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Brief Report

Day-One Pain Reductions After Hip and Knee Replacement When Buprenorphine-Clonidine-Dexamethasone Is Added to Bupivacaine Nerve/Plexus Blocks: A Randomized Clinical Trial

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Abstract

Objective. To compare pain outcome reports of patients undergoing hip or knee replacement who received single-injection nerve/plexus blocks with plain bupivacaine (BPV) with those of patients who received injections of buprenorphine-clonidine-dexamethasone (BCD) admixed with BPV. **Design**. Prospective, parallel-arm, randomized, double-blind trial. **Setting**. A single veterans' hospital. **Subjects**. Ninety-eight veterans scheduled for total hip or knee replacement surgery with spinal as the primary anesthetic. **Methods**. Participants were randomized to BPV-BCD or plain BPV groups. They underwent nerve/plexus blocks in the L2–L4 and L4–S3 distributions in advance of joint replacement surgery. The primary outcome was change in pain from baseline during the postoperative day, as assessed by the total pain score on the short-form McGill Pain Questionnaire-v2 (SF-MPQ-2). Secondary outcomes were pain during movement, pain interference, range of motion, mobility, and quality of recovery. **Results**. On postoperative day one, the SF-MPQ-2 total score for the BPV-BCD group demonstrated greater pain reduction than that of the plain BPV group (mean difference 1.8 points, 95% confidence interval 0.6 to 3.0, $P = 0.003$). The BPV-BCD group also had larger reductions in pain during movement in the surgical joint and less pain interference, along with increased range of hip and knee flexion, compared with the plain BPV group. Outcomes of mobility and quality of recovery were not different between groups. **Conclusions**. Preoperative BPV-BCD blocks in the L2–L4 and L4–S3 nerve distributions for hip and knee replacements led to less pain on postoperative day one and increased knee and hip range of motion, compared with plain BPV blocks. **Trial registration**. ClinicalTrials.gov ID NCT02891798.

Key Words: Nerve Block; Buprenorphine; Clonidine; Dexamethasone; Bupivacaine; Joint Arthroplasty; Total

Introduction

Multimodal perineural analgesia (MMPNA) with nerve block adjuvants such as buprenorphine [1], clonidine [2], and dexamethasone [3] (BCD) can extend the analgesic duration of local anesthetic-based peripheral nerve blocks, when compared with plain local anesthetic [4–6]. Both perineural buprenorphine [1] and clonidine [2] have been shown to have greater perineural than systemic value, though this question remains controversial for dexamethasone. In vitro and in vivo animal studies have demonstrated the neuronal and perineural safety of BCD admixed with local anesthetics [7, 8]. We previously reported results from a series of more than 1,300 patients who underwent various surgical procedures with bupivacaine (BPV)-BCD single-injection MMPNA nerve blocks [9]; these blocks provided an analgesic duration of ~36 hours. By the time of the start of the trial described here, this drug combination had been used in more than 3,000 patients. We recently reported preliminary findings of the present study on analgesia duration, and the MMPNA nerve blocks' duration was 26–39 hours after BPV-BCD vs 11–21 hours after administration of plain BPV in patients who had total hip arthroplasty (THA) and total knee arthroplasty (TKA) [4].

For this study, we obtained Investigational New Drug (IND) status from the U.S. Food and Drug Administration (IND #127171). Extending the duration of blocks with MMPNA may ultimately avoid the need for continuous perineural catheters, a clinically complex procedure that poses risks of infection and catheter retention. In the present article, we specifically report on the primary outcome of pain (and secondary outcomes) because these data were not available for analysis at the time of our last publication [4]. The accompanying invited editorial [10] describes how the study was modified from the original description disclosed to ClinicalTrials.gov. The study hypothesis was that BPV-BCD nerve blocks would lead to less pain on postoperative day one (POD#1) and better range of motion, mobility, and quality of recovery than would plain BPV nerve blocks for these patients undergoing total joint replacement (TJR).

Methods

This double-blind, parallel-arm, randomized controlled trial was conducted at a single United States Veterans Administration (VA) hospital. Participants signed informed consent approved by the Institutional Review Boards from the University of Pittsburgh, the VA Pittsburgh, and the Human Research Protection Office of the Department of Defense. The study was monitored by a Data and Safety Monitoring Board and registered at ClinicalTrials.gov (NCT02891798). This report follows the Consolidated Standards of Reporting Trials (CONSORT).

Participants

Adults 18–85 years old who were scheduled for primary elective TJR, were English speaking, were decision competent, were willing to complete all study visits, were able to walk >3 meters independently, and had a body mass index $\leq 40\ kg/m^2$ were invited to participate. Adults who had major psychiatric disorders, who were at risk of postoperative substance abuse, or who had a contraindication to peripheral nerve block or spinal anesthesia were excluded [4]. Participants were enrolled from November 2016 to October 2018.

Randomization

Allocation to BCD-BPV or plain BPV was performed in a 4:1 ratio because MMPNA was the standard of care at our institution [9]. Randomization used permuted blocks of five and was stratified by procedure (THA, TKA), diabetes, and age (≤69, >69 years). Sequentially numbered and sealed envelopes with assignment allocation were prepared by the data manager and placed by the pharmacist into the automated drug cabinet; the pharmacist was not involved with other study procedures.

