trial, we sought to determine whether a single-shot ISB with LB could provide improved analgesia and decreased opioid use postoperatively in patients undergoing ARCR compared to PB. We hypothesized that post-ARCR analgesia following an ISB with LB would be superior to an ISB using PB.

Methods and Materials

Study design

We performed a single-center, prospective, patient- and surgeon-blinded, randomized-controlled trial to assess the effectiveness of LB versus PB for the ISB. The Institutional Review Board approved this study protocol (IRB HS-18-00636, dated 1/4/19). All study participants gave written informed consent that was approved by the IRB prior to enrolling in the study. This study was registered with ClinicalTrials.gov (NCT03638960) and is reported in accordance with the CONSORT statement guidelines [Supplemental Figure 1].

Study population and selection criteria

All patients scheduled to undergo ARCR at HC3 hospital at Keck Medicine of USC were assessed for eligibility. Patient enrollment occurred from February 2019 to February 2021. Inclusion criteria consisted of medically optimized patients who were scheduled to undergo ARCR. Exclusion criteria included patients who were under 18 years old, pregnant or breastfeeding, non-English speaking, with renal or hepatic dysfunction, with a history of chronic opioid use >90 days, with respiratory compromise, smokers, using workers' compensation, BMI <18 or >35, or with an allergy to local anesthetics or opioids. Withdrawal criteria included patients who chose to opt out of the study, patients lost to follow-up, patients with failed peripheral nerve blocks, and patients with any form of adverse reaction to the nerve block. A planned interim analysis was conducted when two-thirds of the target enrollment of patients had been reached. Given the high cost of LB, the study was to be stopped if, during this analysis, it was found that there was evidence of noninferiority in the primary outcome. Indeed, patient enrollment was stopped after reaching a minimum of 40 patients total, as this number was deemed sufficient to detect a clinically meaningful difference between groups with a power of 75% and an alpha of 0.05.

Patient recruitment and randomization

Patients who met selection criteria were contacted before surgery and informed about the study, including risks and benefits. On the day of surgery, patients were consented by the anesthesiologist performing the nerve block. A designated member of the Acute Pain Team determined the group assignment using the software Research Randomizer.[18] Patients were stratified prior to their randomization. Descriptive factors including age, gender, BMI, and description of rotator cuff injury were noted to assess for possible confounding variables, yet these factors did not affect group assignment. The anesthesiologist performing the peripheral nerve block was notified of the assigned group by the designated member from the Acute

Pain Team; this designated member was not involved in performing the nerve block, follow-up, or analysis. The anesthesiologist performing the block was not blinded to the assignments. None of the anesthesiologists performing the block conducted any of the follow-up or statistical calculations for the study. The patients, surgical team, nursing staff, and all team members who assessed outcomes remained blinded to the group assignments throughout the study.

Study intervention

Preoperatively, all patients received 1000 mg acetaminophen, 400 mg celecoxib, and 600 mg gabapentin via oral administration. Nerve blocks were performed by anesthesiologists with specialized training in regional anesthesia. Ultrasound guidance was used to perform all nerve blocks. An 18-gauge block needle was inserted between the C5 and C6 nerve roots to perform the block; patients in the PB group received a bolus injection with 20 mL of 0.5% PB, while patients in the LB group received 10 mL of 0.5% PB followed by 10 mL of LB (total of 133 mg LB). Patients then underwent general anesthesia for the ARCR and only received intravenous fentanyl for intraoperative analgesia. In the post-anesthesia acute care unit (PACU), patients received oxycodone (for pain scores 3–6) or morphine (for pain scores 7–10) for pain relief. They were also instructed to take scheduled acetaminophen 650 mg orally every 6–8 hours. All patients received a prescription for oxycodone for post-operative analgesia as needed. During the postoperative period, patients were instructed by the surgeon to perform limited passive range of motion of the affected extremity, such as passive flexion and extension of the elbow, wrist, and fingers without movement of the shoulder.

