

AWARD NUMBER: W81XWH-15-1-0294

TITLE: 4-drug Nerve Block versus Plain Local Anesthetic  
for Knee and Hip Arthroplasty Analgesia in Veterans

PRINCIPAL INVESTIGATOR: Brian A. Williams, MD, MBA

CONTRACTING ORGANIZATION: University of Pittsburgh, Pittsburgh, PA

REPORT DATE: December 2021

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Development Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
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| REPORT DOCUMENTATION PAGE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |             |                         |                            | Form Approved<br>OMB No. 0704-0188       |                                           |
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| 1. REPORT DATE<br>December 2021                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             | 2. REPORT TYPE<br>Final |                            | 3. DATES COVERED<br>30Sep2015-29Sep2021  |                                           |
| 4. TITLE AND SUBTITLE<br><br>4-drug Nerve Block versus Plain Local Anesthetic for Knee and Hip Arthroplasty Analgesia in Veterans                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |             |                         |                            | 5a. CONTRACT NUMBER                      |                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |                         |                            | 5b. GRANT NUMBER<br>W81XWH-15-1-0294     |                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |                         |                            | 5c. PROGRAM ELEMENT NUMBER               |                                           |
| 6. AUTHOR(S)<br>Brian A. Williams, MD, MBA<br><br>E-Mail: Wiliamsba@anes.upmc.edu                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |             |                         |                            | 5d. PROJECT NUMBER                       |                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |                         |                            | 5e. TASK NUMBER                          |                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |                         |                            | 5f. WORK UNIT NUMBER                     |                                           |
| 7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)<br><br>UNIVERSITY OF PITTSBURGH                      VA Pittsburgh Healthcare System<br>3520 FIFTH AVE                                      University Drive C<br>PITTSBURGH PA 15213-3320                      Pittsburgh, PA 15240                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |             |                         |                            | 8. PERFORMING ORGANIZATION REPORT NUMBER |                                           |
| 9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)<br><br>U.S. Army Medical Research and Development Command<br>Fort Detrick, Maryland 21702-5012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |             |                         |                            | 10. SPONSOR/MONITOR'S ACRONYM(S)         |                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |                         |                            | 11. SPONSOR/MONITOR'S REPORT NUMBER(S)   |                                           |
| 12. DISTRIBUTION / AVAILABILITY STATEMENT<br>Approved for Public Release; Distribution Unlimited                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |                         |                            |                                          |                                           |
| 13. SUPPLEMENTARY NOTES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |             |                         |                            |                                          |                                           |
| 14. ABSTRACT<br>Enrollment into this study ended January 31, 2020. 138 patients were enrolled/consented, and 112 successfully completed the study. Data verification is now complete and the study is in data analysis only.<br><br>This is our final technical report as our DoD award has ended.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |             |                         |                            |                                          |                                           |
| 15. SUBJECT TERMS<br>Bupivacaine, clonidine, buprenorphine, dexamethasone, nerve block, pain, hip, knee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |             |                         |                            |                                          |                                           |
| 16. SECURITY CLASSIFICATION OF:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |                         | 17. LIMITATION OF ABSTRACT | 18. NUMBER OF PAGES                      | 19a. NAME OF RESPONSIBLE PERSON           |
| a. REPORT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | b. ABSTRACT | c. THIS PAGE            |                            |                                          | USAMRDC                                   |
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## **1. Introduction**

For joint replacement, single-injection nerve blocks with local anesthetics are simple to perform, but only provide 12-16 hours of pain relief that includes muscle weakness. This study evaluated an innovative 36-hour single-injection nerve block that combined a low-concentration local anesthetic with other pain relievers injected near the nerve. In veterans undergoing total hip or knee replacement, we compared single-injection nerve blocks with the plain local anesthetic bupivacaine against a 4-drug combination (including bupivacaine) in veterans undergoing hip or knee replacement surgery. The other 3 drugs were buprenorphine-clonidine-dexamethasone (BCD). Based on these two treatments, the goals are to determine differing effects on (1) pain; (2) physical function; (3) discharge plans after hospital care; (4) satisfaction with treatment and emotional response; and (5) symptoms and adverse events. These outcome domains were measured using both validated and innovative methods. Preoperative baseline survey data were collected, and patient-follow-up took place during days 1-4, and at 2 and 6 weeks after surgery. This research took five years. We found that the 36-hour single-injection 4-drug nerve block had likely potential immediate military relevance, by reducing or eliminating the complexity involved with inserting nerve block catheters in injured soldiers in or near the battlefield before lengthy transport to definitive medical care.

## **2. Keywords**

Bupivacaine, clonidine, buprenorphine, dexamethasone, nerve block, pain, hip, knee

### 3. Accomplishments

#### Section 3.1: MAJOR GOALS

**Task 1.** Task completed at the 2016 Annual Report interval. Administrative, infrastructural, and regulatory affairs: FDA IND submission, review, response, and approval of the full IND.

#### **Task 2. Related to funding-dependent infrastructural and enrollment activity**

**Task #2a:** Administrative, infrastructural, and regulatory affairs: VA Pittsburgh Healthcare System (VAPHS) Institutional Review Board (IRB) submission / revision / approval; creation of Data Safety Monitoring Board DSMB through Pitt; VAPHS office setup; credentialing Pitt-hired research team members at VAPHS; VAPHS physical therapy team finalizing the research template with Pitt-hired physical therapists.

**Task #2b:** Hire, train, and credential physical therapists/recruiters (hired through University of Pittsburgh)

**Task #2c:** Study-specific programming and preparation for, communications, data collection, and data management: finalize Case Report Forms, purchase and programming of laptop PCs.

**Task #2d:** Screening, enrollment, baseline data collection, randomization, surgery, hospitalization

**Task #2e:** Study participant follow-up for six weeks after surgery

**Task #2f:** Periodic regulatory surveillance (IRBs / HRPO, Pitt DSMB, DoD Quarterly/Annual Reports, FDA-IND)

#### **Task 3. Related to scholarly tasks of transforming data into information**

**Task #3a:** Ongoing data entry quality verification

**Task #3b:** Periodic data analyses for professional meeting presentations and DoD annual reports

**Task #3c:** Data reduction, analysis, and interpretation; manuscript preparations, presentations, revisions, and publications

**Task #3d:** Active dissemination of research findings via relevant professional societies

#### Section 3.2: ACCOMPLISHMENTS UNDER THESE GOALS

**Task 1:** Task 1 was completed, and described in the 2016 Annual Report.

Other achievements related to this FDA-IND task was the submission of two peer-reviewed manuscripts that were formulated based on the described requirements. Both were published in the journal *Pain Medicine*, and are attached to the final report.

- Williams BA, Ibinson JW, Gould AJ, Mangione MP. The incidence of peripheral nerve injury after multimodal perineural anesthesia/analgesia does not appear to differ from that following single-drug nerve blocks (2011-2014). *Pain Medicine* 2017; 18: 628–636. PMID# 26896319
- Williams BA, Podnar SM, Bonant SA, Schanck AM. TECHNICAL COMMUNICATION: Admixture of bupivacaine-clonidine-buprenorphine-dexamethasone at the bedside in a tertiary care hospital block room is not associated with any apparent burdens of endotoxin or microbial growth. *Pain Medicine* 2017; 18: 781–785. PMID# 28586444

**Task 2.** Task 2 (a-c) was completed. The reader is referred to the 2016 Annual Report. These tasks were related to funding-dependent infrastructural and enrollment activity. Tasks 2d, 2e, and 2f were all related to active recruitment and protocol implementation, and associated periodic regulatory

surveillance (and ongoing procedures to ensure all activities being accurately tracked and easily accessible for future audit purposes).

Enrollment began in October 2016. Ultimately, 138 subjects were enrolled/consented; 112 subjects successfully completed the study.

### **Task 3.**

Data verification is complete. The study continues in data analysis as other secondary analyses for additional manuscripts are prepared. All data has been collected and the study remains open with the IRB for the sole purpose of preparation of manuscripts.

## **Section 3.3: OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT**

As reported in previous quarterly reports, the Food and Drug Administration contacted Dr. Williams to enlist his participation as a lecturer and session planner for a special *ad hoc* meeting addressing nerve blocks. The session audience entailed the relevant agency employees of the FDA, and the number of invited panelists and/or speakers was approximately ten. This occurred in Bethesda, MD on 18 September 2017. The agenda included an introductory discussion of nerve blocks, how nerve blocks are being utilized, and extrapolating outcomes from one type of block to another, and one type of patient population to another. Dr. Williams was the co-organizer of the curriculum for 4 hr of this day-long session. Dr. Williams' DoD-funded work comprised a significant portion of the day's curriculum. A transcript of the public workshop was never made available.

## **Section 3.4: HOW THE RESULTS WERE DISSEMINATED**

We attach the following 3 manuscripts.

- Williams BA, Ibinson JW, Ritter ME, Ezaru CS, Rakesh HR, Paiste HJ, Gilbert KL, Mikolic JM, Muluk VS, Piva SR. 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 Nov; 21(11):2893-2902. PubMed PMID 33027531.
- Williams BA, Ibinson JW, Mikolic JM, Boudreaux-Kelly MY, Paiste HJ, Gilbert KL, Bonant SA, Ritter ME, Ezaru CS, Muluk VS, Piva SR. Day-one pain reductions after hip and knee replacement when buprenorphine-clonidine-dexamethasone is added to bupivacaine nerve/plexus blocks: A randomized clinical trial. *Pain Med* 2021, PubMed PMID: 34730810
- Williams BA, Ibinson JW, Bonant SA, Gilbert KL, Piva SR. Invited Editorial – A Tale of Two Cohorts: Trials and tribulations of ever-changing orthopedic/acute pain medicine hospital practices while executing military-funded clinical-translational research (2013-2021). *Pain Med* 2021, Accepted for publication, ptab267, associated with ptab325 above. Pending Doi: 10.1093/pm/ptab267. Pending PubMed PMID

We have submitted for possible publication the following two manuscripts, and include the abstracts for each of these:

- Aloziem OU, Williams BA, Mikolic JM, Boudreaux-Kelly MY, Faruque S, Piva SR, Ibinson JW, Switzer GE. Comparison of the 8-Item Short-Form Health Survey and the Quality of Recovery 15-Item scale after primary total hip or knee arthroplasty with regional anesthesia. Submitted to *Anesth Analg*, November 2021.
  - Background: The quality of recovery of patients who have undergone anesthesia has been a longstanding concern of the surgical community. There is no consensus about

how best to measure postoperative quality of recovery. The objective was to provide a robust psychometric basis for recovery measure selection for patients undergoing regional, without general, anesthesia. Goals were to (1) evaluate the pattern of the QoR-15 and SF-8 scores across four time points, pre- to post-surgery, (2) evaluate the degree of conceptual overlap between the instruments and, (3) compare the responsiveness of the two instruments across time.

- Methods: This analysis is based on data from a double-blind randomized, controlled trial comparing two nerve block drug regimens for total joint arthroplasty (TJA). The trial was conducted at a single United States Veterans Administration (VA) hospital with patients recruited November 2016 to January 2020. QoR-15 and global health-related quality of life (SF-8/SF-36) were self-reported prior to surgery, on post-operative day 1, post-operative day 2, and at 6 weeks post-surgery. We used descriptive statistics to examine these parameters across time. The degree of statistical overlap between the QoR-15 with SF-8 scores was examined using Pearson's  $r$ . Relative responsiveness of the QoR-15 and SF-8 was examined using distribution-based methods.
- Results: Average age of the 135 participants was 67 years, 89% were male, 88% were white and most were overweight with an average BMI of 33. QoR-15 mean scores declined from pre-op on the 2 days following surgery but were higher than pre-op by 6 weeks post-op. SF physical component scores (PCS) were low and remained low from pre-op through the two days post-surgery, but were elevated over baseline at 6 weeks post-op. SF mental component scores (MCS) declined from baseline on the 2 days following surgery, but were higher than pre-op at 6 weeks post-op. Associations of the QoR-15 total score and SF-8 PCS and MCS were in the medium (0.30) to large (0.50) range and were statistically significant at  $P \leq 0.01$ . Responsiveness analyses produced effect-size estimates in the medium (0.50) to large range (0.80) for both the QoR-15 and SF summary scales, with particularly large effects observed between earlier time points and 6 weeks post-surgery.
- Conclusion: The QoR-15 and SF-8 instruments performed similarly across the pre- and post-operative time points. The SF-8 has the added benefits of (1) brevity, (2) assessment of physical and mental health components, and (3) being normed to the general population.
- Piva SR, Switzer GE, Mikolic JM, Boudreaux-Kelly MY, Faruque S, Aloziem O, Ibinson JW, Williams BA. Comparing pain measures in the context of total joint replacement among Veterans undergoing exclusively regional anesthesia: Secondary analysis from a randomized trial. Submitted to *Reg Anesth Pain Med*, November 2021.
  - Objective: To evaluate (i) the latent structure of the Defense and Veterans Pain Rating Scale (supplemented with items germane to total joint replacement, DVPRS-TJR), (ii) the relationships among the pain dimensions represented on DVPRS-TJR and the reference-standard Short-Form McGill Pain Questionnaire (version 2, SF-MPQ-2), and (iii) the responsiveness of these two measures.
  - Design: Secondary analyses of Veteran survey responses.
  - Setting: Joint replacement surgery, conducted under exclusively regional anesthesia, in a Veterans' hospital.
  - Subjects: 138 Veterans in a randomized study.
  - Methods: Standard psychometric evaluations entailing correlations, principal components analysis, responsiveness analysis, determination of thresholds of clinically important change, and floor and ceiling effects.
  - Results: Two reliable subscales were identified for the DVPRS-TJR, one including items about pain intensity and interference related to the surgical joint (Cronbach's alpha 0.809), and the other including two pain items on the non-surgical joint. Combining the

subscales of the DVPRS-TJR and SF-MPQ-2 indicated a 2-factor solution. Factor one contained the 4 subscales of the SF-MPQ-2 and the DVPRS-TJR surgical joint subscale, which indicates these subscales represent the same pain dimension. Factor two included the DVPRS-TJR non-surgical joint subscale. Responsiveness analysis demonstrated significant decreases in pain from preoperative to 6-week postoperative for all subscales, and that the DVPRS-TJR and SF-MPQ-2 subscales are similarly responsive (except for the SF-MPQ-2 neuropathic and DVPRS-TJR non-surgical joint subscales, which were both minimally responsive). The thresholds for clinically important change ranged from 0.88 to 1.16 (out of 10) points.