Interventions

We used analgo-sedation intravenously (up to 100 μg fentanyl, 4 mg midazolam, and/or 40 μg dexmedetomidine) after the usual monitors and supplemental oxygen had been applied. Blocks for nerves/plexi originating from the L4–S3 distribution were comprised of 20 mL of 0.1% BPV, with or without the combination of buprenorphine 300 μg, clonidine 25 μg, and dexamethasone 1 mg [4, 9]. Blocks for the L2–L4 distribution were comprised of 20 mL of 0.25% BPV if the patient was nondiabetic and 0.2% BPV if the patient was diabetic [4, 9]. The additives in the L2–L4 blocks and the L4–S3 blocks were identical. The nerve blocks (and antiemetic prophylaxis strategy used, entailing perphenazine and ondansetron, with or without aprepitant [11–14]) were described in detail in our block duration article [4].

Spinal anesthetics were comprised of isobaric bupivacaine (7.5 mg/mL) and sterile water and were administered in the same room as the nerve blocks, with ephedrine and phenylephrine pre-drawn syringes available at the bedside. Intraoperatively, spinal anesthesia was supplemented by propofol sedation and ketamine intermittent boluses for a total of 0.5 mg/kg. Patients received antiemetic prophylaxis preoperatively and intraoperatively. During surgical closure, orthopedic surgeons applied multimodal local anesthesia entailing 30 (body weight <100 kg) or 40 mL (body weight ≥100 kg) of 0.5% bupivacaine, 300 μg of epinephrine, and 30 mg of ketorolac. These procedures and the postsurgical pain management were the same for both study groups [4].

Outcome Measures

The primary outcome was the change in patient-reported pain on POD#1 compared with baseline on the Short-Form McGill Pain Questionnaire-v2 (SF-MPQ-2 [15]) total score, with specific focus on "continuous" and "intermittent" pain subscores. Secondary outcomes were based on previously published recommendations [16] and included: 1) pain intensity and interference assessed by the Defense and Veterans Pain Rating Scale (DVPRS [17–19]), which was modified (mDVPRS) to include questions about pain with movement and at rest, as these predict chronic pain in joint replacement surgery [20]; 2) quality of recovery (QoR) related to postoperative symptoms [21], including those specific to postoperative nausea/vomiting [11–14]; 3) surgical joint range of motion; and 4) mobility measured by self-selected gait speed and standing balance tests [22, 23]. Outcome assessments were performed at baseline (~1 week before surgery), at the primary time point of POD#1, and also at days 2 to 5 and 6 weeks after surgery. The assessments were performed by research staff blinded to group assignment.

Sample Size and Study Interruption

A sample size of 100 participants for THA and 100 for TKA was determined to provide 80% power for primary analysis and was reported previously [4]. However, the target sample size was not achieved, as the study was interrupted because of institutional changes in the standard of care after 98 participants had been enrolled. When the study was planned, the analgesia duration was appropriate for the institutional standard of care that initiated physical therapy on POD#1. However, in mid-2018, same-day physical therapy became the new hospital guideline for TJR. This required a modification of drug dosage, as study participants could not engage in same-day physical therapy because of significant motor and/or sensory-proprioceptive impairment from BPV. The study Data and Safety Monitoring Board suspended study enrollment until revised analgesia of shorter duration enabled safe engagement in same-day physical therapy. The newly modified protocol kept the same block volume and adjuvant doses of BCD but diluted the BPV concentrations to 0.125% for the L2–L4 distribution blocks and 0.0625% for the sciatic nerve (for patients undergoing TKA). This modified drug protocol was approved in May 2019, and the study enrolled a second small cohort of participants from May 2019 until study closeout in January 2020.

Statistical Analysis

Continuous variable normality of distributions was assessed with the Shapiro-Wilk test, where $P < 0.05$ indicated a non-normal distribution; all continuous variables were normally distributed. Baseline values across groups were compared by *t* test or Wilcoxon rank sums test for continuous variables and chi-squared or Fisher's exact tests for discrete variables. Data on SF-MPQ-2 (primary outcome) at POD#1 (primary endpoint) were compared between groups with the *t* test with the Levene correction, when applicable. Outcome measures were analyzed on the basis of difference scores (POD#1 data subtracted from baseline data). We also ran adjusted analyses controlling for stratification factors (THA vs TKA procedure, age, and diabetes status) using linear mixed-models regression with random intercept and unstructured covariance. Data on THA and TKA were pooled for analysis, as they were in our earlier article [4]. We used the same data analysis method for the secondary study outcomes. For all statistical tests, $P < 0.05$ was considered statistically significant. With regard to the smaller-than-expected sample size, we did not adjust alpha for multiple comparisons to prevent type 2 error.

The Data and Safety Monitoring Board recommended not combining data from the main and second study cohorts because of the different BPV concentrations for the nerve blocks. The goal of continuing to collect data after study interruption was to describe whether the observations from the main cohort would replicate after the BPV concentrations had been changed. To that end, we deliberately did not use statistical hypothesis tests for the second cohort. Instead, we ran descriptive statistics for the outcome measures and calculated the means, differences, and 95% confidence intervals across groups, as recommended for pilot studies, to enable visual comparison with results from the main study cohort [24]. All study data were collated and managed with REDCap (project-redcap.org, Nashville, TN, USA) [25]. We used SPSS Statistical Software version 25 (IBM Corp., Armonk, NY, USA).

