Interscalene Block with and without Intraoperative Local Infiltration with Liposomal Bupivacaine in Shoulder Arthroplasty

A Randomized Controlled Trial

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Background: Interscalene brachial plexus blockade (ISBPB) is an effective anesthetic technique for shoulder arthroplasty; however, "rebound pain" can increase the patient's postoperative pain experience and narcotic usage. Exparel (liposomal bupivacaine) injected into the soft tissues at the surgical site has theoretical efficacy for up to 72 hours after administration. The purpose of this study was to evaluate postoperative pain scores and narcotic consumption following shoulder arthroplasty performed with either ISBPB alone or ISBPB and intraoperative Exparel.

Methods: Seventy-eight patients undergoing primary shoulder arthroplasty were randomized to receive an ISBPB with Exparel (39 patients) or without Exparel (39 patients). The primary outcome variable was morphine equivalent units (MEUs) consumed over the first 24 hours after surgery. Secondary outcomes included intraoperative narcotic administration and visual analog scale (VAS) scores for pain (at 0, 8, 16, 24, 48, and 72 hours after surgery).

Results: There were no significant demographic differences between the ISBPB and ISBPB + Exparel groups. Total narcotic consumption over the first 24 hours after surgery was significantly lower in the ISBPB group compared with the ISBPB + Exparel group (mean and standard deviation, 18.9 ± 25.6 MEU versus 35.3 ± 36.7 MEU, $p = 0.009$). VAS pain scores did not differ significantly between groups at any time point during the first 72 hours after surgery.

Conclusions: Patients treated with Exparel required significantly more postoperative narcotics and demonstrated no significant reduction in pain scores over the first 72 hours after primary shoulder arthroplasty. Exparel does not appear to have substantial value when added to a pain protocol that includes an ISBPB.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Pain management after shoulder arthroplasty is an important variable in the perioperative period that can influence participation in physical therapy, discharge from the hospital or outpatient surgery center, and patient satisfaction. With the growing opioid epidemic, national focus has shifted to the use and misuse of opioids in all areas of medicine[1]. Because of this, growing emphasis has been placed on alternative pain management strategies that can reduce narcotic utilization after orthopaedic surgery.

Interscalene brachial plexus blockade (ISBPB) is an effective anesthetic technique for shoulder arthroplasty[2] that is typically associated with minimal opioid utilization both intraoperatively and for the first 8 hours after surgery[3,4]. Rebound pain is an acute pain phenomenon that is encountered during the first few hours after the effects of an ISBPB subside[5]. When rebound pain occurs, it commonly results in a sharp spike in narcotic utilization and increase in pain scores from 8 to 24 hours after shoulder arthroplasty[3,4]. Exparel (bupivacaine liposome injectable suspension), a sustained-release preparation of bupivacaine with U.S. Food and Drug Administration (FDA) approval for surgical site administration, is used as a local analgesic. Multiple studies have demonstrated its safety and

Disclosure: There was no external funding source for this study. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article*, one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work and "yes" to indicate that the author had a patent and/or copyright, planned, pending, or issued, broadly relevant to this work (http://links.lww.com/JBJS/E844).

efficacy in various surgical populations and have indicated a potential for activity for up to 72 hours after surgery[6-8].

Two randomized controlled trials have compared ISBPB to Exparel for pain management after shoulder arthroplasty performed under general anesthesia[3,4]. Both studies demonstrated improved pain scores and less narcotic utilization in the ISBPB group for the first 8 hours after surgery and better pain scores in the Exparel group at 24 hours after surgery. Neither study evaluated patients beyond 24 hours after surgery. Given the problem of rebound pain with ISBPB and the problem of greater early pain scores following intraoperative soft-tissue infiltration with Exparel, neither pain management strategy appeared optimal for both controlling pain and reducing narcotic utilization. The purpose of this study was to evaluate narcotic consumption (over 24 hours) and postoperative pain scores (through 72 hours) after shoulder arthroplasty using a strategy that involved either ISBPB alone or ISBPB with Exparel soft-tissue infiltration. We hypothesized that the addition of Exparel to a pain regimen that included ISBPB would reduce the rebound pain experience and narcotic consumption (over 24 hours) and improve pain scores (through 72 hours).