Data collection

Members from the team who were blinded to the group assignments recorded opioid use in the PACU and on post-operative day (POD) 1, 2, 3, and 7 for each patient. Worst visual analog scale (VAS) pain scores at rest and with movement were recorded during this same period. The cellular phone application Carandas[19] was used by patients to communicate with the team to share pain scores four times a day. Any adverse events including nausea, vomiting, nerve injury, local anesthetic toxicity, unexpected readmission, or emergency room visit up to 1 week post-operatively were recorded by team members who were blinded to group assignments. All data were recorded in a password-protected computer.

Primary outcomes

The primary outcome assessed was the worst VAS score with movement (on a scale of 0–10) on POD 2 given that this is the time point by which plain bupivacaine would lose efficacy while liposomal bupivacaine would still be in effect. Movement was defined as passive range of motion of the extremity as directed by the surgeon.

Secondary outcomes

Secondary outcomes included pain scores and opioid use measured in morphine milligram equivalents (MME) in the PACU and on POD 1, 3, and 7, along with any adverse events. MME was calculated by multiplying the dose of oxycodone or morphine administered in the PACU by its conversion factor.[20]

Statistical analysis

Demographic characteristics and clinical features of the patients were analyzed using frequency distributions in two groups: LB ($n = 18$) and PB ($n = 23$). Continuous variables were presented as median ± interquartile range (IQR), while categorical variables were expressed as *n* (%). To evaluate mean differences between the groups for continuous variables (BMI, age), independent sample t-tests were employed after assessing the normality of the sample. Bivariate analysis on categorical variables was conducted using Fisher exact tests. Two-sided P value < 0.05 was considered statistically significant.

To assess the repeated measures of changes in the primary outcome, longitudinal linear mixed-effects models were utilized. After visually inspecting the linearity between outcomes and POD 1-3, categorical time with indicator variables for POD 2 and POD 3 were used. Patient's age was dichotomized by median of the sample and controlled in all models. Daily measures were further assessed for differences in intervention effect among days by testing a treatment-by-day interaction. Different error covariance structures were selected based on smaller Akaike information criterion (AIC), Bayesian information criterion (BIC) and corrected Akaike information criterion (AICC) values. Intraclass correlation coefficients (ICC) were obtained to estimate within-patient correlation in pain over POD 1-3.

The mean VAS at rest and with movement of POD 1-3 were calculated for each patient because liposomal bupivacaine should be effective between 48–72 hours, and group differences were assessed using t-tests after assessing the normality of the sample. The minimum detectable effect was assessed for average VAS at rest and with movement of the same period. Wilcoxon rank-sum tests were utilized to compare the group difference in PACU VAS at rest, total opioid use measured in MME, and preoperative VAS scores at rest/movement on POD 7 between the two groups.

Results

Study population

A total of 41 patients were analyzed in this study, with 18 patients randomized to LB and 23 randomized to PB [Table 1] No statistically significant differences were found between LB and PB regarding characteristics such as age, sex, race, BMI, type of ARCR, or type of injury.

Trial outcomes

The mean VAS at rest over POD 1-3 was lower but not significantly different among the LB group compared to that of PB. Similarly, the mean VAS with movement during the same period was lower in LB but not statistically significant. There was no difference found in preoperative VAS, PACU VAS, MME, and VAS at rest/movement at POD 7 [Table 2].

Outcome effects obtained by linear mixed effect models

After controlling for age, the average difference in VAS at rest from POD 1-3 between the groups was −0.75, with a 95% confidence interval (CI) of −2.35 to 0.85 ($P = 0.35$). The ICC was 0.51, indicating that approximately half of the total variation in VAS scores can be attributed to within-patient variation in VAS over 3 days [Table 3]. Overall, VAS at rest and movement were not significantly different between groups. The average difference in opioid consumption from POD 1-3 was −1.80 MME (95% CI: −13.27, 9.68; $P = 0.75$) after controlling for age and was thus not statistically significant. The ICC for opioid use was estimated at 0.38.