Results

Of the 571 patients screened in the main study cohort, 473 failed eligibility screening, resulting in 98 enrolled patients (Figure 1). From these, 20 were terminated from the trial early, and 78 patients received the interventions and completed the trial: 62 were allocated to the BPV-BCD group, and 16 were allocated to the plain BPV group (27 THA and 51 TKA). Of the 215 patients screened in the second cohort, 40 were determined to be eligible, and 37 patients received the interventions: 29 were allocated to the BPV-BCD group and 8 were allocated to the plain BPV group (12 THA and 25 TKA; Figure 2). The randomization provided adequate balance across groups with no differences in baseline characteristics (Table 1).

For the main cohort, the SF-MPQ-2 total score during POD#1 demonstrated greater pain reduction in the BPV-BCD group than in the plain BPV group. These differences resulted from pain reduction in both continuous and intermittent subscores of the SF-MPQ-2 (Table 2). For the mDVPRS, all change scores (other than "pain affected mood" and "pain contributions to stress") favored

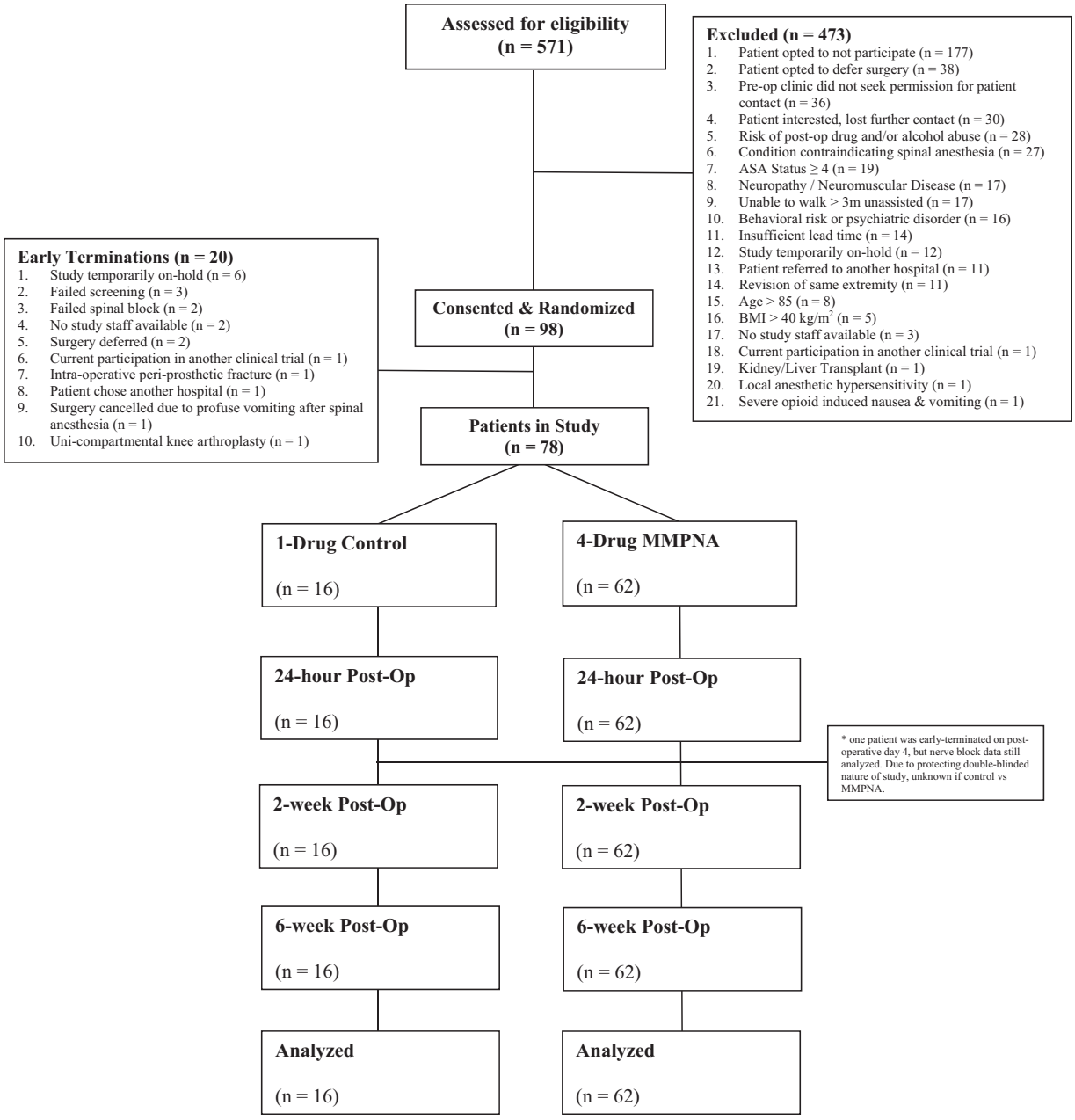

Figure 1. CONSORT diagram: first cohort. Reproduced, with permission, from Williams BA, Ibinson JW, Ritter ME, et al. Extended perineural analgesia after hip and knee replacement when buprenorphine-clonidine-dexamethasone is added to bupivacaine: Preliminary report from a randomized clinical trial. Pain Med 2020;21(11):2893–902. PubMed PMID 33027531, Oxford Publishing.