Materials and Methods

This study was approved by our institutional review board, was registered at www.ClinicalTrials.gov (NCT03253198), and followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Fig. 1). From August 1, 2016, until February 15, 2017, patients undergoing primary total or reverse shoulder arthroplasty for osteoarthritis or cuff tear arthropathy, respectively, were included. All operations were performed at a single institution by 1 of 4 fellowship-trained shoulder surgeons. Patients were excluded if they had a psychiatric illness as defined by a comorbid diagnosis of bipolar disorder or schizophrenia, were undergoing revision arthroplasty or surgery for a diagnosis of fracture, had a Workers' Compensation/disability/litigation

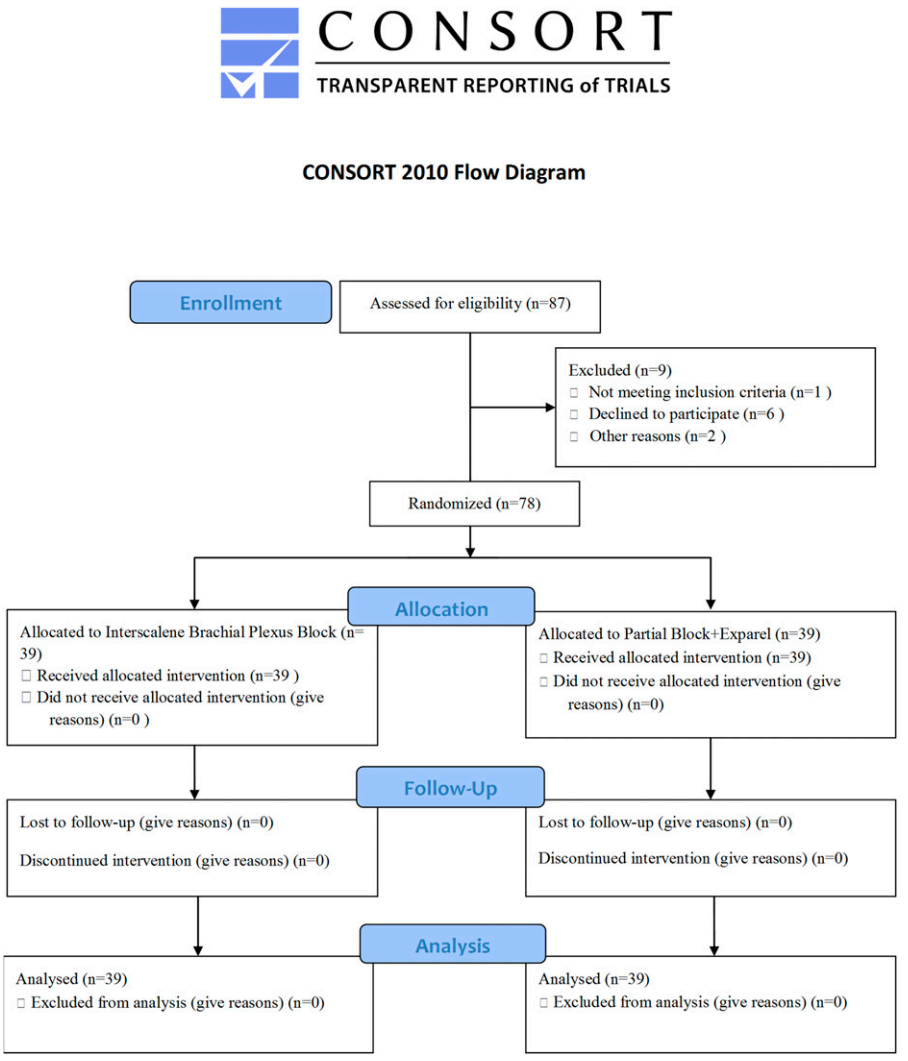

Fig. 1

CONSORT guidelines flow diagram.

TABLE I Preoperative Variables

Variable	ISBPB	ISBPB + Exparel	P Value
Age* *(yr)*	71.2 ± 8.6 (55.4-88.0)	68.6 ± 10.0 (36.5-86.8)	0.255
Male:female *(no.)*	24:15	19:20	0.363
Body mass index* *(kg/m²)*	28.9 ± 6.0 (19.3-43.9)	28.9 ± 5.8 (18.8-46.1)	0.962
Anatomic:reverse total shoulder arthroplasty *(no.)*	26:13	25:14	1.0
Charlson comorbidity index*	0.78 ± 1.15 (0-4)	0.44 ± 0.79 (0-3)	0.140
Short-acting narcotic usage *(no.)*	3 (8%)	3 (8%)	1.0
Non-narcotic analgesic usage *(no.)*	13 (33%)	11 (28%)	0.807
Preoperative VAS pain score*	4.4 ± 2.9 (0-10)	5.3 ± 2.7 (0-10)	0.185