For the worst VAS pain scores on POD 1, 2, 3, and 7, no significant differences were observed in worst VAS pain scores between the groups. For MME administration, there were no significant differences between the PB and LB groups on any of the postoperative days. Overall, the differences in VAS pain scores at rest and with movement, as well as the opioid use between the two groups were insignificant [Table 4].

Discussion

In this single-center, prospective randomized controlled trial, we compared the ISB administered with LB versus PB in patients undergoing ARCR. While both forms of the ISB demonstrated effective pain control and low opioid requirement, our study found no difference in patient-reported pain scores at rest and with movement, as well as no difference in opioid use within the first 7 days postoperatively. To our knowledge, this is the first blinded, randomized controlled trial examining postoperative pain using movement and rest as variables to compare ISBs with LB versus PB in ARCR patients.

Currently, no major physician society explicitly recommends the routine use of LB over PB, given the increased cost of the liposomal formulation and controversy over added benefit.[21,22] Our results align with this growing literature suggesting that LB and PB provide similar overall pain relief and opioid consumption after shoulder surgery.[23–25] Specifically regarding ARCR, our findings are consistent with Verdecchia *et al.*'s[26] study demonstrating that compared to a placebo nerve block, the ISB with LB demonstrated no significant difference in pain scores on POD 1 and 2, opioid consumption, and pain score after passive range-of-motion exercises. Similarly, our results are consistent with Flaherty

Table 1: Demographic/clinical characteristics for all participants by randomized group[a]

Variable	Group		*P*
	Liposomal bupivacaine (*n*=18)	Bupivacaine (*n*=23)	
Sex *n* (%)			0.76
Male	10 (55.56)	11 (47.83)	
Female	8 (44.44)	12 (52.17)	
Age median±IQR	62.00±20.00	57.00±16.00	0.12
Body Mass Index (BMI) kg/m² median±IQR	29.21±6.67	29.14±6.10	0.69
Race *n* (%)			0.76
Caucasian	14 (77.78)	15 (65.22)	
Asian	0 (0.00)	1 (4.35)	
Black	0 (0.00)	2 (8.70)	
Hispanic	3 (16.67)	3 (13.04)	
Other	1 (5.56)	2 (8.70)	
Type of ARCR[b] *n* (%)			1.00
Complete	14 (77.78)	17 (73.91)	
Partial	4 (22.22)	6 (26.09)	
Type of Injury *n* (%)			0.34
Multiple	8 (44.44)	6 (26.09)	
Subscapularis	0 (0.00)	2 (8.70)	
Supraspinatus	10 (55.56)	15 (65.22)	

[a]Fisher's exact tests were used to obtain *P* value for *n* (%); Independent *t*-tests were used to obtain *P* value for mean±SD; Wilcoxon rank-sum test was used to obtain *P* value for median±SD. [b]ARCR=arthroscopic rotator cuff repair

Table 2: VAS and total opioid use for all participants by randomized group[a]

Variable	All Patients (*n*=41)	Group		*P*
		Liposomal bupivacaine (*n*=18)	Bupivacaine (*n*=23)	
Pre-op VAS[b]	32	12	20	0.70
median±IQR	4.00±5.00	3.50±5.00	4.50±7.00	
PACU[c] VAS at Rest	40	18	22	0.50
median±IQR	0.00±9.00	0.00±6.00	0.00±9.00	
Total Opioid Use, MME	34	15	19	0.16
median±IQR	5.00±15.00	15.00±20.00	0.00±15.00	
VAS at Rest - POD7	34	15	19	0.46
median±IQR	3.50±4.00	4.00±4.00	3.00±4.00	
VAS with Movement - POD7	34	15	19	0.77
median±IQR	5.00±4.00	5.00±5.00	5.00±5.00	
Average VAS at Rest (POD 1-3)	40	18	22	0.36
median±IQR	4.00±3.33	3.83±3.00	4.33±4.00	
Average VAS with Movement (POD 1-3)	40	18	22	0.14
median±IQR	5.17±4.17	4.83±3.33	5.83±4.67	