BPV-BCD (Table 2). When adjusted modeling was conducted for each pain outcome (in Table 2, main cohort) with adjustment for stratification factors, inclusion of all factors did not change the significance of study drug on listed measurements. However, diabetes was also associated with higher SF-MPQ total scores and listed subscores, and older age group was also associated with more pain at rest and with movement on the mDVPRS ($P < 0.05$ for each), over and above the BPV-BCD drug treatment effect.

The results from the second cohort did not show any differences (Table 2).

The Supplementary Data show exploratory pain outcome data in the main cohort stratified by surgical procedure, demonstrating that SF-MPQ-2 continuous pain reductions were present after THA and TKA in patients receiving BPV-BCD, while TKA patients also had lower intermittent and total SF-MPQ-2 pain scores after BPV-BCD. Meanwhile, both THA and TKA patients receiving BPV-BCD treatment had lower mDVPRS scores at rest and with movement, as well as lower scores involving pain activity interference and pain sleep interference; TKA BPV-BCD patients also had lower scores involving pain affecting mood (Supplementary Data). There were

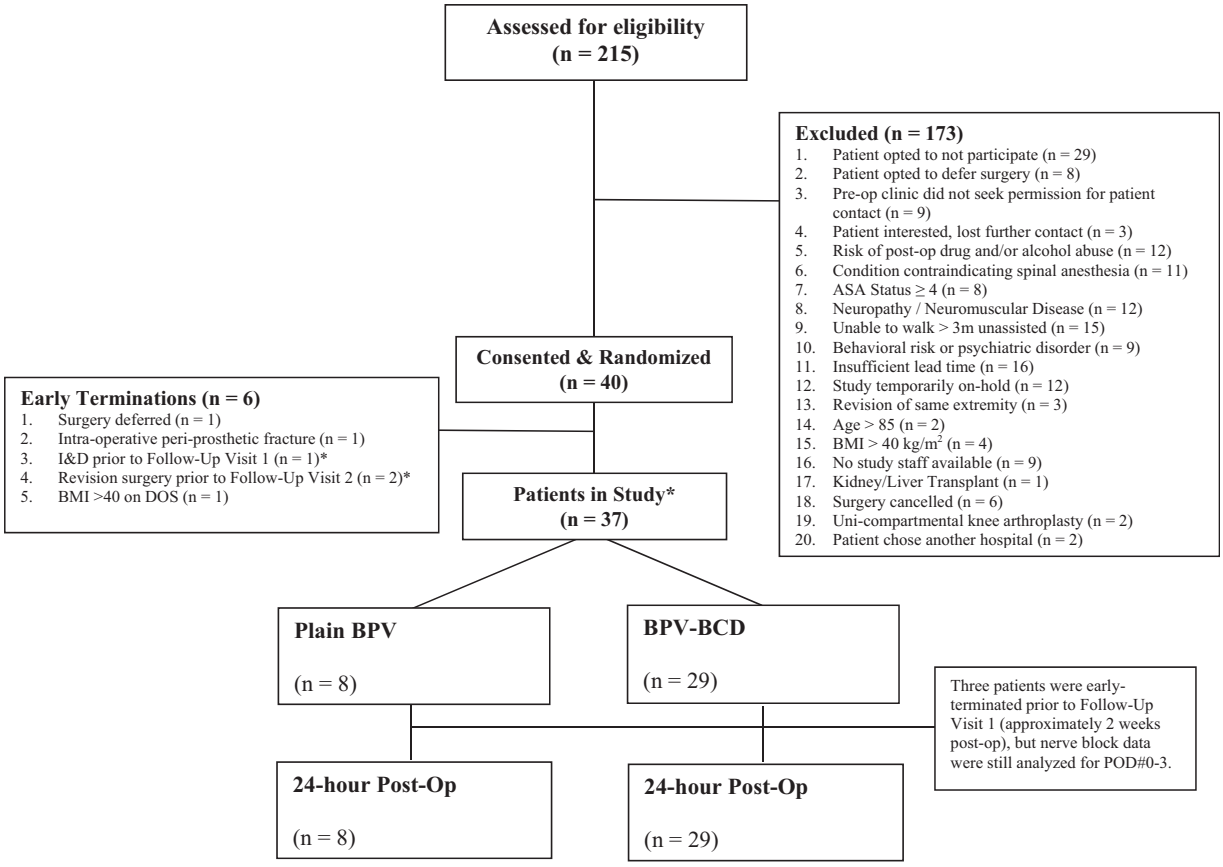

Figure 2. CONSORT diagram: second cohort.

no treatment group differences for the SF-MPQ-2 or items in the mDVPRS at the 6-week follow-up (data not shown).