*The values are given as the mean and SD with the range in parentheses.

claim, were unable to consent for enrollment or to complete a postoperative pain survey, had had a known adverse drug reaction or had an allergy to the medications used, had chronic pain syndrome (including reflex sympathetic dystrophy, fibromyalgia, and chronic diffuse musculoskeletal pain), were taking long-acting narcotic pain medications (including extended-release narcotic pain medications and methadone), or had hepatic disease.

Data regarding demographics, medical comorbidities, usage of short-acting narcotics, and usage of non-narcotic analgesics were collected prospectively. After informed consent was obtained, patients were randomized, by a computer random-number generator, to receive a preoperative ISBPB with or without intraoperative periarticular local anesthetic infiltration with Exparel. No preoperative oral analgesic regimen was used. Baseline preoperative pain scores were obtained with a visual analog scale (VAS) on the day of surgery. Preoperatively, ISBPBs employing 15 mL of 0.5% ropivacaine were performed by 1 of 6 anesthesiologists experienced with the use of ultrasound-guided regional anesthesia. At the completion of the shoulder arthroplasty and prior to skin closure, the patients in the Exparel group underwent intraoperative infiltration of 20 mL of Exparel (266 mg of 1.3% bupivacaine), diluted in 20 mL of saline solution, into the shoulder capsule, subscapularis, deltoid, pectoralis major, and subcutaneous tissues using a previously described technique[3]. The total dose of local anesthetic was within the maximum allowable range based on weight for all patients.

Intraoperative narcotic administration was at the discretion of the same 6 anesthesiologists who performed the ISBPBs in this study. The need for narcotics was generally determined on the basis of physiologic indicators of pain, which include hypertension and tachycardia. All patients were provided a patient-controlled analgesic pump in the post-anesthesia care unit (PACU). The pump dispensed hydromorphone with the dosage and frequency titrated on the basis of the patient's pain for the first 24 hours after surgery. No additional oral narcotics were routinely ordered over the first 24 hours after surgery. In cases of ineffectiveness or reactions to hydromorphone, patient-controlled analgesia (PCA) pumps were altered to dispense either morphine or fentanyl. Acetaminophen was utilized to treat fever in the perioperative setting on an as-needed basis. No other analgesic or non-steroidal anti-inflammatory medications were given during the first 24 hours. The primary outcome variable was morphine equivalent units (MEUs) consumed over the first 24 hours after surgery. Additional outcomes measures included intraoperative MEUs consumed, VAS score for pain (at 0, 8, 16, 24, 48, and 72 hours), time in the operating room, hospital length of stay, intraoperative complications (fracture, vascular injury, and anesthesia-related), and acute postoperative complications (medical, nerve injury, dislocation, hematoma, and wound).

Statistics were compared between groups using the Student t test for normally distributed variables, the Mann-Whitney U test for variables that were not normally distributed, and the Fisher exact test for categorical variables. The MEU total in the first 24 hours was normalized by group with the natural log transformation so a t test was used to analyze it; however, raw means and standard deviations (SDs) were presented for ease of interpretation. A p value of <0.05 was considered significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23 (IBM). Based on an

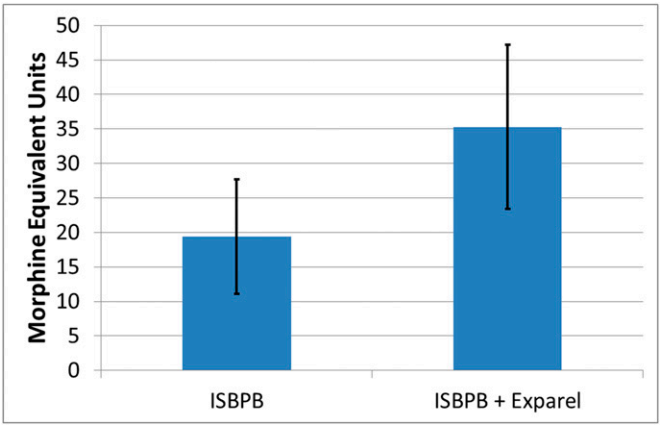

Fig. 2

Narcotic usage. Error bars indicate 95% confidence interval.