[a]Fisher's exact tests were used to obtain *P* value for *n* (%); Independent *t*-tests were used to obtain *P* value for mean±SD; Wilcoxon rank-sum test was used to obtain *P* value for median±SD. [b]The visual analog scale (VAS) is a pain rating scale from 0 ("no pain") to 10 ("worst pain"). [c]PACU=post-anesthesia care unit, MME=morphine milligram equivalents, POD=postoperative day

Table 3: Estimates of average group difference in primary outcomes

Outcome	Estimate[a]	Adjusted 95% CI[b]	Adjusted *P*	ICC
VAS at Rest (POD 1-3)				
Liposomal bupivacaine vs. Bupivacaine	−0.75	(−2.35, 0.85)	0.35	0.51
VAS with Movement (POD 1-3)				
Liposomal bupivacaine vs. Bupivacaine	−1.39	(−3.26, 0.48)	0.14	0.64
Opioid Use – MME (POD 1-3)				
Liposomal bupivacaine vs. Bupivacaine	−1.80	(−13.27, 9.68)	0.75	0.38

[a]Estimates of mean difference of (Liposomal bupivacaine – Bupivacaine). [b]CI=confidence interval, ICC=intraclass correlation coefficients, VAS=visual analog scale, POD=postoperative day, MME=morphine milligram equivalents

Table 4: Postoperative daily measure comparison in primary outcomes

Liposomal bupivacaine vs. Bupivacaine	Estimate[a]	Adjusted 95% CI[b]	Adjusted, *P*
VAS at Rest			
POD 1	−1.12	(−3.95, 1.71)	0.86
POD 2	−0.85	(−3.71, 2.00)	0.95
POD 3	−0.29	(−3.13, 2.56)	1.00
VAS with Movement			
POD 1	−1.72	(−5.24, 1.80)	0.71
POD 2	−1.52	(−4.17, 1.13)	0.55
POD 3	−0.93	(−3.99, 2.14)	0.71
Opioid Use – MME			
POD 1	−1.59	(−24.27, 21.10)	1.00
POD 2	−6.76	(−32.12, 18.61)	0.97
POD 3	2.95	(−13.85, 19.76)	1.00

[a]Estimates of mean difference of (Liposomal bupivacaine – Bupivacaine). [b]CI=confidence interval, VAS=visual analog scale, POD=postoperative day, MME=morphine milligram equivalents

et al.'s[27] randomized study comparing ARCR patients who received an ISB with LB versus PB that showed no difference in pain scores and opioid consumption at postoperative 48 hours and 72 hours, respectively. Likewise, our data corresponds well with Hattrup *et al*.'s[28] and Elmer *et al*.'s [29] randomized trials studying LB versus PB in ISBs for total shoulder arthroplasty that collectively demonstrated no clinically relevant advantage between the two formulations in terms of postoperative pain score, opioid use, patient satisfaction, and length of hospital stay. Furthermore, in Kim *et al*.'s[30] randomized study comparing ISBs with LB versus PB and perineural dexamethasone, both forms of the block provided effective analgesia and no difference in opioid consumption, readiness for post-anesthesia care unit discharge, or adverse events. Even when comparing a preoperative ISB with ropivacaine versus an intraoperative periarticular injection of LB, Schumaier *et al*.'s[31] results showed no clinically important difference in narcotic consumption, VAS pain scores, length of stay, pain-related phone calls, pain-related readmissions, or number of narcotic refills. With median pain scores not surpassing 5/10 and median opioid usage not exceeding 15 MME for both LB and PB groups, our findings agree with the referenced literature that while ISBs with LB or PB both serve as effective modes of pain control with opioid limiting qualities, the supposed superiority in analgesia of LB versus PB remains controversial.