In the main cohort, there were no differences in the QoR-15 total score or the nausea/vomiting score on POD#1 (Table 3), indicating that there was no effect of perineural buprenorphine on postoperative nausea/vomiting with the perphenazine/ondansetron antiemetic strategy [11–14] used. There were also no differences in the standing balance test or in gait speed between BPV-BCD–treated and plain BPV–treated patients. Significant differences were found, however, between drug treatment groups, favoring BPV-BCD for the knee and hip range of motion on POD#1, particularly flexion (Table 3). Adjusted modeling for stratification factors did not cancel the treatment-related significant findings. In the second cohort, no differences were seen (Table 3). There were no differences between groups at 6-week follow-up for these secondary outcomes (data not shown).

Discussion

The study results supported the hypothesis that BPV-BCD blocks lead to less pain on POD#1 than do plain BPV blocks for patients undergoing THA or TKA. This was confirmed by our primary (SF-MPQ-2) and secondary (mDVPRS) outcomes of pain. The present article complements our first report [4] from this randomized trial that demonstrated longer analgesic duration in the BPV-BCD group than in the plain BPV group for patients undergoing primary TJR with dual blocks in the L2–L4 and L4–S3 distributions. This finding verifies the short-term superiority of BPV-BCD over plain BPV, similar to the results that reported perineural BCD (admixed with ropivacaine) being superior to systemic BCD (and perineural ropivacaine) for shoulder arthroplasty [5]. In our study, there was no apparent pain detriment from BCD adjuvant use on subsequent postoperative days in the hospital or at 6 weeks. Study findings also indicate that the improved analgesia from BPV-BCD seems to help with early recovery of range of motion in the operated joint.

In our retrospectively reviewed prospective case series of BPV-BCD blocks for TJR [9], we found a surprising association of higher rebound pain with 2 mg perineural dexamethasone per block than with 1 mg dexamethasone. On the basis of this, as well as other systemic concerns and potential complications of escalating perineural dexamethasone, we felt it was important to use two additional adjuvants (buprenorphine and clonidine) to confer further analgesic duration [4] and potential anti-hyperalgesic benefits.

The original knowledge translation purpose of this study was to test the quality of pain relief after a

Table 1. Baseline characteristics and care utilization for patients undergoing THA or TKA

	Main Cohort (THA and TKA)			Second Cohort (THA and TKA, Exploratory Only)	
Characteristic	BPV-BCD (n=62)	Plain BPV (n=16)	*P* Value	BPV-BCD (n=29)	Plain BPV (n=8)
Baseline demographic and biomedical					
Age, years, mean (SD)	67 (7)	66 (8)	0.617 (W)	66 (8)	67 (7)
Female, n (%)	6 (10%)	1 (6%)	0.669	5 (17%)	1 (13%)
Body mass index, kg/m^2, mean (SD)	33 (5)	32 (5)	0.707 (W)	33 (4)	34 (4)
Race, n (%)			0.678		
White	53 (85%)	15 (94%)		26 (90%)	8 (100%)
Non-White	9 (15%)	1 (6%)		3 (10%)	0
Hispanic or Latino, n (%)	0 (0%)	0 (0%)	N/A	0 (0%)	0 (0%)
College/trade school education or more, n (%)	29 (47%)	10 (63%)	0.262	15 (52%)	2 (25%)
Lives alone, n (%)	16 (26%)	4 (25%)	0.948	8 (28%)	1 (13%)
Diabetes, n (%)	23 (37%)	6 (38%)	0.976	7 (24%)	3 (38%)
On chronic opioids/tramadol, n (%)	8 (13%)	2 (13%)	0.966	5 (17%)	1 (13%)
Currently smoking, n (%)	6 (9%)	1 (6%)	0.669	none	none
ASA-PS, n of II/n of III	11/51	3/13	0.925	7/22	1/7
CIRS total score, mean (SD)	20 (3)	20 (2)	0.788 (W)	20 (2)	22 (3)
Care utilization					
Pre-OR midazolam, mg, mean (SD)	1.9 (0.3)	1.8 (0.4)	0.637	1.3 (0.8)	1.6 (0.7)
Pre-OR fentanyl, μg, mean (SD)	91 (21)	86 (29)	0.423	84.5 (27.1)	91 (19)
*Pre-OR dexmedetomidine, μg, mean (SD)	22 (14)	20 (3)	0.660	22 (12)	20 (n = 1, no SD)
Hospital length of stay, hours, mean (SD)	83 (47)	69 (24)	0.263	68 (21)	64 (19)
Study procedure, n of Hip/N of knee	21/41	6/10	0.786	20/9	5/3

ASA-PS= American Society of Anesthesiologists Physical Status classification; CIRS= Cumulative Illness Rating Scale; hip= patients undergoing THA, who received lumbar (both cohorts) and parasacral (main cohort only) plexus blocks; knee= patients undergoing TKA, who received femoral and sciatic nerve blocks; N/A= not analyzed or not applicable; OR = operating room.

For the main cohort, continuous variables were assessed with ANOVA for normally distributed data and with Wilcoxon rank-sum tests for non-normally distributed data, as indicated by (W) after the *P* values.