- Conclusions: The newer DVPRS-TJR is valid for use among Veterans undergoing TJR.

### **Section 3.5: PLANS DURING THE NEXT REPORTING PERIOD**

This is our final technical report; the award period has ended. We are likely to revise manuscripts in review, as indicated, and possibly write other secondary analyses from our data set. We remain grateful for this opportunity to serve those who have served. We remain available to any DoD pain management authorities who wish to discuss our research findings, and potential applicability to real-time care.

## **4. Impact**

See “Presentations” in Section 6 below

“Nothing to Report” applies to the following sections

(given that our manuscript of the primary study findings was just archived recently in PubMed):

**Section 4.1: IMPACT ON THE DEVELOPMENT OF THE PRINCIPAL DISCIPLINE**

**Section 4.2: IMPACT ON OTHER DISCIPLINES**

**Section 4.3: IMPACT ON TECHNOLOGY TRANSFER**

**Section 4.4: IMPACT ON SOCIETY BEYOND SCIENCE AND TECHNOLOGY**

## **5. Changes / Problems**

**Section 5.1: CHANGES IN APPROACH AND REASONS FOR CHANGE**

and

**Section 5.2: ACTUAL OR ANTICIPATED PROBLEMS OR DELAYS  
AND ACTIONS OR PLANS TO RESOLVE THEM**

No changes to report for this final report.

**Section 5.3: CHANGES THAT HAD A SIGNIFICANT IMPACT ON EXPENDITURES**

No changes to report for this final report.

**Section 5.4: SIGNIFICANT CHANGES IN USE OR CARE OF HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS**

Animals, biohazards, and/or select agents are not applicable.

There were no significant changes in the care of human subjects in our studies.

## 6. Products

### Section 6.1: Publications, conference papers, and presentations

- Williams BA, Ibinson JW, Gould AJ, Mangione MP. The incidence of peripheral nerve injury after multimodal perineural anesthesia/analgesia does not appear to differ from that following single-drug nerve blocks (2011-2014). *Pain Medicine* 2017; 18: 628–636. PMID# 26896319
- Williams BA, Podnar SM, Bonant SA, Schanck AM. TECHNICAL COMMUNICATION: Admixture of bupivacaine-clonidine-buprenorphine-dexamethasone at the bedside in a tertiary care hospital block room is not associated with any apparent burdens of endotoxin or microbial growth. *Pain Medicine* 2017; 18: 781–785. PMID# 28586444
- Williams BA, Ibinson JW, Ritter ME, Ezaru CS, Rakesh HR, Paiste HJ, Gilbert KL, Mikolic JM, Muluk VS, Piva SR. Extended Perineural Analgesia After Hip and Knee Replacement When Buprenorphine-Clonidine-Dexamethasone Is Added to Bupivacaine: Preliminary Report from a Randomized Clinical Trial. *Pain Medicine* 2020; 2893-2902.
- Williams BA, Ibinson JW, Mikolic JM, Boudreaux-Kelly MY, Paiste HJ, Gilbert KL, Bonant SA, Ritter ME, Ezaru CS, Muluk VS, Piva SR. Day-one pain reductions after hip and knee replacement when buprenorphine-clonidine-dexamethasone is added to bupivacaine nerve/plexus blocks: A randomized clinical trial. *Pain Medicine* 2021, PubMed PMID: 34730810
- Williams BA, Ibinson JW, Bonant SA, Gilbert KL, Piva SR. Invited Editorial – A Tale of Two Cohorts: Trials and tribulations of ever-changing orthopedic/acute pain medicine hospital practices while executing military-funded clinical-translational research (2013-2021). *Pain Medicine* 2021, Accepted for publication, pnab267, associated with PMID 34730810 above. Doi/PMID pending.

### Presentations

18 September 2017, two invited lectures by the Food and Drug Administration  
<https://www.fda.gov/Drugs/NewsEvents/ucm571360.htm>

- Multimodal Perineural Analgesia: Bupivacaine-CLON-BPRE-DXMS, Ropivacaine-CLON-BPRE-DXMS, and Midazolam-CLON-BPRE-DXMS - An Overview of One Center's Work
- Regional vs. General Anesthesia for Common Orthopedic Surgeries:  
 An Overview of One Career Perspective

Books / other: Nothing to report

**“Nothing to Report”** applies to the following sections:

**Section 6.2: WEBSITES**

**Section 6.3: TECHNOLOGIES / TECHNIQUES**

**Section 6.4: INVENTIONS / PATENTS / LICENSES**

**Section 6.5: OTHER**

## 7. Participants & Other Collaborating Organizations

### Section 7.1: INDIVIDUALS THAT WORKED ON THE PROJECT

*Name:* Brian A. Williams, MD, MBA  
*Project Role:* PI / PD  
*Researcher Identifier (e.g. ORCID ID):* 0000-0002-5290-121X  
*Nearest person month worked:* 5  
*Contribution to Project:* Dr. Williams managed the activities as described above.

*Name:* Sara R. Piva, PT, PhD  
*Project Role:* Lead co-investigator for physical therapy / rehabilitation  
*Researcher Identifier (e.g. ORCID ID):* TBD  
*Nearest person month worked:* 3  
*Contribution to Project:* Dr. Piva coordinated all activities related to physical therapy care and assessment, including hiring and training of physical therapists, developing documents for data collection, manual of operations, and overseeing regulatory paperwork related to physical therapy care and assessment.

*Name:* Samantha Bonant, MS, CCRP  
*Project Role:* Regulatory Specialist Coordinator  
*Researcher Identifier (e.g. ORCID ID):* TBD  
*Nearest person month worked:* 6 (originally forecasted as 0.9)  
*Contribution to Project:* Ms. Bonant handled all regulatory submissions, including IRB, FDA, IDSMB and DoD submissions.  
*Funding Support:* Veterans Health Foundation, plus DOD sponsorship.

*Name:* Karen Gilbert  
*Project Role:* Study Coordinator  
*Researcher Identifier (e.g. ORCID ID):* TBD  
*Nearest person month worked:* 12  
*Contribution to Project:* Ms. Gilbert is the lead coordinator, and was responsible for constructing the Manual of Operating Procedures, among many other coordination and educational activities  
*Funding Support:* Veterans Health Foundation, plus DOD sponsorship

### Section 7.2: CHANGES IN THE ACTIVE OTHER SUPPORT OF THE PD/PI(S) OR SENIOR/KEYPERSONNEL

Nothing to report

### SECTION 7.3: OTHER ORGANIZATIONS INVOLVED AS PARTNERS

Nothing to report

## 8. Special Reporting Requirements

See attached final Quad Chart.

## 9. Appendices

- Quad Chart
- Manuscripts:
  - Williams BA, Ibinson JW, Gould AJ, Mangione MP. The incidence of peripheral nerve injury after multimodal perineural anesthesia/analgesia does not appear to differ from that following single-drug nerve blocks (2011-2014). *Pain Medicine* 2017; 18: 628–636. PMID# 26896319
  - Williams BA, Podnar SM, Bonant SA, Schanck AM. TECHNICAL COMMUNICATION: Admixture of bupivacaine-clonidine-buprenorphine-dexamethasone at the bedside in a tertiary care hospital block room is not associated with any apparent burdens of endotoxin or microbial growth. *Pain Medicine* 2017; 18: 781–785. PMID# 28586444
  - Williams BA, Ibinson JW, Ritter ME, Ezaru CS, Rakesh HR, Paiste HJ, Gilbert KL, Mikolic JM, Muluk VS, Piva SR. 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 Nov; 21(11):2893-2902. PubMed PMID 33027531.
  - Williams BA, Ibinson JW, Bonant SA, Gilbert KL, Piva SR. Invited Editorial – A Tale of Two Cohorts: Trials and tribulations of ever-changing orthopedic/acute pain medicine hospital practices while executing military-funded clinical-translational research (2013-2021). *Pain Med* 2021, Accepted for publication, pnab267, associated with pnab325 above. Doi/PMID pending.
  - Williams BA, Ibinson JW, Mikolic JM, Boudreaux-Kelly MY, Paiste HJ, Gilbert KL, Bonant SA, Ritter ME, Ezaru CS, Muluk VS, Piva SR. Day-one pain reductions after hip and knee replacement when buprenorphine-clonidine-dexamethasone is added to bupivacaine nerve/plexus blocks: A randomized clinical trial. *Pain Med* 2021, PubMed PMID: 34730810

# 4-Drug Nerve Block vs Plain Local Anesthetic for Knee & Hip

Log Number: 13232002 – Prospective Randomized Clinical Trial at the VA Pittsburgh

Award Number: W81XWH-15-1-0294



PI: Brian A. Williams, MD, MBA

Org: The University of Pittsburgh

Award Amount: \$1,950,591

## Study/Product Aim(s)

- Demonstrate analgesic superiority of 4-drug nerve block after elective joint arthroplasty when compared against single-injection nerve blocks with plain bupivacaine (BPV)
- Determine whether this analgesic superiority postoperatively translates to equal or superior physical therapy outcomes
- Also track all study participants with validated outcome surveys, to quantify veteran-centered clinical outcome measures
- Military relevance: Is the described 4-drug single-injection (BPV-BCD) nerve block sufficiently robust to reconsider current nerve block continuous infusions that are complex to insert and maintain in the battlefield theater (Level 3, possibly earlier)?

## Approach

Prospective randomized triple-blinded clinical trial of n=200 veterans undergoing knee (n=100) or hip (n=100) replacement.

BCD: buprenorphine-clonidine-dexamethasone

| Significant Outcome Differences on DVPRS Scores based on 4-Drug Block | Main Cohort* |               |              |                                             |
|-----------------------------------------------------------------------|--------------|---------------|--------------|---------------------------------------------|
|                                                                       | Baseline     | Post-op Day 1 | Change Score | Study Drug Mean Difference (95% CI) P-value |
|                                                                       | Mean (SD)    | Mean (SD)     | Mean (SD)    |                                             |
| <b>Secondary</b>                                                      |              |               |              |                                             |
| mDVPRS ‡ - Pain at rest                                               | -            | -             | -            | 3.8 (2.3, 5.3) P<0.001                      |
| BPV-BCD                                                               | 5.1 (2.0)    | 3.1 (2.9)     | 1.9 (2.6)    | -                                           |
| Plain BPV                                                             | 4.6 (2.6)    | 6.5 (2.6)     | -1.9 (2.8)   | -                                           |
| mDVPRS - Pain with movement                                           | -            | -             | -            | 3.4 (1.7, 5.1) P<0.001                      |
| BPV-BCD                                                               | 6.6 (1.8)    | 4.1 (3.2)     | 2.5 (3.0)    | -                                           |
| Plain BPV                                                             | 7.0 (1.7)    | 7.9 (2.1)     | -0.9 (3.3)   | -                                           |
| mDVPRS – Pain activity interference                                   | -            | -             | -            | 3.1 (0.7, 5.4) P=0.012                      |
| BPV-BCD                                                               | 6.0 (2.2)    | 4.8 (4.0)     | 1.2 (4.4)    | -                                           |
| Plain BPV                                                             | 6.5 (2.4)    | 8.3 (2.4)     | -1.8 (3.5)   | -                                           |
| mDVPRS – Pain sleep interference                                      | -            | -             | -            | 2.5 (0.3, 4.8) P=0.026                      |
| BPV-BCD                                                               | 4.3 (2.8)    | 3.7 (3.4)     | 0.6 (4.0)    | -                                           |
| Plain BPV                                                             | 5.1 (3.1)    | 7.0 (2.4)     | -1.9 (3.9)   | -                                           |

## Timeline and Cost

| Activities                                            | CY | 16           | 17           | 18           | 19           |
|-------------------------------------------------------|----|--------------|--------------|--------------|--------------|
| Regulatory (FDA / IRB) / infrastructure               |    |              |              |              |              |
| Screening, enrollment, study-specific hospitalization |    |              |              |              |              |
| One-month study participant follow-up                 |    |              |              |              |              |
| Ongoing regulatory issues, and scholarly output       |    |              |              |              |              |
| <b>Estimated Budget (\$K)</b>                         |    | <b>\$587</b> | <b>\$545</b> | <b>\$550</b> | <b>\$269</b> |

## Goals/Milestones

**CY16-18 Goals** – In QuadChart Archive

**CY19-21 Goals** ☒ Submit manuscripts for peer-reviewed publication

- 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 Nov; 21(11):2893-2902. PMID 33027531.
- Day-one pain reductions after hip and knee replacement when buprenorphine-clonidine-dexamethasone is added to bupivacaine nerve / plexus blocks: A randomized clinical trial. (See DVPRS outcomes above in QuadChart). *Pain Med* 2021, PMID 34730810 (ePub ahead of issue).
- Invited Editorial – A Tale of Two Cohorts: Trials and tribulations of ever-changing orthopedic/acute pain medicine hospital practices while executing military-funded clinical-translational research (2013-2021). *Pain Med* 2021, Accepted for publication, pnab267, associated with PMID 34730810 above.