Despite these shared findings, our study does contrast with other literature that suggests LB provides improved analgesia to PB via the ISB for shoulder surgery.[32,33] For instance, in Finkel *et al*.'s[34] study on total shoulder replacement, patients given an ISB with LB reported decreased postoperative

pain scores at 24–48 hours, 48–72 hours, and 72–96 hours compared to those given an ISB with PB, dexamethasone, and epinephrine, though no difference in total 120-hour postoperative opioid consumption was reported. Additionally, in Hillesheim *et al*.'s[35] study on ARCR, patients given an ISB with PB demonstrated increased opioid use in POD 1 and 2 compared to patients given a periarticular injection of LB; still, less pain was reported on postoperative day 1 for patients given PB and cumulative opioid use remained similar. Moreover, in a mixed population of patients undergoing ARCR and shoulder replacement surgery who received ISBs, Vandepitte *et al*.[17] found patients given LB reported higher satisfaction and lower worst pain in the first postoperative week despite also showing similar functionality of the surgical arm, sleep duration, time to first opioid request, overall opioid consumption, and occurrence of adverse events. Although our study does show a trend indicating decreased opioid use as well as decreased pain scores at rest and with movement on POD 1-3 for the LB group compared to the PB group, this estimate of mean difference is not statistically significant and does not provide a minimally clinically important difference.[36] Given that our study focused on ARCR patients only, challenges may arise in making direct comparisons with studies including shoulder replacement, as shoulder replacement is a more invasive procedure and is performed via an open approach, altering the pain profile of patients in comparison to those who undergo ARCR.[37] As such, multicenter clinical trials are necessary to examine the efficacy and cost effectiveness of LB when used in ISBs as part of multimodal pain regimens following ARCR surgery.[38] Afterall, a single dose of LB costs around 100 times more than a single dose of PB with prices at $334 for a 266 mg vial versus $3 for the same dose, respectively.[39]

The main strength of our study was that our sample patients were randomized and blinded to their specific treatment. Along with the patients, the surgeons performing the ARCR and staff involved in the perioperative care of the patients were blinded to the treatment, thereby minimizing observer bias. An additional strength is that the demographics of the patients in the two treatment groups were similar and showed no differences in age, gender, race, height, or weight.

One limitation of our study is the small sample size; our study presents findings on the efficacy of LB with a sample of only 41 patients. To examine the efficacy and cost effectiveness of LB, further investigation with larger sample sizes is warranted. Another limitation is that the anesthesiologists providing the injections were not blinded—however, this decision to keep the anesthesiologist not blinded was to ensure patient safety and because LB physically appears different from PB in the vial, thereby making it difficult for the anesthesiologist to remain blinded. Future studies could implement other strategies to blind the anesthesiologist by utilizing tinted tubing and syringes.

The VAS scores or MME recorded in this study may have been confounded by pain that patients were experiencing from sources outside of the shoulder itself—for example, patients experiencing concurrent pain from other joints due to comorbidities or from a prolonged stay in a rigid hospital bed may have confounded the VAS or MME. Additionally, patients who receive biceps tenodesis with their ARCR were more likely to have pain along the T2 dermatome. We attempted to minimize this potential confounding variable by asking each patient for the severity of their pain caused by the shoulder specifically and how much pain medication was being taken for that specific shoulder pain. A final limitation is that not all types of ARCRs involve the same type or extent of surgery, meaning that each patient underwent different degrees of ARCR surgeries. This point suggests that patients who underwent more extensive surgeries likely experienced more pain than those who underwent less extensive surgeries. Subgroup analyses based on the type of ARCR done could have been conducted to account for this possible confounding factor.