*Dexmedetomidine was available as an alternative sedative to midazolam for veterans with post-traumatic stress disorder. This was used for only nine and four main-cohort BPV-BCD and plain BPV patients, respectively, and for five second-cohort BPV-BCD patients; these mean (SD) values reflect the totals of only the patients who received dexmedetomidine.

prolonged nerve block by BPV-BCD in TJR, for possible use in active-duty soldiers with lower-extremity polytrauma. We forecast utility of the described BPV-BCD single-injection nerve blocks before prolonged transport for definitive medical care. Moreover, the clinical analgesic duration value combined with the relatively low cost of BPV-BCD could be considered in scenarios for which liposome bupivacaine (off-label in these contexts) may be considered.

For the small second cohort of 37 participants, although the upper bound of the confidence intervals suggest larger pain reductions in the BPV-BCD group, the confidence intervals were wide, and all crossed zero. Larger studies testing the modified dose protocol (en route to same-day physical therapy) are needed.

Additionally, both drug regimens seem safe. In the operating room, there were no differences for continuous phenylephrine infusion for blood pressure support (58/91 BPV-BCD patients from the main and second cohorts, respectively [64%], vs 18/24 plain BPV patients from both cohorts [75%], $P = 0.744$ by chi-squared test), indicating that perineural clonidine did not appear to adversely affect hemodynamics. In the operating room and post-anesthesia care unit, no patients required naloxone for respiratory depression, indicating that perineural buprenorphine was well tolerated from a respiratory standpoint.

As previously reported [4], there was one possibly block-related adverse event. One patient had foot drop after TKA, which spontaneously resolved over the subsequent 12–16 weeks. Electromyography was ordered 3 months after surgery and showed deep peroneal nerve acute and subacute denervation changes. The subgluteal sciatic block for this patient was placed with ultrasound guidance; the intraoperative tourniquet time was 125 minutes at 300 mm Hg. This patient received the BPV-BCD treatment. Common peroneal nerve palsy can occur frequently in small studies after TKA (0–10%) [26]; however, the incidence in consecutive case series (of large size) ranges from 0.3% to 1.3% [26].

There were several study limitations. First, the study interruption occurred after 98 veterans had been enrolled (78 completed cases) in the main study cohort, which limits the generalizability of the results. Another

Table 2. Changes in pain outcome from baseline to POD#1 in the BPV-BCD and plain BPV groups

	Main Cohort*				Second Cohort†			
Pain Outcomes	Baseline Mean (SD)	POD#1 Mean (SD)	Change Score Mean (SD)	Study Drug Mean Difference (95% CI) *P* Value	Baseline Mean (SD)	POD#1 Mean (SD)	Change Score Mean (SD)	Study Drug Mean Difference (95% CI)
Primary								
SF-MPQ-2‡—total	-	-	-	1.8 (0.6 to 3.0) $P = 0.003$	–	-	–	0.9 (-1.1 to 2.8)
BPV-BCD	3.3 (1.8)	1.5 (1.8)	1.8 (2.0)	-	3.7 (1.9)	1.7 (1.9)	1.9 (2.4)	-
Plain BPV	3.0 (1.2)	3.0 (2.5)	0.0 (2.4)	-	3.2 (2.2)	2.2 (1.6)	1.1 (2.4)	-
SF-MPQ-2—continuous subscore	-	-	-	2.6 (1.2 to 4.0) $P < 0.001$	-	-	-	1.8 (-0.7 to 4.3)
BPV-BCD	4.2 (2.0)	1.9 (2.0)	2.3 (2.4)	–	4.5 (2.1)	2.2 (2.3)	2.3 (2.8)	-
Plain BPV	4.1 (2.0)	4.5 (2.4)	−0.3 (2.8)	–	4.1 (2.8)	3.6 (2.5)	0.5 (4.0)	-
SF-MPQ-2—intermittent subscore	-	-	-	1.7 (0.1 to 3.2) $P = 0.038$	-	-	-	0.7 (-2.0 to 3.5)
BPV-BCD	4.2 (2.4)	1.4 (2.1)	2.7 (2.7)	-	4.8 (2.2)	1.9 (2.6)	2.8 (3.3)	-
Plain BPV	4.2 (1.5)	3.1 (3.1)	1.1 (3.3)	-	4.3 (3.5)	2.1 (2.1)	2.1 (3.6)	-
Secondary								
mDVPRS§—pain at rest	-	-	-	3.8 (2.3 to 5.3) $P < 0.001$	-	-		0.9 (-1.8 to 3.6)
BPV-BCD	5.1 (2.0)	3.1 (2.9)	1.9 (2.6)	–	5.0 (2.2)	3.8 (3.1)	1.2 (3.1)	-
Plain BPV	4.6 (2.6)	6.5 (2.6)	−1.9 (2.8)	–	5.1 (2.1)	4.8 (2.8)	0.4 (4.0)	-
mDVPRS—pain with movement	-	-	-	3.4 (1.7 to 5.1) $P < 0.001$	-	-		1.9 (-0.9 to 4.6)
BPV-BCD	6.6 (1.8)	4.1 (3.2)	2.5 (3.0)	–	6.4 (1.9)	4.3 (3.3)	2.1 (3.6)	-
Plain BPV	7.0 (1.7)	7.9 (2.1)	−0.9 (3.3)	–	6.8 (1.7)	6.5 (1.8)	0.3 (2.3)	-
mDVPRS—pain activity interference	-	-	-	3.1 (0.7 to 5.4) $P = 0.012$	-	-		1.8 (-1.8 to 5.5)
BPV-BCD	6.0 (2.2)	4.8 (4.0)	1.2 (4.4)	–	5.8 (2.2)	4.8 (4.2)	1.1 (4.6)	-
Plain BPV	6.5 (2.4)	8.3 (2.4)	−1.8 (3.5)	–	6.4 (1.7)	7.1 (4.2)	−0.8 (4.4)	-
mDVPRS—pain sleep interference	-	-	-	2.5 (0.3 to 4.8) $P = 0.026$	-	-		1.1 (-2.9 to 5.0)
BPV-BCD	4.3 (2.8)	3.7 (3.4)	0.6 (4.0)	-	4.9 (2.9)	4.3 (3.7)	0.6 (4.4)	-
Plain BPV	5.1 (3.1)	7.0 (2.4)	−1.9 (3.9)	-	4.1 (3.1)	4.6 (4.7)	−0.5 (6.3)	-
mDVPRS—pain affected mood	-	-	-	1.3 (-0.4 to 3.0) $P = 0.120$	-	-		0.7 (-2.4 to 3.7)
BPV-BCD	4.4 (2.8)	2.0 (2.5)	2.4 (2.9)	-	4.3 (3.2)	2.4 (2.7)	1.9 (3.2)	-
Plain BPV	5.9 (2.8)	4.8 (3.6)	1.1 (3.5)	-	4.5 (3.6)	3.3 (3.7)	1.3 (5.4)	-
mDVPRS—pain contributions to stress	-	-	-	0.8 (-0.9 to 2.5) $P = 0.368$	-	-		1.1 (-1.9 to 4.2)
BPV-BCD	4.6 (3.0)	2.0 (2.6)	2.6 (3.0)	-	4.9 (3.3)	2.0 (2.6)	2.9 (3.2)	-
Plain BPV	6.4 (3.1)	4.6 (3.5)	1.8 (3.0)	-	5.4 (3.0)	3.6 (4.1)	1.8 (5.5)	-