assumption that a 35% decrease in narcotic consumption would be clinically relevant[5,9,10], an a prior power estimation indicated that the number of patients required to achieve 80% power at alpha = 0.05 was 37 per group. Three studies were used to generate this estimation: (1) a meta-analysis of 23 randomized controlled trials (1,090 patients) comparing ISBPB with a control for shoulder surgery that showed a 48% difference in pain medication usage between groups[5], (2) a randomized controlled trial of adding dexmedetomidine to levobupivacaine for interscalene block in arthroscopic shoulder surgery that showed a 48% reduction in pain medication usage between groups[10], and (3) a randomized controlled trial of adding buprenorphine to levobupivacaine for ISBPB after shoulder surgery showing a 45% reduction in pain medication usage between groups[9].

Results

From August 1, 2016, until February 15, 2017, 39 patients were randomized to receive ISBPB and 39 patients were randomized to receive ISBPB + Exparel. The mean age (and SD) was 71.2 ± 8.6 years in the ISBPB group and 68.6 ± 10.0 years in the ISBPB + Exparel group (p = 0.255). There were no significant differences between groups in terms sex, body mass index, preoperative utilization of short-acting narcotics or nonnarcotic analgesia, type of arthroplasty performed, or preoperative VAS pain scores (Table I).

Total narcotic consumption over the first 24 hours after surgery averaged 18.9 ± 25.6 MEU in the ISBPB group and 35.3 ± 36.7 MEU in the ISBPB + Exparel group (p = 0.009) (Fig. 2). Intraoperative narcotic consumption averaged 10.6 ± 5.3 MEU in the ISBP group and 12.3 ± 5.1 in the ISBPB + Exparel group (p = 0.174). The VAS pain scores did not differ significantly between the ISBPB and ISBPB + Exparel groups at any time point during the first 72 hours after surgery (Fig. 3).

Seven patients (18%) in the ISBPB group and 7 patients (18%) in the ISBPB + Exparel group had a VAS pain score of >5 in the PACU. The mean length of hospital stay was 1.5 days in both groups (p = 0.56). No intraoperative complications or acute postoperative complications occurred in either group. One patient in each group had persistent ulnar nerve paresthesias at 3 months after surgery. There were no postoperative complications that could be related to the ISBPB or the Exparel infiltration.

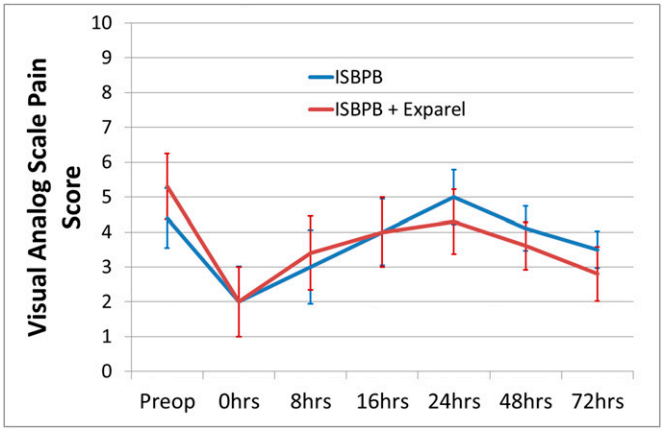

Fig. 3

VAS pain scores. Error bars indicate 95% confidence interval.

Discussion

ISBPB is known to provide excellent pain relief for the first 8 hours after shoulder surgery. Unfortunately, the benefits of the ISBPB subside beyond 8 hours, and rebound pain can dramatically increase the patient's postoperative pain experience and narcotic consumption. Infiltration of the soft tissues with Exparel alone is known to yield a more consistent pain experience during the first 24 hours after surgery but worse pain scores between 0 and 8 hours compared with those for patients treated with ISBPB[3]. For these reasons, a combined approach that includes both ISBPB and Exparel could theoretically optimize both early and delayed pain experience after shoulder arthroplasty. In this randomized controlled trial, patients treated with ISBPB and Exparel required significantly more postoperative narcotics than patients treated with ISBPB alone and there was no significant reduction in pain scores over the first 72 hours after primary shoulder arthroplasty.