**Budget Expenditure to Date** (as of 08 November 2021)

Budget: \$1,950,591.00

Actual Expenditure:\$1,940,062.99

Updated: Pittsburgh, PA; 10 November 2021

## PERSPECTIVE & COMMENTARY

### Commentary

# The Incidence of Peripheral Nerve Injury After Multimodal Perineural Anesthesia/Analgesia Does Not Appear to Differ from That Following Single-Drug Nerve Blocks (2011–2014)

### Introduction

Recently, we reported on the *in vitro* [1] and *in vivo* [2] animal safety (rat) of four-drug nerve block (multimodal perineural anesthesia–analgesia, or MMPNA) combinations involving bupivacaine (BPV [2]), ropivacaine (RPV [1]), or midazolam (MDZ [1,2]) with the following three preservative-free injectable drugs: clonidine, buprenorphine, and dexamethasone [1,2] (hereafter abbreviated as CBD). In addition, we provided clinical benchmark data for patients having received nerve blocks with combined BPV-CBD [3] and MDZ-CBD [4]. The chronological time frame for these previous clinical benchmark reports [3,4] was July 2011 through March 2014. The current report covers intermediate and long-term peripheral nerve injury (PNI) outcomes for  $n = 1830$  patient-block encounters dating from July 2011 through December 2014.

We define a “patient-block encounter” as a uniquely identified patient encounter receiving one or more nerve blocks on a specific day for pre- and intra-operative anesthesia/analgesia, immediate postoperative analgesia, or rescue postoperative analgesia on a day after surgery, typically during the same hospital stay. The blocks used for these 1830 patient-block encounters were composed primarily of BPV-CBD ( $n = 1726$ ; 94.3%), or MDZ-CBD ( $n = 104$ ; 5.7%). Patients who were having surgery related to a current or previous surgical site infection typically did not have blocks that included perineural dexamethasone ( $n = 109/1830$ , or 6%).

The objective of this report is to present complication-related quality improvement (QI) data from our institution in the epidemiologic context of such data published elsewhere regarding the risk of PNI complications related to surgery itself (without specific nerve block considerations) or specifically related to nerve blocks typically using local anesthetics only (in the absence of multiple or any perineural adjuvants).

In our institution (Veterans Affairs Pittsburgh Healthcare System, VAPHS), the lead author was charged with

creating a regional anesthesia (RA) and analgesia program for patients eligible for peripheral nerve blocks. The VAPHS Medical Executive Board approved the lead author’s recommendation to routinely use the described four-drug nerve blocks off-label. These single-injection nerve blocks are typically placed before surgery to provide postoperative analgesia and intraoperative anesthesia when feasible. Pursuant from institutional approval was the need to collect QI data prospectively (within 2 weeks after the block encounter) to evaluate dose-specific comparative effectiveness (block duration and rebound pain, which we previously reported [5,6]). Additional QI data were later collected retrospectively to determine perineural complications and to establish MMPNA safety. In accordance with Veterans Health Administration Handbook 1058.05, this manuscript was processed for authentication of nonresearch status of the described activities prior to submission to this journal. The VAPHS institutional review board declared these clinical operations “not research” at the time of program initiation (mid-2011) and annually since then during required reviews.

### Methods

**Definition of perineural complication.** This medical record review identified patients who had EMG examinations after the date of the described patient-block encounter. Included was a review of the EMG consultation order, and the specific progress notes time-associated with the EMG order. The review also entailed the screening of postoperative notes by the surgical team following up on the patient for any notes indicating potential PNI symptoms that were traceable to the site of the needle injection for the performed blocks, but for which EMG was not ordered. This medical record review did not track complications (e.g., intraoperative hypotension, postoperative nausea/vomiting) other than neurologic symptoms in the distribution of the surgery and/or nerve block(s).

**Patient selection for data analysis of QI-reportable occurrences, and data collation.** From July 1, 2011 through December

31, 2014, there were  $n = 1830$  patient-block encounters involving MMPNA in an all-inclusive QI database. For QI purposes, electronic medical records with patient identifiers for cases 1 through 800 were screened by author AJG, including postoperative notes by the surgical team and/or any other relevant progress notes (e.g., neurology, physical medicine and rehabilitation) that may have indicated possible PNI outcomes. In addition, all electronic medical records were screened for any EMG testing procedures that were done before or after the index MMPNA patient-block procedure-encounters. After screening, author AJG provided a summary list to the lead author (BAW) for a detailed QI review of these cases to determine the relationship of the EMG reports to the needle location of the block performed and the symptoms for which the postoperative EMG was ordered to specifically evaluate. The presence of preoperative or postoperative spine problems was evaluated by the lead author to determine the relationship of spine pathology level to previous or future QI issues (e.g., cervical spine abnormality that was diagnosed before versus brachial plexus-based patient complaint after having undergone a brachial plexus block). For patients in whom EMG was not ordered, the lead author reviewed the electronic medical record details involving preoperative symptoms, timing of onset of postoperative symptoms, operative notes, coinciding spine pathology, and timing of symptom resolution, if applicable. For cases 801 through 1830, the lead author was responsible for both screening and conducting a detailed review of all records. In other words, all 1830 patient-block encounter medical records were reviewed not only for the presence of any EMG testing, but also for the presence of potential PNI symptoms without evidence of EMG testing.

The following block types were recorded during QI data-sheet collation: (i) brachial plexus below the clavicle (typically axillary), (ii) brachial plexus above the clavicle (typically interscalene or supraclavicular), (iii) L2–L4 only (i.e., psoas compartment, femoral, or saphenous), (iv) L2–L4 and L4–S3 in which the L2–L4 block was specifically at the level of the psoas compartment, (v) L2–L4 and L4–S3 in which the L2–L4 was specifically of the femoral nerve in the groin, and (vi) popliteal sciatic with or without a separate saphenous nerve block (i.e., specifically for foot-ankle surgery). The timing of EMG testing was recorded as follows: (i) no pre- or postoperative EMG testing of the relevant nerve distribution, (ii) only preoperative EMG testing without postoperative EMG testing, (iii) postoperative EMG testing without any preoperative EMG testing, and (iv) both preoperative and postoperative EMG testing. For any postoperative EMG testing, we specified in our collated dataset if the electronic medical record indicated that the ordering provider (e.g., surgical team) mentioned in the medical record a specific concern about the nerve block as the reason for the EMG referral (i.e., no-yes dichotomous variable). Dichotomous variables were assigned accordingly if an identified EMG lesion correlated with the needle location for the block used. Patients were not

contacted as part of this QI review. However, if the surgical team deemed it appropriate, they notified the anesthesia service on a discretionary basis of any possible complications of which they felt the anesthesia service needed to be aware, and such notification may have involved the anesthesia care team member contacting the patient as part of the care process and follow-up.

*Coinciding 30-day mortality data from the Veterans Affairs Surgical Quality Improvement Project (VASQIP[7]), 2006–2014.* The VA National Surgery Office (NSO) publishes a quarterly report to provide the Veterans Integrated Service Network (VISN) Surgical Work Group and Facility Surgical Work Groups, as defined in Veterans Health Administration (VHA) Handbook 1102.01, with a standardized set of surgically relevant information upon which to evaluate local and VISN surgical delivery systems, best practices, and the overall quality of surgery services. The NSO Quarterly Report is designed to facilitate a community of surgical practice and the delivery of high-quality and timely surgical services to our nation's veterans. For this manuscript, we will present only 30-day VASQIP morbidity and mortality data originating from the Orthopedics category at VAPHS. Of note, for VASQIP NSO quarterly reports, orthopedic mortality may have included orthopedic spine or other cases for which regional anesthesia was not an available care option. In addition, VASQIP NSO quarterly reports involve the comparison of a single VA hospital (e.g., VAPHS, and an “observed 30-day mortality”) against aggregate VA nationwide data (“expected 30-day mortality”) in creating “observed-to-expected” 30-day morbidity and mortality ratios. One limitation of VASQIP mortality data is that all 30-day mortalities are captured in the numerator, but not all survivals are captured in the denominator (as VASQIP represents a minimum sampling per institution that is to include all morbidities/mortalities in the numerator). Therefore, we will present quarterly trend data for VAPHS orthopedics before and after the start of our MMPNA nerve-block service. We will perform associated (i.e., association, not causation) statistical analyses of before and after aggregate data (30-day O-E mortality ratios) with the understanding that the mortality ratios for both “observed” and “expected” do not include the full denominator of surgical survivors.

We also tracked elective joint replacement mortalities throughout the 2006–2014 period (with complete denominators), and compared before and after the Acute Pain Medicine/Regional Anesthesia specialty service was inaugurated in July 2011.

## Statistical Analyses

As a retrospective review of a QI database not originally intended for scientific/extramural reporting, there were no detailed analysis plans *a priori*. Descriptive statistics (proportions, 95% confidence intervals) are provided, and associated conclusions are presented as simply a comparison of our 95% confidence intervals against complication rates reported in the literature.

For the O-E 30-day morbidity/mortality ratios, raw ratios between zero and one were translated as “lower than national VA trend,” while raw ratios greater than one were translated as “higher than national VA trend.” However, as these raw ratios varied from greater than one to less than one, we were required to transform the raw ratio data to establish a “true zero.” To do so, each raw ratio data point was squared (i.e., raised to the second power) for proportional comparisons of the O-E ratio.<sup>1</sup> Mortality data were then compared before versus after the Acute Pain Medicine/Regional Anesthesia Service was established (2006 through June 2011, then July 2011 through December 2014) using the student’s t-test.

For the “before–after” absolute mortality calculations after elective joint replacement surgery (knee and hip, with known case denominators), associated differences in this outcome were evaluated using the Fisher’s Exact Test. These O-E data and before–after joint replacement mortality data were analyzed with IBM SPSS v21 statistical software (IBM SPSS®, Chicago, IL).

## Results

*Total encounters, and categorizing blocks for surgery versus blocks for analgesia.* From July 1, 2011 until December 31, 2014, there were a total of 1830 patient-block encounters involving the Acute Pain Medicine/Regional Anesthesia Service utilizing MMPNA. Of note, 51% (n=937) of these blocks were used for “surgical anesthesia” (involving a higher concentration of local anesthetic to provide operating conditions not requiring other general or regional anesthesia). The remainder were typically designed for “postoperative analgesia,” meaning that the block was also combined with a spinal anesthetic (n=685; 77%) or a general anesthetic (i.e., with a secured airway, n=210; 23%) to achieve necessary surgical conditions. Most (n=1748; 96%) blocks were placed before surgery, and most patients (n=1339; 73%) were nondiabetic at the time of the block.

*Types and timing of blocks performed, and postoperative frequency of EMG testing.* The types of blocks performed are categorized in Table 1.

Of the EMG reports available on the computerized medical records for the patients associated with these n=1830 patient-block encounters, (i) n=242 EMGs were performed only before the surgery/block, (ii) n=58 EMGs (n=34 lower extremity and n=24 upper extremity) were performed only after the day-of-surgery/block, and (iii) n=15 had EMGs both before and after the surgery/block (n=14 of these were upper extremity surgery-blocks, and one was foot-ankle). The EMG studies performed only before the surgery/block (n=242) were excluded from subsequent analysis, and n=73 EMGs were included for analysis. Four of these 73 EMGs were repeat postoperative EMGs, so there were 69 total patients with any postoperative EMG.

There were n=38 upper extremity patient EMGs, and n=35 lower extremity patient EMGs (73 EMGs total across 1830 patient-block encounters, or 4%). Of the 73 total patient-block encounter EMGs, n=54 were nondiabetic and n=19 were diabetic.

Electronic medical records were reviewed for the 69 patients who underwent the total of 73 postoperative EMG evaluations. Before the EMGs were performed, 13 of the patient-specific EMG order/consultations indicated concerns specifically relevant to the nerve block performed. The other 56 patients’ EMGs were ordered for reasons in which no concern regarding the nerve block was specified; 55 of these 56 patients’ EMG reports did not indicate any findings suggestive of a lesion traceable to the nerve block injection, but one of these reports was unable to rule out a possible specific PNI case (not necessarily traceable to the block site) distinguished from long-standing preoperative pathology attributable to the lumbar spine (and previous spine surgery). Therefore, of 13 EMGs specifically ordered to address nerve block concerns, 2 were “definite” PNI cases (2/1830, or 0.11%), and 4 were “possible” PNI cases. Adding the 1 “possible” PNI case from the 56 EMGs ordered (unrelated to block concerns) leads to 2 “definite” and 5 “possible” (from the 13 EMGs concerned with the nerve block) and yields an incidence of 7/1830 (0.38%) “definite or possible” PNI.

## EMG Case Details

*Popliteal (with or without saphenous, n=328).* Of the seven numerator patients with definite or possible lesions on EMG, one had a popliteal-saphenous block for surgical anesthesia and a definite PNI lesion (“definite POP,” 1/328, 0.3%, 95% CI: 0.05%, 1.7%) and one had a possible PNI popliteal-saphenous analgesic block combined with a spinal (“possible POP-SPI” case, with cumulative popliteal risk being 2/328, 0.6%, 95% CI: 0.17%, 2.20%). The definite POP case (who was not diabetic and had no previous symptomatic complaints) on the postoperative EMG was found to have profound bilateral peripheral lower extremity neuropathy, and a presumably new lesion traceable to the block needle in the popliteal fossa. It is conceivable that this case may have instead involved postoperative bilateral inflammatory neuropathy after one-sided surgery with regional anesthesia, as has been reported recently [8]. Meanwhile, the possible POP-SPI case had diffuse bilateral EMG findings, and a common peroneal EMG focus “of questionable significance.” The lumbar spine MRI of the possible POP-SPI case also showed some anatomic lesions unrelated to the block. The consulting neurologist ultimately ascribed a diagnosis of “intermittent sciatica” for the possible POP-SPI case.