*The main cohort had 62 participants in the BPV-BCD group and 16 participants in the plain BPV group (27 THA and 51 TKA).

†The second cohort had 29 participants in the BPV-BCD group and 8 in the plain BPV group (12 THA and 25 TKA).

‡The SF-MPQ-2 total score was used to measure quality and intensity of pain. Its continuous and intermittent pain subscores were used to characterize these two qualities of pain relevant to TJR. The total score and subscores range from 0 to 10, and higher scores indicate more pain.

§The DVPRS is a graphic pain rating scale on which patients can rate their pain on a scale of 0–10, with 10 being the worst possible pain; it includes four questions on how the prior 24 hours' pain has affected the patient's activity, sleep, mood, and stress. We modified the DVPRS (mDVPRS) to include questions about pain with movement and at rest.

Table 3. Changes in quality of recovery, physical function, and range of motion at baseline and POD#1 in the BPV-BCD and plain BPV groups

	Main Cohort*				Second Cohort†			
Outcomes of Quality of Recovery, Physical Function, and Range of Motion	Baseline Mean (SD)	POD#1 Mean (SD)	Change Score Mean (SD)	Study Drug Mean Difference (95% CI) *P* Value	Baseline Mean (SD)	POD#1 Mean (SD)	Change Score Mean (SD)	Study Drug Mean Difference (95% CI)
QoR‡ total	–	–	–	13 (-5 to 32) *P* = 0.142				−24 (-63 to 15)
BPV-BCD	111 (26)	106 (20)	−6 (32)	–	120 (15)	104 (22)	15 (23)	–
Plain BPV	108 (28)	90 (24)	−19 (24)	–	129 (18)	89 (38)	40 (46)	–
QoR nausea/vomiting				−0.4 (-2.4 to 1.6) *P* = 0.701				0.3 (-2.4 to 3.1)
BPV-BCD	9.1 (2.7)	9.4 (2.0)	0.3 (3.4)		10 (0)	8.3 (3.4)	1.7 (3.4)	
Plain BPV	8.1 (4.0)	8.8 (3.1)	0.7 (4.0)		9.9 (0.4)	8.5 (3.5)	1.4 (3.5)	
Physical function								
Standing balance test§	–	–	–	−0.5 (-1.4 to 0.4) *P* = 0.287	-	-		−0.8 (-2.1 to 0.4)
BPV-BCD	3.7 (0.6)	2.0 (1.6)	−1.8 (1.6)	–	3.6 (0.8)	2.8 (1.5)	0.9 (1.5)	–
Plain BPV	3.4 (0.9)	1.1 (1.5)	−2.3 (1.3)	–	3.9 (0.4)	2.1 (1.6)	1.8 (1.7)	–
Gait speed, m/s¶	–	–	–	−0.08 (-0.27 to 0.11) *P* = 0.411	-	-		−0.09 (-0.26 to 0.08)
BPV-BCD	0.80 (0.23)	0.25 (0.12)	−0.56 (0.22)	–	0.87 (0.17)	0.33 (0.15)	−0.52 (0.17)	–
Plain BPV	0.90 (0.24)	0.27 (0.09)	−0.64 (0.29)	–	0.86 (0.19)	0.32 (0.13)	−0.60 (0.18)	–
Range of motion‖								
Knee flexion (°)	–	–	–	−17 (-31 to -3) *P* = 0.017	-	-		−6 (-17 to 29)
BPV-BCD	125 (11)	83 (16)	−42 (19)	–	121 (15)	94 (18)	−26 (23)	–
Plain BPV	123 (13)	64 (25)	−60 (23)	–	126 (9)	94 (14)	−32 (18)	–
Knee extension °)	–	–	–	1 (-3 to 4) *P* = 0.663	-	-		−1 (-4 to 6)
BPV-BCD	−1 (3)	−7 (4)	7 (5)	–	−3 (5)	−5 (2)	1 (5)	–
Plain BPV	−2 (5)	−8 (4)	6 (6)	–	−1 (2)	−3 (1)	2 (3)	–
Hip abduction (°)	–	–	–	−3 (-8 to 14) *P* = 0.603	-	-		−2 (-17 to 22)
BPV-BCD	23 (6)	23 (9)	0 (13)	–	26 (8)	29 (9)	−4 (14)	–
Plain BPV	22 (8)	19 (6)	3 (7)	–	16 (13)	18 (8)	−1 (9)	–
Hip flexion (°)	–	–	–	−26 (-44 to -7) *P* = 0.008	-	-		−10 (-17 to 37)
BPV-BCD	87 (5)	66 (18)	−21 (18)	–	84 (11)	82 (12)	−2 (17)	–
Plain BPV	88 (4)	41 (16)	−47 (16)	–	69 (37)	57 (31)	−12 (24)	–