The increased need for narcotics in patients treated with combined ISBPB and Exparel is surprising. One possible explanation is a "double rebound" phenomenon in which patients experienced rebound pain both after the effect of the ISBPB subsided and after the effect of the Exparel subsided, resulting in a heightened utilization of narcotics. Alternatively, there may have been subtle differences in pain tolerance between the groups that were not adequately addressed by randomization. Importantly, a minimal clinically important difference in MEUs has not been identified, and while the 16.4-mg difference between our groups was statistically significant, it may not be clinically relevant. Regardless, it does not appear that the addition of Exparel is advantageous for reducing narcotic utilization after shoulder arthroplasty when an ISBPB is used and it may actually have negative consequences. It did not appear that the heightened narcotic utilization in the ISBPB + Exparel group had an influence on hospital length of stay. There remains concern that increased narcotic utilization in the hospital setting is a risk factor for narcotic dependence or misuse after discharge. Opioids prescribed during and after surgery may trigger long-term use by patients regardless of whether they are opioid-tolerant, were taking opioids regularly before surgery, or had ever been exposed to opioids in the past[11-14]. Given the increased cost and lack of a demonstrable benefit, even without a formal cost-effectiveness analysis, adding Exparel to a pain regimen that already includes ISBPB does not appear to be a cost-effective strategy.

With regard to pain experience, the patients in the 2 groups had similar mean VAS pain scores at all time points during the first 72 hours as well as similar rebound pain, with a spike of approximately 3 points on the VAS between 0 and 24 hours after surgery. After 24 hours, pain scores steadily

decreased in both groups. It does not appear that the addition of Exparel to ISBPB can eliminate rebound pain. A randomized controlled trial of shoulder arthroplasty demonstrated a more consistent pain experience in a group that underwent local soft-tissue infiltration with Exparel (without ISBPB), with mean pain scores ranging between 3 and 4 on the VAS for the first 24 hours[3]. In comparison, a group treated with ISBPB (without Exparel) had a more variable pain experience, with mean VAS pain scores ranging from approximately 1 to 5 points for the first 24 hours[3]. Given the similar pain profiles in the 2 groups in our study, it appears that the use of an ISBPB (or the lack thereof), and not the addition of Exparel, dictates the pain experience. In a recent randomized controlled trial of patients undergoing primary knee arthroplasty, periarticular injection of Exparel compared with bupivacaine HCl did not result in any clinically relevant or statistically significant improvement in VAS pain scores or narcotic consumption for the first 96 hours after surgery[15]. Similar studies will be needed to determine whether there is any clinical value to using Exparel as opposed to standard bupivacaine HCl in shoulder arthroplasty.

This study has a number of limitations. Because these pain management strategies were evaluated only in primary shoulder arthroplasty, the results cannot be extrapolated to other types of surgery. Our study was underpowered to demonstrate smaller differences between groups; greater samples size would have addressed this limitation. At the start of the study, we hoped to enroll more patients in order to improve our ability to analyze secondary variables; however, given the removal of Exparel from our formulary, our secondary analysis was weakened. Tashjian et al. reported that the minimal clinically important difference in VAS pain scores after shoulder arthroplasty is 1.4 points[16], and at no time point was the difference in VAS scores between our ISBPB and ISBPB + Exparel groups >0.7 point. Consequently, even if the differences between groups had been statistically significant, they would not have been clinically important. This study did not include groups of patients treated with interscalene catheters, oral or intravenous multimodal pain medication strategies, or PCA alone. Because our primary objective was to determine the benefit, or lack thereof, of adding Exparel to ISBPB as a pain management strategy, we did not include these groups. We did not perform a formal cost analysis; however, one was not appropriate given the lack of benefit demonstrated with the addition of Exparel. We did not track narcotic utilization beyond 24 hours after surgery, and do not know the influence of increased postoperative narcotic utilization on the risk of dependence or addiction. Finally, although all 4 surgeons used a standardized and previously described technique for the Exparel injection[3], this technique was not rigorously validated and could have influenced the results. However, one would expect some variability with any injection protocol.

In this randomized controlled trial, ISBPB alone outperformed ISBPB + Exparel with regard to narcotic utilization in the first 24 hours and was equivalent to ISBPB + Exparel with regard to pain scores in the first 72 hours after shoulder arthroplasty. Thus, Exparel does not appear to have substantial value when added to a pain protocol that already includes ISBPB. Further research is necessary to determine the optimal pain management strategy for shoulder arthroplasty. ■

NOTE: The authors acknowledge the efforts of Carol Foltz for statistical support.

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