*Interscalene (n=278).* One of the seven “definite or possible” patients had an interscalene block for surgical anesthesia (“possible ISB case,” 1/278, 0.4%, 95% CI: 0.06%, 2%). The ISB case manifested as a winged scapula postoperatively that was undocumented

**Table 1** Totals per block procedure type (n = 1830 patient-block encounters overall), and definite/possible PNI cases based on EMG testing

| Category                                                            | N                            |
|---------------------------------------------------------------------|------------------------------|
| <b>Axillary</b>                                                     | 315                          |
| • No definite or possible EMG cases                                 |                              |
| <b>Interscalene/supraclavicular</b>                                 | 278                          |
| • One possible PNI case (see ISB)                                   |                              |
| <b>Femoral or psoas compartment</b>                                 | 113                          |
| without L4–S3 block                                                 |                              |
| • No definite or possible PNI cases                                 |                              |
| <b>Psoas compartment lumbar plexus</b>                              | 494                          |
| <b>plus L4–S3 block</b> (i.e., 988 total blocks)                    |                              |
| For hip                                                             | 300 (i.e., 600 total blocks) |
| • One definite L2–L4 PNI case (see HIP-LUM)                         |                              |
| • One possible L4–S3 PNI case (see HIP-PS)                          |                              |
| Caudal to hip                                                       | 194 (i.e., 388 total blocks) |
| • Two possible L4–S3 PNI cases (see LUM-SCI knee and LUM-SCI ankle) |                              |
| <b>Femoral and sciatic</b>                                          | 298 (i.e., 596 total blocks) |
| • No definite or possible PNI cases                                 |                              |
| <b>Popliteal</b>                                                    | 328                          |
| with or without saphenous/femoral                                   |                              |
| • One definite PNI case (see POP)                                   |                              |
| • One possible PNI case (see POP-SPI)                               |                              |
| <b>Other</b>                                                        | 4                            |
| • No definite or possible PNI cases                                 |                              |

PNI: peripheral nerve injury; EMG: electromyography.

See text for the individual case descriptions.

There were two definite cases of PNI (2/1830, 0.11%) and five possible cases of PNI (5/1830, 0.27%).

preoperatively. The occupational mechanism of injury leading to the need for the surgical procedure was an abrupt “heavy tugging” of a free-falling 300-lb (136-kg) weight on a pulley, resulting in a distal biceps rupture and a possibly undetected simultaneous isolated long thoracic nerve injury. We attribute the EMG finding to the mechanism of injury and not to the block, but still conservatively categorize the case as “possible.”

*Lumbar plexus psoas compartment block with either parasacral or gluteal sciatic block (n = 494).* Four of the remaining seven “definite or possible” patients had lumbar plexus blocks with either parasacral or gluteal sciatic L4–S3 blocks. Two of these four patients had spinal anesthesia with preoperative psoas compartment and parasacral blocks for hip surgery. One lesion was traceable to the lumbar plexus (“definite HIP-LUM”). The other lesion was traceable to the proximal sciatic nerve at the level of the long head of the biceps (“possible HIP-PS,” of questionable proximity of the parasacral injection site; the primary causative factor was indeterminate, but favoring surgical stretch over the injection site, perhaps in a “double crush” phenomenon). The third of four patients (“possible LUM-SCI knee”) had surgical lumbar plexus and gluteal sciatic anesthetic blocks for knee

replacement. The fourth of four patients (“possible LUM-SCI ankle”) had lumbar plexus and sciatic blocks for many ankle procedures. Therefore, the risk proportion calculation, given that this category includes two anatomically separate blocks, is: one “definite” case/494 patients, 0.2%, 95% CI: 0.07%, 0.6%; versus four “definite or possible”/494 patients, 0.8%, 95% CI: 0.28%, 2.4%). So in these 494 patients, 988 total blocks (excluding spinals) were performed; our 95% confidence intervals conservatively reflect “patients” (n = 494), not “blocks” (n = 988).

The definite HIP-LUM case had two normal EMGs at our hospital facility, reflecting a normal L2–L4 peripheral sensory exam, but two “second opinion” EMGs at outside hospitals performed paraspinous EMG/myography showing a profound lesion within the lumbar plexus itself that our hospital’s EMGs did not specifically test for.

The possible HIP-PS case first manifested symptoms 2 weeks postoperatively. The lesion was localized in the proximal sciatic nerve distribution, in that the long head of the biceps was affected during myography (failing to rule out surgical stretch), but the gluteal musculature was unaffected (less favoring a parasacral plexus needle

lesion). Therefore, the EMG was partially able to favor surgical stretch and partially rule out the focal needle injection site. This possible HIP-PS patient was reported to be a noncompliant diabetic, which may have complicated matters postoperatively (including the absence of symptoms until 2 weeks postoperatively), all of which factor against the PNI focus being the parasacral block injection site. The possible LUM-SCI knee PNI case (total knee replacement) had a known problematic lumbar spine, diabetes with peripheral polyneuropathy, and had recorded in the medical records a statement that he also encountered many of his postoperative symptoms preoperatively. There was no EMG myography testing for gluteal/hamstring evaluation for a complete evaluation of the sciatic nerve on the possible LUM-SCI knee patient, because this patient underwent EMG testing while therapeutically anticoagulated with warfarin.

The possible LUM-SCI ankle case was a diabetic who had previously undergone three major lumbar spine surgeries in our institution and seven foot/ankle procedures. In two separate postoperative EMG reports (in 2013 and 2014), the interpretation was unable to exclude a superimposed ipsilateral L5–S1 focal versus neuraxial radiculopathy, given a longstanding sensory-motor peripheral polyneuropathy with chronic axonal loss.

*Conservative approach to expand the risk probability and its 95% confidence interval.* In a separate chart review of patients not referred for EMG, there were seven cases of abnormal postoperative physical exam findings that were judged (by authors BAW and JW) to be possibly block related, for which there was no EMG ordered to appropriately evaluate. Based on the proportions described above, we will assume that if these seven had had EMGs ordered, three may have proven to be positive. Therefore, in our conservative estimation, the risk of PNI from MMPNA injections that has been (or may be) traceable to the site of nerve block injection is 10/1830, or 0.55%. The 95% confidence interval of this incidence is 0.27% to 1.08%.

*Coinciding 30-day orthopedic morbidity/mortality data from the Veterans Affairs Surgical Quality Improvement Project (VASQIP[7]), 2006–2014 (Figure 1).* In January 2011, our institution implemented a new “preoperative optimization” program (“Interdisciplinary Medical Perioperative Assessment Consultation Treatment,” abbreviated as IMPACT) that can be summarized as reasonably equivalent to the advances described in the literature addressing perioperative surgical homes [9]. In July 2011, the regional anesthesia team was created, but was not fully operational on a daily basis until February 2012. Before the creation of the IMPACT program and regional anesthesia team, the overall O-E ratios for morbidity and mortality were 1.18 (1.04, 1.33) and 1.24 (0.93–1.59), respectively. After the regional anesthesia team was created and through December 2014, the O-E ratios were 0.72 (0.50, 0.97) and 0.22 (0.00, 0.74;  $P = 0.001$  for

both morbidity and mortality, respectively, based on the t-test). These values represent (based on transformed ratio statistics to a common zero) reductions in observed-to-expected morbidity and mortality ratios of 22% and 58%, respectively. We were statistically unable to delineate morbidity/mortality reductions traceable specifically to the perioperative surgical home equivalent versus the effect of near-ubiquitous regional anesthesia and reduction in GETA use. Unfortunately, we were also unable to track proportions of complicated patients that were elective orthopedic procedures (e.g., TKA, THA, with full surgical-home equivalent workup 2011–2014) versus emergency procedures (e.g., hip/femur fracture repair with no elective workup and health status optimization). Therefore, we are unable to speculate about the trade-off of PNI complications with the advent of the new block team (we do not have PNI data from 2006–2012 during the GETA-only era) in exchange for reduced 30-day mortality (as we are unable to delineate reduced mortality as being from GETA avoidance versus better preoperative selection and optimization), but we include our “before-after” mortality data in an effort to allow other research teams to generate hypotheses and calculate sample sizes.

*Coinciding 30-day orthopedic mortality data after THA and TKA from institutional data, 2006–2014 (Table 2).* From 2006–2010, there were three TKA 30-day mortalities (2006, 2009, 2010) and three (two in 2008 and one in 2010) THA 30-day mortalities. There were no THA/TKA 30-day mortalities from 2011 through 2014 ( $P = 0.014$ , by Fisher’s Exact Test).

## Discussion

The complexities of forecasting the risk of PNI, irrespective of neurolocation technique, have recently been published (2015) in the Second Practice Advisory of the American Society of Regional Anesthesia and Pain Medicine [10]. For common PNB techniques entailing the use of plain local anesthetics, the rates of PNI after interscalene brachial plexus block, axillary brachial plexus block, and femoral nerve block have been reported as 2.84% (95% CI: 1.33–5.98%), 1.48% (95% CI: 0.52–4.11%), and 0.34% (95% CI: 0.04–2.81%), respectively, based on detailed review of prospective randomized studies to date as of 2007 reported by Brull et al. ( $n = 10,309$ ) [11]. In a single-institution study (Fredrickson and Kilfoyle [12]) of 1010 consecutive peripheral nerve blocks with plain local anesthetics, new, all-cause, neurological symptoms were present in 56/690 blocks (8.2%; 95% CI: 6.8–10.2%) at day 10, 37/1010 (3.7%; 95% CI: 2.7–5.0%) at 1 month, and 6/1010 (0.6%; 95% CI: 0.27–1.3%) at 6 months [12]. Most symptoms in this [12] study were due to causes unrelated to the block: 4 of 1010 were ultimately unrelated to the block, but for the other 2/1010 (0.2%), attribution to the block could not be ruled out. In another

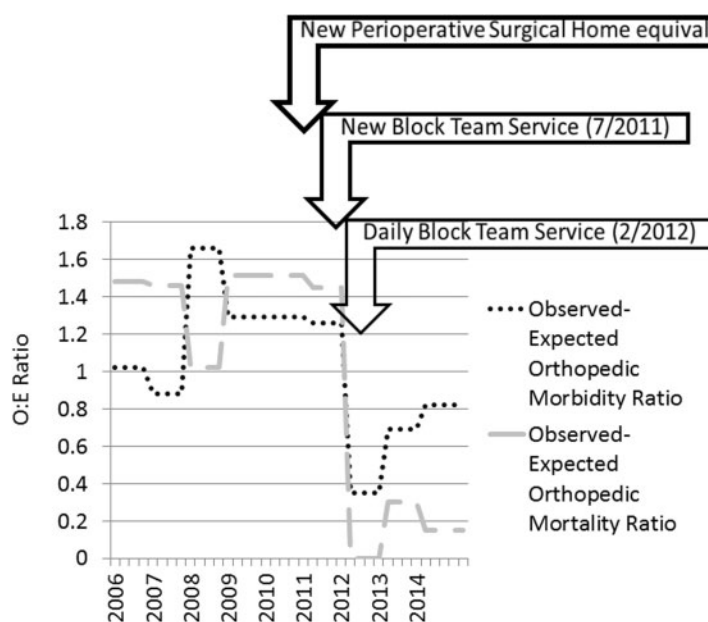


**Figure 1** Reductions in institutional orthopedics morbidity and mortality observed-to-expected ratios. The X-axis represents the timeline of 2006–2014 orthopedics cases performed at the VA Pittsburgh Health System. The Y-axis O:E ratio represents the observed-to-expected ratio of morbidity (dotted black line) and mortality (dashed gray line) for tracked cases in quarterly VASQIP reports from the VA Central National Surgery Office (see text for details). The “observed” value represents actual complications observed during a quarterly audit (at VA Pittsburgh), which is compared with “expected” complications based on the same summed quarterly audit of all VA hospitals nationwide. The ratio value of 1 indicates that the VA Pittsburgh morbidity/mortality rates match those of national trends for the same time period. Less than 1 indicates the VA Pittsburgh having better outcomes than those of national trends (a ratio of 0.5 indicates half the complication rate of national). Greater than 1 indicates the VA Pittsburgh having less satisfactory outcomes than those in national trends (a ratio of 2.0 indicates twice the complication rate of national). The timeline arrows at the top of the graph reflect the inauguration of the perioperative surgical home in January 2011, the start of the block team in July 2011, and the fully-staffed daily block team in February 2012. Note that all complications recorded are irrespective of hospital inpatient status (i.e., not routed through the perioperative surgical home equivalent, such as hip fracture patients) versus outpatient status (outpatients routed through the surgical home equivalent, such as for knee or hip replacement). Quarterly data are annualized for ease of interpretation. Based on the t-test, the before versus after *P* value of the O:E ratios were *P* = 0.001 for both morbidity and mortality (see text for details). No further statistical delineation of the effects of the surgical home versus block team was possible.

study, the Australasian Collaboration (Barrington et al. [13]) cites a PNI incidence of 0.04% and a 95% confidence interval of 0.08 to 1.1 per 1000 (0.008–0.11%); this study counted each block in the denominator (7156 blocks among 6069 patients). Watts and Sharma [14] reported a 0.22% PNI incidence (*n* = 1065 consecutive blocks over a 12-month period), while Laur et al. [15] reported a 0.32% short-term PNI incidence (*n* = 4363, 14 cases over a 15-month period).