*The first cohort had 62 participants in the BPV-BCD group and 16 participants in the plain BPV group (27 THA and 51 TKA).

†The second cohort had 29 participants in the BPV-BCD group and 8 in the plain BPV group (12 THA and 25 TKA).

‡QoR = quality of recovery, with the total score ranging from 0 to 150 and the nausea/vomiting parameters scoring from 0 to 10. Higher values represent higher quality of recovery (a "10" score for nausea/vomiting indicates "none").

§The standing balance test involved three consecutive increasingly difficult balance tests in which patients attempted to stand without other support as foot position changed from side-to-side, semi-tandem, and tandem conditions. Only one attempt was permitted for each stance, and if the participant failed one aspect of the test, subsequent aspects were not attempted. Score ranges from 0 to 4. Higher values represent better standing balance.

¶Gait speed was measured in meters per second with a stopwatch while subjects walked a 4-meter path at their regular pace. The test was repeated twice, and the fastest trial recorded. Gait speed was measured when patients had recovered sufficient motor strength (including full range of motion of the ankle joint) and energy level to be tested out of bed (n = 53 in BPV-BCD group; n = 13 in plain BPV group). Higher scores indicate faster gait speed.

‖Knee range of motion was assessed in patients undergoing TKA (n = 39 in BPV-BCD group; n = 9 in plain BPV group), whereas hip range of motion was assessed in patients undergoing THA (n = 20 in BPV-BCD group; n = 6 in plain BPV group). Range of motion was assessed with a standard goniometer with participant in a supine position, using passive movement. Higher values represent more movement. For knee extension, negative values represent flexion contracture.

limitation is the 4:1 randomization allocation, which happened because, at the time the grant application was written, the BPV-BCD was our institution's standard of care for perineural analgesic drugs (in the absence of institutional support for a nerve block catheter service). Our low enrollment rate (e.g., 17% in the main study cohort) and exclusions after randomization due to study interruption or changes in surgical procedure (e.g., additional fixation of periprosthetic fracture) could also adversely influence the generalizability of the study results. Last, although we intended to collect data for POD#2 through POD#5, these data were not analyzed because most patients were discharged from the hospital on POD#2, resulting in an insufficient sample size.

Recent evidence from meta-analysis of liposomal bupivacaine demonstrates either no clinical benefit or clinically insignificant benefit for nerve blocks (vs plain BPV) [27, 28], which did not necessarily include the types of blocks performed for the present trial. We feel that BPV-BCD provides an efficacious and extremely low-cost alternative to patent-protected liposome bupivacaine for clinical analgesic benefit the day of and day after surgery.

In the accompanying Invited Editorial [10], we share a summary of other clinical case series recently published in *Pain Medicine* addressing the potential role of BCD-based perineural motor-sparing (or mobilization-enhancing) analgesia.

To conclude, results based on validated surveys of pain and range of motion were superior on POD#1 in the patients who received BPV-BCD. There was no apparent pain detriment on subsequent postoperative days in the hospital or at 6 weeks. These BPV-BCD blocks were generally well suited to POD#1 physical therapy efforts. These findings complement our previous report [4] that BPV-BCD provided 26–39 hours of analgesia in the L2–L4 and L4–S3 nerve distributions after hip or knee replacement, compared with 11–21 hours for plain BPV. Furthermore, with the use of the described multimodal perphenazine-ondansetron antiemetic regimen [11–14], postoperative nausea and vomiting were not influenced by the use of perineural buprenorphine in the BPV-BCD group.

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Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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