Conclusions

There was no difference in pain scores or MMEs after ARCR with an ISB using LB versus PB. Given the increased cost associated with the use of LB and the variation of multimodal pain regimens worldwide, multicenter clinical trials are necessary to examine the clinical benefit and cost effectiveness of LB in patients undergoing ARCR.

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Key Points Summary

Question:

Does an interscalene block with liposomal bupivacaine provide superior analgesia and lower opioid requirement compared to plain bupivacaine in patients undergoing arthroscopic rotator cuff repair (ARCR)?

Findings:

For patients undergoing arthroscopic rotator cuff repair, a single shot interscalene block with liposomal bupivacaine

does not produce a significant difference in postoperative analgesia and opioid use as compared to plain bupivacaine.

Meaning:
This study demonstrates that the cost of liposomal bupivacaine currently does not warrant replacing plain bupivacaine in interscalene blocks for this patient population.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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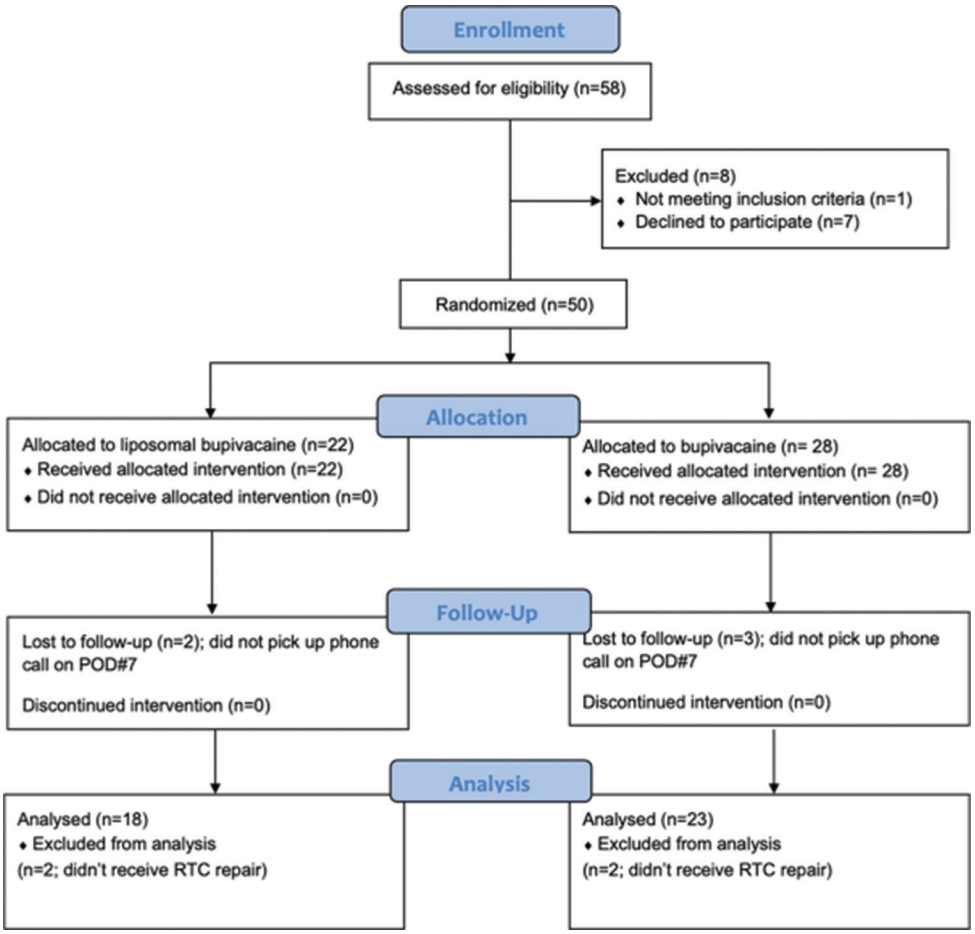

Supplemental Figure 1: CONSORT diagram. CONSORT indicates Consolidated Standards of Reporting Trials