We took a deliberate and conservative approach by (i) categorizing positive EMGs with questionable involvement of the needle location as potentially attributable to the block (in isolation or as part of a “double-crush” phenomenon) and (ii) adding three cases to the numerator (i.e., patients who did not have EMGs). These conservative tabulations led to our 0.55% risk estimate with

a 95% confidence interval of 0.27% to 1.08%. We are confident based on this detailed review of 1830 patient-block encounters that there were not any missed complications, with the exception of patient relocation or death (<1%). However, of the seven EMG-specific cases in the numerator, the following five cases are questionable at best for block-related PNI: POP-SPI, ISB, HIP-PS, LUM-SCI knee, and LUM-SCI ankle. Subtracting these five cases from the numerator, along with subtracting the theoretical three additional numerator cases that did not have EMG, yields a risk incidence of 2/1830 (0.11%), with a 95% CI of 0.03%–0.4%.

A frequent complex case under the auspices of our teaching institution’s Acute Pain Medicine/Regional Anesthesia service is elective total hip arthroplasty (THA, *n* = 237 in our data set). In literature review, the risk of

**Table 2** Institutional 30-day mortality after THA/TKA from 2006 through 2014

| Year                                                                                            | All THA | All TKA | Overall    | 30-day mortalities |
|-------------------------------------------------------------------------------------------------|---------|---------|------------|--------------------|
| 2006                                                                                            | 39      | 45      | 84         | 1 (TKA)            |
| 2007                                                                                            | 62      | 81      | 143        |                    |
| 2008                                                                                            | 57      | 89      | 146        | 2 (THA)            |
| 2009                                                                                            | 63      | 91      | 154        | 1 (TKA)            |
| 2010                                                                                            | 81      | 113     | 194        | 2 (THA and TKA)    |
| <b>Total: 0.8% 30-day mortality 2006–2010 (all GA)</b>                                          |         |         | <b>721</b> | <b>6</b>           |
| 2011                                                                                            | 63      | 84      | 147        |                    |
| 2012                                                                                            | 87      | 135     | 222        |                    |
| 2013                                                                                            | 90      | 110     | 200        |                    |
| 2014                                                                                            | 76      | 106     | 182        |                    |
| <b>Total: No 30-day mortalities in 751 cases, <math>P = 0.014</math> by Fisher's Exact Test</b> |         |         |            |                    |

PNI (from all causes, not just those related to nerve blocks) from hip replacement ranges from 0.2% to 8% [16]. We had one lumbar plexus PNI case traceable to the injection site (definite HIP-LUM patient above), and one L4–S3 PNI case that did not involve the gluteal musculature on EMG, but did involve the long head of the biceps (possible HIP-PS patient above with uncontrolled diabetes). There was one other patient with post-operative symptoms (but no EMG) that were deemed to be possibly block related. There were also 19 THA patients with negative EMGs ( $n=4$ ), and no EMGs but L2–S3 symptoms ( $n=15$ ) not traceable to the block (based on surgical notes and/or procedural descriptions). So the overall THA PNI risk in our teaching institution was 9% (22/237, approximating the 8% range reported by Zappe et al. [16]). We consider our findings to be in a generally accepted risk range for rare complications after THA with proximal peripheral nerve blocks ( $n=1-3$  out of 237, 0.4–1.3%, for dual blocks of the lumbar and parasacral plexi).

Lumbar plexus blocks (in combination with parasacral blocks for hip surgery or in combination with gluteal sciatic blocks for lower extremity surgery distal to the hip) have the least available data regarding risk epidemiology. To our knowledge, the largest series reported to date entails 394 blocks performed in France during a voluntary hotline data collection report in a 10-month period from 1998–1999 ( $n=158,000$  blocks; lumbar plexus block-related major complication rate of 0.8% [17]). Our series of lumbar plexus blocks for surgical anesthesia and/or postoperative analgesia to date has since well surpassed  $n=500$  (July 2011–December 2014,  $n=494$ ). In our case series of  $n=494$  patients (through December 2014) having undergone lumbar plexus block, we reiterate from above that 13 patients had EMGs ordered that were specifically addressing postoperative concerns of the perioperative nerve block. Of these 13 patients, 7 had lumbar plexus blocks, with 4 being for hip replacement and 3 for knee replacement. In total, only one of the seven EMGs had plexus injury traced to the lumbar plexus needle injection site.

This was for hip surgery using an analgesic block with BPV-CBD.

During the July 2011–December 2014 time period, in addition to the 13 EMGs above that were ordered citing concerns with the perioperative nerve blocks, there were 56 other patients with EMGs ordered without specific mention of nerve block concerns. Of these 56, 5 patients had lumbar plexus blocks and none of these EMGs showed evidence of damage in proximity to the lumbar plexus site of injection (with one of these cases, LUM-SCI ankle, having a possible “unable to rule out” status). Therefore, 1/494 (0.2%; 95% CI: 0.04%–1.14%) of our patients having lumbar plexus blocks had definite PNI evidence per EMG at the site of injection.

Our overall objective of presenting these benchmark QI outcome data is to narrow down the scope of future research hypotheses involving MMPNA. Based on our institution's limited sample size in the context of the world's literature, we do not detect trends of PNI specifically traceable to the use of MMPNA in our institution when compared with all blocks performed worldwide using plain local anesthetics. As a QI-driven clinical activity, there are restrictions in data gathering and synthesis that forbid identifying preoperative/postoperative opioid requirements (e.g., related to possible PNI symptom management) and other factors related to general health status (i.e., “trade-off” of one set of possible complications [from peripheral nerve block]) for another [from GETA]). None of our observations should be interpreted as suggestive for future (and acknowledged off-label) clinical practice. Due diligence in preclinical research has been done with respect to known neuronal safety (*in vitro* [1], CBD adjuvants) and more recently with respect to drug compatibility and *in vivo* safety in laboratory animals [2]. Previously published [3,4] in this journal is our report of associated block durations and rebound pain scores observed after these MMPNA blocks, but (as a clinical pathway) these outcomes were not compared with a plain local anesthetic control group. We reiterate that in the absence of an industry

sponsor, such research (or hypothesis generation for such research) would either occur slowly or not at all. Perhaps future research across several coordinated centers may help better delineate risk incidence (while narrowing the 95% confidence interval by increasing the sample size), although funding for such research (i.e., involving drugs that are no longer patent-protected, and not involving delineation of perineural mechanism of action) may not necessarily come from conventional sources beyond interinstitutional cooperation.

## Conclusions

In this single-institution QI data review involving 1830 patient-block encounters entailing over 2600 blocks with multimodal perineural analgesia for either surgical anesthesia or postoperative analgesia, our patient-specific incidence of definite PNI was 0.11% (2/1830). When including possible PNI cases with EMG testing ( $n=5$ ) and possible PNI cases that did not have EMG testing ( $n=3$ ), our conservative estimate for PNI risk is 0.55% (10/1830).

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**Funding sources:** This manuscript is linked thematically to the translational study underwritten by the Department of Defense (OR090012, to author BAW) Peer Reviewed Orthopaedic Research Program (PRORP), Translational Research Partnership Award (TRPA), of the Office of the Congressionally Directed Medical Research Programs (CDMRP). However, no funds or resources were used from this funded study for the content listed in this report.

## Authors' Contributions

B.W. led in the preparation of the manuscript, led the design and conduct of the quality improvement data query (preparatory to research), and analyzed all data. J.I. assisted in the preparation of the manuscript, reviewed the content of the quality improvement data

query (preparatory to research), and contributed text and context to the narrative. A.G. assisted in the preparation of the manuscript, performed a significant portion of the quality improvement data query, and contributed text and context to the narrative. M.M. assisted in the preparation of the manuscript, was central in the original quality improvement data query, and reviewed all data and text/context presented. All authors approved this manuscript.

## Acknowledgments

The contents of this manuscript do not reflect the views of the Department of Veterans Affairs or the United States Government. VA Pittsburgh Health System is acknowledged for support of the author group.

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## ACUTE & PERIOPERATIVE PAIN SECTION

### Technical Note

# Technical Communication: Admixture of Bupivacaine-Clonidine-Buprenorphine-Dexamethasone at the Bedside in a Tertiary Care Hospital Block Room Is Not Associated with Any Apparent Burdens of Endotoxin or Microbial Growth

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**Funding sources:** This manuscript is linked thematically to the upcoming prospective randomized clinical trial underwritten by the Department of Defense (Broad Agency Announcement 13232002, to author BAW). However, no funds or resources were used from this funded study for the content listed in this report as study funding was in part predicated on gaining Food and Drug Administration–Investigational New Drug Application approval.

**Disclosures:** Brian Williams led in the preparation of the manuscript. He led the design and conduct of the described experiments. Brian Williams approved this manuscript. Shirley Podnar assisted in the preparation of the manuscript. She reviewed the content of the entire manuscript, with special attention to both the experimental methods and pharmacy specifications for

drug mixing. Shirley Podnar approved this manuscript. Samantha Bonant assisted in the preparation of the manuscript. She reviewed the content of the entire manuscript, with special attention to regulatory matters from our institutional review board and from the Food and Drug Administration. Samantha Bonant approved this manuscript. Allison Schanck assisted in the preparation of the manuscript. She contributed text and context to the narrative related to the hospital physical plant engineering issues related to heating, ventilation, and air conditioning (HVAC). Allison Schanck approved this manuscript.

**Conflicts of interest:** There are no conflicts of interest to report.

### Introduction

Recently, we described in vitro [1] and in vivo [2] safety (in rats) of four-drug nerve block (multimodal perineural anesthesia–analgesia [MMPNA]) combinations involving bupivacaine (BPV [2]), ropivacaine (RPV [1]), or midazolam (MDZ [1,2]) with the following three preservative-free injectable drugs: clonidine, buprenorphine, and dexamethasone (hereafter abbreviated as CBD) [1,2]. In addition, we reported 1) clinical analgesic duration benchmark data for patients having received nerve blocks with combined BPV-CBD [3] and MDZ-CBD [4] and 2) benchmark patient perineural safety data [5]. These reports encompassed the time period from July 2011 through December 2014, and our patient care quality improvement program continues as of this writing. The current report entails the technical issue of the four-drug block mixture at the bedside, and the theoretical microbiology-related risks of such mixtures.

Our research team recently gained prospective clinical trial research funding for the comparison of BPV-CBD against plain BPV in lower extremity nerve blocks. In the regulatory proceedings for this research funding, we were required by our institutional review board (IRB) to submit an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA). In serial communications with the FDA regarding the IND process, one of the directives was for our team to provide details how BPV-CBD would be compounded, including the provision of microbial and endotoxin data to support the sterility of the compounded product via perineural administration (personal communication from FDA, IND 127171 Full Clinical Hold correspondence, August 26, 2015).

The specific aim of this manuscript is to describe the experimental methods used and results obtained to support the sterility of BPV-CBD mixed at the bedside in the block room of our tertiary care Veterans Hospital. The submission of the results of this experiment for publication was approved by the Veterans Affairs Pittsburgh Healthcare System Institutional Review Board Section for Non-Human Subjects Research (MIRB ID#03262, June 9 and June 20, 2016).

## **Methods**

### *Overview*

The required evaluation of drug compound sterility occurred in two separate phases: endotoxin assessment and assessment for microbial growth. For both phases, the experimental condition was the presence or absence of nonsterile and sterile gloves at the time of mixing: 1) no gloves, 2) nonsterile nitrile gloves (Microflex Corp., Reno, NV, USA), and 3) sterile gloves (Biogel, Norcross, GA, USA).

All drug mixing occurred in our institution's block room, the heating/ventilation/air conditioning (HVAC) specifications entailing six to seven air exchanges per hour. This procedure room has three patient bays and two access doors that were routinely left open to foot and gurney traffic. The three patient bays used full-length curtains for patient privacy, and the block cart used for mixing was located behind a plastered wall no less than 18 feet (5.5 meters) from either door. In our routine clinical practice (since 2011) of BPV-CBD mixtures, all drugs were compounded at this block cart (Figure 1A) or a similar block cart 80 feet (24 meters) away (outside a glass-encased isolated patient bay used for infection control precaution patients) (Figure 1B). Neither block cart featured any specific HVAC engineering involving a vacuum hood (an ISO class 5 environment, as specified in USP 797).

The block cart surface was cleaned with a standard antiseptic wipe (Super Sani-Cloth, Professional Disposables International, Inc., Orangeburg, NY, USA), then the hands of the drug mixer (author BAW) were

cleansed with Purell hand sanitizer (GOJO Industries, Akron, OH, USA).

### *Drug Mixing Protocol*

The methods used for this mixing protocol were compliant with published recommendations, such as using aseptic technique, swabbing the drug container with alcohol, and wearing hat and mask during drug preparation into sterile syringes [6]. The nerve block mixtures performed for these experiments were not used for patient care. For drug preparation, the indicated quantities of injectable preservative-free bupivacaine (source vial of 30 mL of 5 mg/mL, Hospira, Lake Forest, IL, USA), buprenorphine (300 mcg/mL, 1 mL source vial, PAR Pharmaceutical, Woodcliff Lake, NJ, USA), and dexamethasone (10 mg/mL, 0.1 mL, 1 mL source vial, Fresenius Kabi, Warrendale, PA, USA) were withdrawn from single use containers and injected into an empty sterile syringe. A single dose syringe of injectable clonidine (25 mcg, in 0.25 mL from a source vial of 10 mL, Mylan Pharmaceuticals, Morgantown, WV, USA) was added to this syringe along with a sufficient quantity of preservative-free 0.9% sodium chloride (Hospira, 20 mL source vial) to provide a total volume of 20 mL (Table 1). As controls, we also prepared plain bupivacaine syringes: The required quantity of injectable preservative-free bupivacaine (10 mL of 5 mg/mL) was withdrawn from a single use container and injected into an empty syringe. A sufficient quantity of preservative-free 0.9% sodium chloride (10 mL) was then added to the syringe to provide a total volume of 20 mL. Author SMP witnessed and documented the preparation of all syringes.

### *Endotoxin Testing*

We used the following methodology to address the issue of endotoxin parameters, en route to verifying the sterility of the drugs. The equipment we used for sample testing was the Endosafe device (Charles River Laboratories International [three useful websites describing the testing device are listed here: [http://www.criver.com/files/pdfs/emd/endotoxin/endosafe\\_pts\\_and\\_regulatory\\_requirements\\_fda\\_guide.aspx](http://www.criver.com/files/pdfs/emd/endotoxin/endosafe_pts_and_regulatory_requirements_fda_guide.aspx), [http://www.criver.com/files/pdfs/emd/endotoxin/qc\\_en\\_d\\_endosafe\\_pts\\_datasheet.aspx](http://www.criver.com/files/pdfs/emd/endotoxin/qc_en_d_endosafe_pts_datasheet.aspx), <http://www.criver.com/files/pdfs/emd/endotoxin/endosafe-pts-and-regulatory-requirements.aspx>]). This is an FDA-approved limulus amoebocyte lysate (LAL) testing system that is compliant with USP 85 (United States Pharmacopeial Convention, Interim Revision Announcement, April 1, 2011) FDA requirements. Within three hours after the syringes were prepared in the described conditions, all aliquots were extracted from the syringes and processed through the Endosafe device (one aliquot at a time, approximately 15 minutes per aliquot), per manufacturer specifications. All syringes were prepared beginning at approximately 12:30 PM ET, and all Endosafe tests were complete by approximately 3:15 PM ET. Of note, in preliminary testing a few days prior, there were prompts



**Figure 1** Photographs of nerve block procedure carts in our institution. **A)** Shows the nerve block cart located in the procedure room with three patient bays, with the bays separated by curtains. The camera is in the third of three procedural bays, and the other two procedural bays are on the left and right side of the photograph. The heating/ventilation/air conditioning (HVAC) specifications of this procedure room entail six to seven air exchanges per hour. **B)** Shows the nerve block cart positioned in the hall (no specific HVAC specifications for air exchanges) outside two separate isolation rooms (each with 6–7 air exchanges per hour) where nerve blocks are performed. To date, all of our institution’s nerve block mixtures have been prepared at one of these two carts.

from the Endosafe device regarding the need for further dilution than those given in our original 1:1 mixtures. After telephone consultation with Charles River

Laboratories, we diluted the mixtures to 1:10 (with the device still prompting further dilution) and 1:100 (which ultimately gave all negative responses for this test).

**Table 1** Mixtures compared with respect to endotoxin burden and microbial growth

| Drug and concentration; volume of source vial | Four-drug combination* | Bupivacaine only, mL |
|-----------------------------------------------|------------------------|----------------------|
|                                               | Volume, mL             |                      |
| Bupivacaine 150 mg/30 mL (5 mg/mL)            | 10                     | 10                   |
| Clonidine 1 mg/10 mL                          | 0.25                   | 0                    |
| Buprenorphine 300 mcg/1 mL                    | 1                      | 0                    |
| Dexamethasone 10 mg/1 mL                      | 0.1                    | 0                    |
| 0.9% sodium chloride                          | 8.65                   | 10                   |
| Total volume of syringe                       | 20                     | 20                   |

\*Four-drug combination: bupivacaine-clonidine-buprenorphine-dexamethasone.

### Microbial Testing

In collaboration with the Pathology and Laboratory Medicine section of our institution, a standard procedure was established to ascertain microbial colony counts obtained from compounding procedures. These mixing proceedings occurred weeks after the aforementioned endotoxin experiments. Again, the BPV-CBD, plain, and saline control syringes were prepared aseptically by author BAW and witnessed by coauthor SMP as described above; there was no syringe dilution for this experiment. The syringes were all then delivered to the microbiology laboratory for processing. Aliquots of 100  $\mu$ L volume were dispensed onto blood agar plates from each syringe. Aliquots were then evenly distributed across the surface of the plate using Lazy-L spreaders (Sigma-Aldrich, St. Louis, MO, USA). The plates were then incubated at 35°C and examined for bacterial growth at 24, 48, and 72 hours, respectively. The plates were also incubated at 35°C and examined for fungal growth at 24, 48, and 72 hours, respectively. After 72 hours, the plates were removed from the incubator and examined for fungal growth at five days, 10 days, and finalized at 14 days.

### Statistical Analyses

All test results were negative, so no statistical analyses were required.

## Results

### Endotoxin Testing

There was no endotoxin detected in any samples of the 1:100 diluted syringes. The undiluted syringes and 1:10 diluted syringes were not interpretable by the device, likely (per phone consultation with the device manufacturer) related to exceeding osmolality limits.

### Microbial Testing

There was no microbial (neither bacterial nor fungal) growth in any of the blood agar plates throughout the 14-day period.

After review of the results above, the FDA removed the Full Clinical Hold and concluded that the clinical trial may be initiated upon IRB approval. The FDA recommendation during the study was to ensure that the perineural administration of the four-drug nerve block (or plain bupivacaine control block) occurred within one hour of aseptic drug preparation in the syringe.

## Discussion

We summarize the proceedings of our response to the Full Clinical Hold applied by the FDA on our IND application for the study of BPV-CBD as follows. Both endotoxin testing and microbial testing were negative for all samples, irrespective of the wearing of gloves or sterility of the gloves. It is noteworthy that we were required by the manufacturer of the endotoxin testing device to dilute the mixture to 1:100 to sufficiently minimize the solute concentration (of primarily local anesthetic) to allow for device interpretation of the injectate; obviously, such dilutions would also dilute endotoxin generated from the mixture, if such existed. The coinciding negative microbial testing offsets any concerns of the nuance of drug mixture dilution. Aside from the question of glove use, there were other aseptic preparation measures such as isopropyl alcohol hand rinse (e.g., Purell), the donning of a mask and hat, and aseptic decontamination wipes to the top surface and drawer fronts of our nerve block cart. This type of block cart arrangement (Figure 1) was the mixing location of our institutional standard of care four-drug nerve block mixtures since our program inception in 2011. The negative findings (verifying sterility) are supportive of both our current practice of drug preparation and the practice we aim to use for the prospective study. In our practice to date (over 3,000 patients with single- or dual-injection blocks), we have had no focal infectious concerns at the site of injection, to our knowledge. Our findings also support (related to any sterility concerns) the potential use of the four-drug combination by the study sponsor's (Department of Defense's) medical services in combat and/or other austere environments [7].

These proceedings and our findings have potential patient benefits when considering interdisciplinary policy

within a hospital. In our recent reports published in this journal [3,5], we described an associated analgesic duration from BPV-CBD exceeding a mean of 30 hours, with potential adjuvant dose response–driven improvements in rebound pain. Favorable durations such as this (with single-injection blocks) may reduce perineural catheter burden.

For a hospital that may have previously used perineural catheters, the multidrug combination as a single injection (initiated in an effort to replace a perineural catheter program) may generate procedural sterility questions. Such questions may specifically entail sterility of a multidrug combination for a single-injection nerve block prepared outside the confines of an ISO class 5 environment, that is, within a biological safety cabinet as noted within the standards of USP 797. For some facilities, the nerve block solutions are prepared in the operating room (15 air exchanges per hour) or a procedure room in close proximity to the operating room (e.g., 6–7 air exchanges per hour). In our facility, there are designated block carts in the latter-listed procedure rooms (Figure 1) used for the preparation of nerve block solutions. Our standard practice for mixing nerve blocks on these carts includes hand sanitizing, decontamination of the block cart surface table, and using sterile syringes, needles, and single dose vials. These practices of our group were considered both sufficient and acceptable by the FDA and did not entail a formal declaration of sterile glove use (or any glove use, after the described hand cleansing) superimposed upon these other measures. In context, the risk of clinically relevant infectious complications from perineural catheters has been cited as 0–3% [8].

Regarding the FDA's recommendation for our study that all drugs be administered within one hour of bedside preparation (despite being free from endotoxin and microbial growth), we reiterate from our team's recent publication in this journal [2] that the BPV-CBD mixture (in an ISO class 5 environment) is chemically compatible (without the precipitation of solute or loss of drug constitution) for at least 14 days after preparation. If such syringes were prepared within a hospital aseptically by pharmacists under the ISO class 5 conditions stated by USP 797 and refrigerated, then the block team would certainly have more flexibility regarding when to administer the block relative to the anticipated timing of surgery.

## Conclusions

Some facilities do not have the benefit of access to ISO class 5 environments and/or a satellite pharmacy to prepare nerve block mixtures. At our facility, standard procedures for preparation were followed, including but not limited to donning hat and mask, hand sanitization, decontamination of the mixing surface, and using a sterile syringe and needle to access single dose vials. The negative results of our endotoxin and microbial growth assessments offer preliminary assurances regarding the sterility of a four-drug nerve block mixture prepared in the "Immediate Patient Treatment Area," that is, outside

the confines of a biological safety cabinet and within the limited time frames previously described. These measures were deemed acceptable by the FDA in their approval of our IND application. We re-emphasize that the four-drug combination described, along with our mixing method, should otherwise be considered "off-label."

## Acknowledgments

The contents of this manuscript do not reflect the views of the Department of Veterans Affairs or the United States Government. VA Pittsburgh Health System is acknowledged for support of the author group.

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# Extended Perineural Analgesia After Hip and Knee Replacement When Buprenorphine-Clonidine-Dexamethasone Is Added to Bupivacaine: Preliminary Report from a Randomized Clinical Trial

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Funding sources: This study was underwritten by a grant (to Dr. Williams) from the Department of Defense, United States, DoD Award No. W81XWH-15-1-0294. The US Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014, was the awarding and administering acquisition office. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the FY14 DoD USAMRMC Broad Agency Announcement under Award No. W81XWH-15-1-0294. The professional effort of author HJP was underwritten by the Foundation for Anesthesia Education and Research Medical Student Summer Research Fellowship.

Disclaimer: The opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense or the Veterans Health Administration.

Disclosure and conflicts of interest: Delineated above; no conflicts.

## Abstract

**Objective.** We tested the hypothesis that buprenorphine-clonidine-dexamethasone (BCD) extends perineural analgesia compared with plain bupivacaine (BPV) nerve blocks used for hip and knee replacement surgery. **Design.** Prospective, parallel-arms, randomized, double-blind trial. **Setting.** A single veterans' hospital. **Subjects.** Seventy-eight veterans scheduled for total hip or knee replacement with plans for spinal as the primary anesthetic. **Methods.** Participants underwent nerve/plexus blocks at L2–L4 and L4–S3 in advance of hip or knee joint replacement surgery. Patients were randomized to receive BPV-BCD or plain BPV in a 4:1 allocation ratio. Patients answered four block duration questions (listed below). Time differences between treatments were analyzed using the *t* test. **Results.** Significant ( $P < 0.001$ ) prolongation of the time parameters was reported by patients after the BPV-BCD blocks ( $N = 62$ ) vs plain BPV ( $N = 16$ ). The time until start of postoperative pain was 26 vs 11 hours (mean difference = 15 hours, 95% CI = 8 to 21). The time until no pain relief from the blocks was 32 vs 15 hours (mean difference = 17 hours, 95% CI = 10 to 24). The time until the numbness wore off was 37 vs 21 hours (mean difference = 16 hours, 95% CI = 8 to 23). The time until the worst postoperative pain was 39 vs 20 hours (mean difference = 19 hours, 95% CI = 11 to 27). **Conclusions.** BPV-BCD provided 26–39 hours of perineural analgesia in the L2–L4 and L4–S3 nerve distributions after hip/knee replacement surgery, compared with 11–21 hours for plain BPV.

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

## Introduction

Perineural adjuvants such as buprenorphine [1], clonidine [2], and dexamethasone [3] (abbreviated as BCD when combined) are commonly added to peripheral nerve blocks to prolong analgesic duration. Safety studies have been conducted in vitro (rat) combining BCD with ropivacaine [4] and in vivo (rat) combining BCD with bupivacaine (BPV) [5]. One prospective clinical trial found BCD to be beneficial when added to ropivacaine as an interscalene block for total shoulder arthroplasty [6]. Another trial found BPV-BCD to be beneficial for 36 hours as a single-injection adductor canal block for total knee arthroplasty (TKA), when compared with a continuous infusion of plain BPV with epinephrine [7]. We previously reported a benchmark case series of >1,300 patients (from 2011 to 2014) who underwent various types of surgery with BPV-BCD nerve blocks [8]. For the current study, we tested the hypothesis that single-injection nerve blocks comprised of BPV-BCD provide prolonged perineural analgesia vs single-injection plain BPV nerve blocks (at L2–L4 and L4–S3) used for total hip arthroplasty (THA) and TKA.

There is no approved medication for prolongation of L2–L4 and L4–S3 blocks (i.e., liposomal bupivacaine is not approved by the US Food and Drug Administration [FDA] for lower extremity peripheral nerve block). We specifically gained Investigational New Drug approval status from the FDA to study BPV-BCD; BPV-BCD was the off-label institutional standard of care [8] from 2011 until study inception (in 2016), encompassing ~3,000 patients. Ideally, prolongation of the analgesic duration of a single-injection nerve block may avoid the need for placement of a continuous nerve block catheter. The specific aim of this preliminary report was to describe the analgesic duration of single-injection BPV-BCD in comparison with single-injection plain BPV.

## Methods

### Study Design and Oversight

This study was a parallel-arm, double-blind, randomized clinical trial conducted at a single Veterans Affairs (VA) hospital. The study was approved by the Food and Drug Administration (Investigational New Drug [IND] 127171). Participants signed an informed consent document approved by the institutional review boards from the VA Pittsburgh Health System (VAPHS) and the University of Pittsburgh, as well as the Human Research Protection Office of the Department of Defense. The study was also monitored by an independent data and safety monitoring board. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines and was registered at ClinicalTrials.gov (NCT02891798).

### Study Population

The patients enrolled were scheduled to undergo primary TKA or primary THA, and the eligible ages were 18 to 85 years. Exclusion criteria entailed significant behavioral risks or refractory major psychiatric disorders; revision surgery on the same extremity; an American Society of Anesthesiologists (ASA) Physical Status classification of IV or higher; a surgically fused lumbar spine at L2–L4, or a spinal cord simulator, or other condition that would contraindicate or prohibit the safe conduct of spinal anesthesia; significant risk for postoperative substance abuse or immediate postoperative substance abuse withdrawal symptoms (alcohol, cocaine, enrolled in methadone or buprenorphine opioid withdrawal program, etc.); undergoing TKA/THA for a tumor; or contraindications (e.g., anaphylaxis) to BPV or BCD. Inclusion criteria entailed fluency in the English language, decision competence, willingness and ability to provide written informed consent, ability to complete the study's schedule of assessments, ability to walk >3 m without an assisting device, and having a body mass index (BMI)  $\leq 40$ .

After the patient signed consent, and in the days to weeks before surgery, the patient engaged in preoperative baseline surveys and physical therapy assessments. These, along with postoperative surveys, physical therapy exercises, and testing, will be reported in a separate manuscript.

### Randomization and Blinding

Before the start of the trial, the study statistician (JMM) prepared the randomization sequence using a computerized random number generator, which was then placed in sequentially numbered and sealed envelopes with the allocation assignment. The allocation ratio was 4:1 to BPV-BCD or BPV; this unbalanced design was used because the BPV-BCD was the standard of care at VAPHS. The randomization was done in blocks of five and stratified by total joint replacement (knee and hip), presence or not of diabetes, and age ( $\leq 69$  and  $>69$ ). Immediately before surgery, a pharmacist from the Investigational Drug Service at VAPHS formalized the placement of the envelope into the automated drug cabinet, with the allocation assignment for each patient and with detailed instructions for drug mixing for the L2–L4 and L4–S3 blocks. The preservative-free drugs were mixed by a certified registered nurse anesthetist who was otherwise not involved with patient care. All other clinical and research staff were blinded to the nerve block treatment received, including the anesthesiologist, patient, and research coordinator.

### Interventions

The L4–S3 blocks (gluteal or subgluteal approach to the sciatic nerve for TKA and parasacral block for THA) were 20 mL of 0.1% BPV, with or without the combination of buprenorphine 300  $\mu$ g, clonidine 25 mcg, and

dexamethasone 1 mg. The L2–L4 blocks (anterior approach to the femoral nerve for TKA and psoas compartment lumbar plexus block for THA) were also 20 mL, but were 0.25% BPV if the patient was a nondiabetic and 0.2% if the patient was a diabetic. The additives in the L2–L4 blocks were the same as in the L4–S3 blocks. The L2–L4 BPV concentrations chosen, in light of the use of the BCD adjuvants, were based on our institutional standard of care for analgesic blocks with BPV that evolved over the preceding several years [8]. The L4–S3 concentration of 0.1% BPV, irrespective of diabetes status, was selected in an effort to minimize motor block below the knee; we had previously [8] used BPV 0.125% for nondiabetics and 0.1% for diabetics for the L4–S3 distribution. Doses of BCD were also selected based on our previously reported benchmark [8]. Opioid side effects from perineural buprenorphine are acknowledged [1], particularly postoperative nausea and vomiting (PONV); our long-standing group practice is to provide oral preoperative perphenazine and intravenous ondansetron as routine antiemetic prophylaxis [9–11]. Aprepitant was added for additional prophylaxis for patients (N = 21) deemed at additional risk.

Patients received intravenous sedation for their nerve blocks (up to 4 mg of midazolam, 100 mcg of fentanyl, and/or 40 mcg of dexmedetomidine) after appropriate monitors and supplemental oxygen were applied in the preoperative block room. For TKA, femoral and gluteal or subgluteal sciatic nerve blocks were placed using nerve stimulator and/or ultrasound guidance. For THA, lumbar (psoas compartment) and parasacral plexus blocks were placed using nerve stimulator guidance. Spinal anesthetics comprised of hypobaric bupivacaine were then administered in the same preoperative block procedure room. Spinal anesthesia was supplemented intraoperatively by intravenous propofol sedation and ketamine in intermittent boluses to a total of 0.5 mg/kg (of ketamine).

### Multimodal Analgesia

The surgeons applied periarticular injections during surgical closure: For TKA, these included the posterior capsule and surrounding posteromedial and posterolateral structures, extensor mechanism, synovium, capsule, pes anserinus (at the medial border of the tibial tuberosity), anteromedial capsule, and periosteum, iliotibial band, collateral ligaments and origins, and subcutaneous tissue. For THA, these periarticular injections included the anterior capsule, iliopsoas tendon and insertion site, abductors, fascia lata, gluteus maximus and its insertion, posterior capsule and short external rotators, synovium, and subcutaneous tissue. The typical injection entailed 40 mL of 0.5% bupivacaine with 300 µg of epinephrine and 30 mg of ketorolac.

Postoperative oral analgesia was comprised of every-12-hours standing orders for sustained-release acetaminophen (1,300 mg), sustained-release dextromethorphan

(60 mg), salsalate (500 mg), and ascorbic acid (500 mg) [12]. Oxycodone 5–10 mg was prescribed every four hours as needed for pain, while oxycodone 5 mg was prescribed every two hours for before and/or after physical therapy. During approximately the first half of the clinical trial, before the public declaration of the opioid epidemic, the surgeons also had available oral sustained-release morphine 15 mg to prescribe for patients (N = 37) in whom such a formulation was deemed advantageous, specifically at bedtime on the day of surgery, consistent with the preceding institutional standard of care. Hydromorphone IV 0.5 mg was also available for refractory severe pain. Two patients had a history of adverse reaction to oxycodone, so combined hydrocodone/acetaminophen was used instead. In accordance with the Centers for Disease Control and Prevention (and related) guidelines for morphine milligram equivalent calculations of opioid consumption, 1 mg of oral morphine was considered equivalent to 0.67 mg of oral oxycodone [13], 1 mg of oral hydrocodone [13], and 0.05 mg of IV hydromorphone [14].

### Outcomes

Outcomes were based on the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [15]. Several survey instruments were employed; at the time of obtaining informed consent for the study, participants were administered a baseline battery of written surveys, and these written surveys were repeated each postoperative day through the course of hospital admission. The results of these surveys will be reported in a separate manuscript. For the current preliminary report, the primary survey upon which we report is the Defense and Veterans Pain Rating Scale (DVPRS) [16–18]. Therefore, the highest pain score (on a 0–10 scale) recorded on the DVPRS, the time of this highest pain score, and opioid consumption in oral morphine equivalents comprise the body of data presented in this preliminary report. In addition, based on the precedent set by YaDeau et al. (2016) [6], we report herein on four questions asked to patients to address nerve block duration: 1) “At what time did your knee/hip start having pain?”; 2) “When did the nerve block stop providing pain relief?”; 3) “When did the numbness of the nerve block entirely wear off?”; and 4) “At what time was your worst knee/hip pain?” These four questions were asked at the same time as the administration of the DVPRS survey, which was in the morning before physical therapy on every postoperative day in the hospital. Therefore, patients were asked to recall these times from overnight or the day before. We also tracked time to first opioid consumption, with the caveat that the institutional standard of care during the first part of the clinical trial (N = 37) allowed for opioid consumption in patients before any complaints of pain in the context of patients taking an oral analgesic (15 mg sustained-release

morphine) before attempting to fall asleep, in an effort to not have pain awaken the patient in the middle of the night. These questions were asked, and on each postoperative day in the hospital, the DVPRS day with the highest-reported pain score (0–10) was collated, along with the corresponding four questions' responses addressing block duration. We also queried the veteran's electronic medical record for "time to first requested opioid" and "time to first scheduled opioid." Again, the scheduled opioid, if taken, was 15 mg of sustained-release morphine, while the first requested opioid was either oral oxycodone (5–10 mg) or IV hydromorphone (0.5 mg).

### Sample Size

We based our sample size on our most robust data, nerve block duration (time to peak pain score) from our observational data [8]. We considered a doubling of the nerve block duration (an estimated 15 hours for plain BPV, an estimated 30 hours for BPV-BCD) to be a clinically significant difference. We forecasted that as a single drug (and based on historical literature), the standard deviation of plain BPV duration would be half of the 15-hour projected duration (i.e., 7.5 hours). Due to likely variability in study participant responsiveness to the four-drug BPV-BCD mixture, we predicted that the standard deviation of the BPV-BCD treatment would also be half of the projected 30-hour duration (i.e., 15 hours). Using a two-tailed  $t$  test with  $\alpha = 0.05$ , 20 patients per procedure for plain BPV treatment and 80 patients with the BPV-BCD treatment would yield 95% statistical power. The 4:1 allocation ratio of BPV-BCD to plain BPV was selected also because the BPV-BCD combination was the institutional standard of care before the clinical trial was conceived. We forecasted that this sample size would also accommodate our multiple secondary aims (to be reported along with the study's primary aim in a separate manuscript). Regarding study dropouts, attrition of six active control treatment patients ( $N = 14$  with plain BPV) and of 24 BPV-BCD-treated patients ( $N = 56$ ) would still yield just over 80% statistical power. All power calculations were performed using IBM SPSS SamplePower, version 3.0.1 (Chicago, IL, USA).

### Study Interruption

The sample size determined before the study began was  $N = 100$  patients to undergo primary THA and  $N = 100$  patients to undergo primary TKA; these sample sizes were ultimately not achieved. The grant application with this described methodology was first submitted in late 2013, before our institution routinely engaged patients in same-day physical therapy (SDPT) after surgery. By early 2018, SDPT became the new hospital guideline for patients undergoing primary THA and TKA, such that by mid-2018, it became apparent to the research team that no study patients would reliably engage in SDPT due

to frank numbness from the described L2–4 and L4–S3 blocks. As a result of this new SDPT standard in postoperative care, the study's independent Data Safety Monitoring Board suspended all study enrollment until revised care protocols and study methods that enabled SDPT were approved by the Institutional Review Board of both the hospital (VA Pittsburgh Healthcare System [VAPHS]) and university (University of Pittsburgh), and also by the Human Research Protection Office of the Department of Defense.

Therefore, this report represents outcomes of the first cohort of patients ( $N = 78$ :  $N = 51$  TKA patients and  $N = 27$  THA patients) (Figure 1, CONSORT Diagram), with the specific data in this report focused on patient responses of block duration. We enrolled a second cohort of patients, and we plan to report on the original primary aim of the study (pain survey responses) in the context of multiple simultaneous physical therapy outcomes (as secondary aims).

### Data Management and Statistical Analysis

Values for "time to worst pain" and the other listed questions were compared across treatment groups using the  $t$  test with respect to race, gender, age (69 or under vs 70 and over), diabetes status, and ASA Physical Status (II vs III). No demographic variables were significantly associated with "time to worst pain" or any other block duration time data, so the analyses were not adjusted for these demographic factors. Block duration time data were normally distributed, so the  $t$  test was used to compare time outcomes after plain BPV vs BPV-BCD.

We also reviewed the medical record (in real time, during hospital admission) to estimate block duration and maximum pain (relative to baseline pain with movement as recorded on the DVPRS), similar to the block duration and rebound pain data (worst pain score reported after the effects of the nerve block dissipate) reported in our retrospective benchmark case series [8]. In the medical record notes, block duration was estimated to be time of the peak pain score (presumably with movement) minus the time of block placement. We then correlated these (primarily) nurse-charted pain scores with the patient-reported pain scores on the DVPRS at the time that the worst postoperative pain was encountered. We also correlated (Pearson method) the block duration patient reports ("time to start pain," "time to no pain relief," "time until numbness wore off," and "time to worst pain") with each other and with the estimated block duration based on the medical record and nurse-charted peak pain score reports. For these correlations, we refer to correlation coefficients of 0.70 and higher as "high positive," coefficients of 0.50 to 0.69 as "moderate positive," and statistically significant coefficients with values between 0.30 to 0.49 as "low positive" [19].

Study data were collated and managed using REDCap [20] data capture tools at the VAPHS. For all statistical

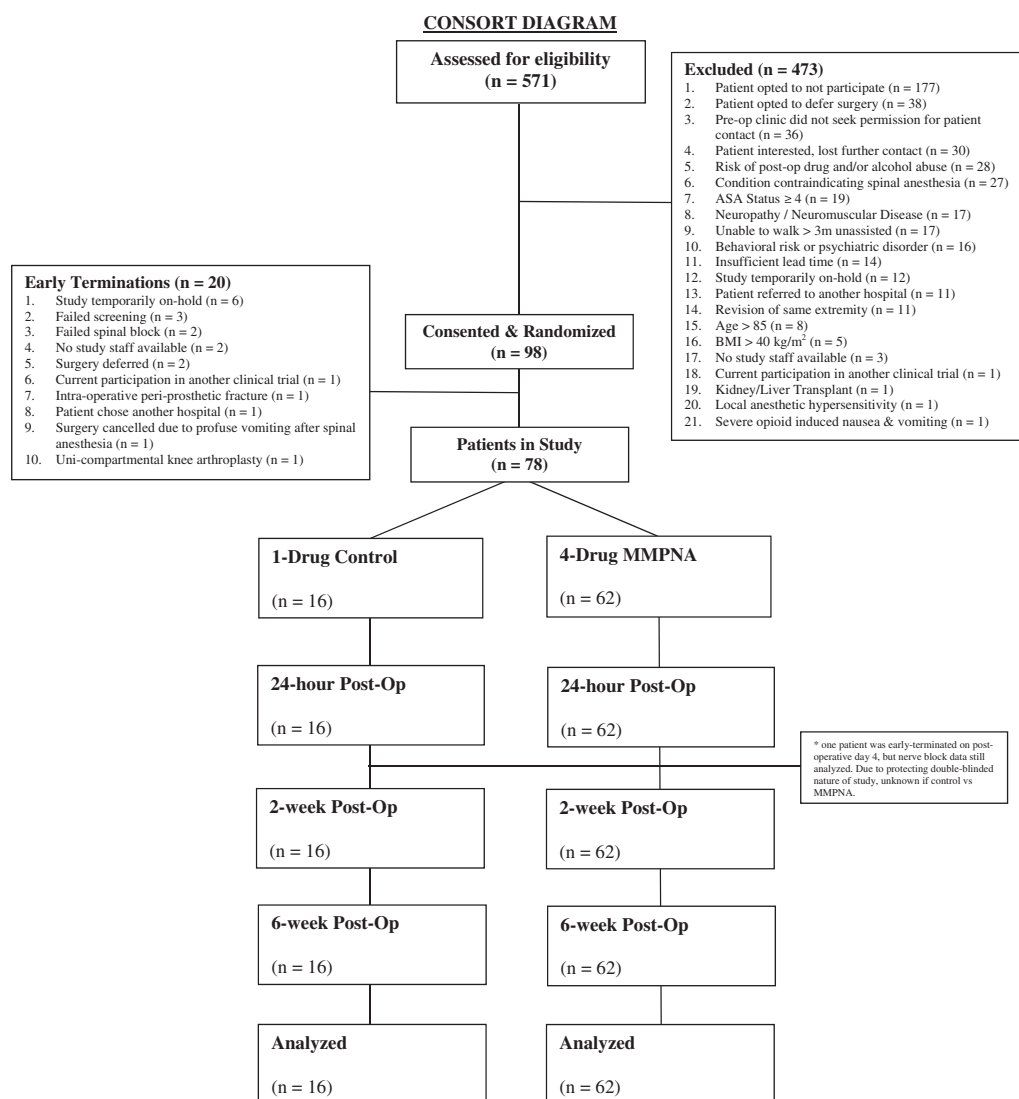


**Figure 1.** Consolidated Standards of Reporting Trials diagram.

tests,  $P < 0.05$  was considered statistically significant. All data were analyzed using SPSS Statistical Software (version 25; Armonk, NY, USA).

## Results

We screened 571 people, of whom 473 were not eligible due to failing study inclusion/exclusion criteria ( $N = 151$ ), programmatic reasons ( $N = 145$ ), or not willing to participate ( $N = 177$ ), resulting in 98 patients enrolled in the study (Figure 1). Of the 98 enrolled, 20 were early terminations for reasons that happened in the weeks between enrollment and randomization (10 for programmatic reasons, three failed screening) or early terminations for reasons that happened during surgery ( $N = 7$ ). This resulted in 78 patients ( $N = 16$  plain BPV,  $N = 62$  BPV-BCD) who received the allocated protocol for study interventions and were available for this preliminary analysis.

Demographic variables are summarized in Table 1. Block duration data for THA vs TKA are listed in Table 2, after which block duration data for hip vs knee replacement are pooled. Table 3 lists the outcomes of this preliminary report, block duration data (hours) based on treatment group, with THA/TKA data pooled. Significant prolongation of all four patient-reported time parameters ( $P < 0.001$ ) was noted after the BPV-BCD blocks. This included i) time to start of pain: 26 vs 11 hours (mean difference = 15 hours, 95% CI = 8 to 21); ii) time to no pain relief: 32 vs 15 hours (mean difference = 17 hours, 95% CI = 10 to 24); iii) time to resolution of numbness: 37 vs 21 hours (mean difference = 16 hours, 95% CI = 8 to 23); and iv) time to worst pain: 39 vs 20 hours (mean difference = 19 hours, 95% CI = 11 to 27). There was no difference in opioid consumption time when the first dose was scheduled (the bedtime dose,  $N = 37$ ). For patients who did not have a scheduled first opioid dose, the time to first opioid was 21 hours after BPV-BCD ( $N = 29$ ) and seven hours after plain BPV

**Table 1.** Demographic data

| Parameter                         | BPV-BCD    | Plain BPV  | P Value |
|-----------------------------------|------------|------------|---------|
| No.                               | 62         | 16         | N/A     |
| Knee/hip replacement, No.         | 41/21      | 10/6       | 0.786   |
| Male/female, No.                  | 56/6       | 15/1       | 0.669   |
| ASA-PS II/III, No.                | 11/51      | 3/13       | 0.925   |
| BMI, mean (SD), kg/m <sup>2</sup> | 32.6 (4.6) | 31.9 (5.1) | 0.586   |
| Diabetes (no/yes), No.            | 39/23      | 10/6       | 0.976   |
| Age ( $\leq 69/\geq 70$ ), No.    | 40/22      | 11/5       | 0.751   |
| Age, mean (SD), y                 | 66.7 (7.4) | 65.6 (7.6) | 0.575   |
| Race/ethnicity, No.               |            |            |         |
| Caucasian                         | 53         | 15         | 0.678   |
| African American                  | 8          | 1          | 0.676   |
| Other                             | 1          | 0          | 1.000   |
| Hispanic                          | 0          | 0          |         |

ASA-PS = American Society of Anesthesiologists Physical Status classification; BMI = body mass index; BPV = bupivacaine; BPV-BCD = bupivacaine-buprenorphine-clonidine-dexamethasone.

(N=9, mean difference = 14, 95% CI = 1 to 27,  $P = 0.035$ ). Patients requiring IV hydromorphone significantly differed between treatments ( $P = 0.03$  by Fisher exact test): nine of 16 plain BPV control patients (56%) vs 15/62 (24%) of patients who received BPV-BCD.

Worst pain scores (mean and SD) as reported by the patient on the DVPRS postoperatively (relative to baseline pain with movement as recorded on the DVPRS) did not significantly differ based on BPV-BCD vs plain BPV treatment (0.1 [2.4] vs 1.3 [2.9],  $P = 0.124$ ), but these data may have been underpowered. Worst pain scores as determined from medical record review (based on peak pain scores recorded by nursing or physical therapy staff) also did not differ based on BPV-BCD vs plain BPV (again relative to baseline, 0.8 [2.2] vs 1.8 [2.5],  $P = 0.125$ ); again, these data may have been underpowered. With respect to the moderately positive correlation

**Table 2.** Block duration time parameters after hip vs knee replacement, before data pooling

| Parameter                      | Surgical Procedure | No. | Mean (SD), h | P Value |
|--------------------------------|--------------------|-----|--------------|---------|
| Time to start of pain          | TKA                | 47  | 21.8 (11.7)  | NS      |
|                                | THA                | 25  | 24.3 (13.9)  |         |
| Time to no pain relief         | TKA                | 37  | 27.3 (12.8)  | NS      |
|                                | THA                | 17  | 30.4 (14.4)  |         |
| Time to resolution of numbness | TKA                | 35  | 31.6 (14.4)  | NS      |
|                                | THA                | 18  | 35.2 (12.4)  |         |
| Time to worst pain             | TKA                | 47  | 34.6 (14.6)  | NS      |
|                                | THA                | 26  | 34.3 (18.0)  |         |
| Time to first prn opioid       | TKA                | 46  | 17.9 (10.3)  | NS      |
|                                | THA                | 26  | 15.1 (19.7)  |         |
| Time to first scheduled opioid | TKA                | 26  | 15.3 (6.3)   | NS      |
|                                | THA                | 11  | 15.7 (7.3)   |         |

The number of subjects is not the same for all variables due to some patients leaving the items blank or indicating “unsure” on the survey.  
prn = as needed; THA = total hip arthroplasty; TKA = total knee arthroplasty.

**Table 3.** Block duration time parameters after hip or knee replacement, based on nerve block treatment group

| Parameter                                               | Block Treatment | No. | Mean, h | Difference (95% CI), h | P Value |
|---------------------------------------------------------|-----------------|-----|---------|------------------------|---------|
| Time to start of pain                                   | BPV-BCD         | 57  | 25.7    | 14.6                   | <0.001  |
|                                                         | Plain BPV       | 15  | 11.2    | (8.2 to 20.9)          |         |
| Time to no pain relief                                  | BPV-BCD         | 41  | 32.4    | 17.0                   | <0.001  |
|                                                         | Plain BPV       | 13  | 15.3    | (9.9 to 24.1)          |         |
| Time to resolution of numbness                          | BPV-BCD         | 40  | 36.6    | 15.6                   | <0.001  |
|                                                         | Plain BPV       | 13  | 21.1    | (7.8 to 23.3)          |         |
| Time to worst pain                                      | BPV-BCD         | 57  | 38.6    | 18.8                   | <0.001  |
|                                                         | Plain BPV       | 16  | 19.9    | (11.0 to 26.6)         |         |
| Block duration note estimate*                           | BPV-BCD         | 59  | 34.2    | 11.8                   | 0.002   |
|                                                         | Plain BPV       | 15  | 22.3    | (4.5 to 19.2)          |         |
| Time to first prn opioid                                | BPV-BCD         | 56  | 19.6    | 12.2                   | 0.002   |
|                                                         | Plain BPV       | 16  | 7.4     | (4.6 to 19.8)          |         |
| Time to first scheduled opioid                          | BPV-BCD         | 30  | 15.7    | 1.3                    | 0.649   |
|                                                         | Plain BPV       | 7   | 14.4    | (-4.3 to 6.8)          |         |
| Time to first prn opioid in absence of scheduled opioid | BPV-BCD         | 29  | 21.0    | 14.0                   | 0.035   |
|                                                         | Plain BPV       | 9   | 7.0     | (1.1 to 27.0)          |         |

The number of subjects is not the same for all variables due to some patients leaving the items blank or indicating “unsure” on the survey.

BPV = bupivacaine; BPV-BCD = bupivacaine-buprenorphine-clonidine-dexamethasone; prn = as needed.

\*Block duration note estimate is the physician's estimate of analgesic duration (in hours) using solely the peak pain data as charted by nurses and/or physical therapists. This was the methodology used for analgesic duration in our original benchmark report [8].

**Table 4.** Pearson correlation coefficients of nerve block duration data time parameters

| Parameter                      | Time to<br>“Start Pain” | Time to<br>“No Pain Relief” | Time Until<br>“Numbness Wore Off” | Time to<br>“Worst Pain” | Block Duration<br>Note Estimate* | Time to First<br>prn Opioid |
|--------------------------------|-------------------------|-----------------------------|-----------------------------------|-------------------------|----------------------------------|-----------------------------|
| Time to “start pain”           | 1.0                     | 0.643**                     | 0.525***                          | 0.519***                | 0.406***                         | 0.228                       |
| Time to “no pain relief”       |                         | 1.0                         | 0.780***                          | 0.723***                | 0.456***                         | 0.413**                     |
| Time until “numbness wore off” |                         |                             | 1.0                               | 0.666***                | 0.393**                          | 0.377**                     |
| Time to “worst pain”           |                         |                             |                                   | 1.0                     | 0.381**                          | 0.420***                    |
| Block duration note estimate*  |                         |                             |                                   |                         | 1.0                              | 0.320**                     |
| Time to first prn opioid       |                         |                             |                                   |                         |                                  | 1.0                         |

For these correlations, we refer to correlation coefficients of 0.700 and higher as “high positive,” coefficients of 0.500 to 0.699 as “moderate positive,” and statistically significant coefficients with values between 0.30 to 0.499 as “low positive” [19].

prn = as needed.

\*Block duration note estimate is the physician’s estimate of block duration (in hours) using solely the peak rebound pain data as charted by nurses and/or physical therapists. This was the methodology used for block duration in our original benchmark report [8].

\*\* $P < 0.01$ ;

\*\*\* $P < 0.001$ .

**Table 5.** Cumulative oral morphine equivalent consumption for every additional 24 hours following BPV vs BPV-BCD nerve blocks for total knee or total hip arthroplasty

| Time Elapsed, h | BPV (N = 16),<br>Cumulative mg | BPV-BCD (N = 62),<br>Cumulative mg | Mean Difference<br>(95% CI) | P Value* |
|-----------------|--------------------------------|------------------------------------|-----------------------------|----------|
| 24 (N = 78)     | 80                             | 42                                 | 38<br>(17 to 58)            | <0.001   |
| 48 (N = 78)     | 149                            | 93                                 | 56<br>(20 to 91)            | 0.003    |
| 72 (N = 59)     | 186                            | 123                                | 63<br>(12 to 115)           | 0.016    |
| 96 (N = 31)     | 200                            | 132                                | 68<br>(9 to 127)            | 0.024    |

Data are presented as mean, in milligrams. The presence of perineural buprenorphine was not incorporated into the OME calculations. There were significant differences in cumulative daily OME consumption at every 24-hour interval.

BPV = bupivacaine; BPV-BCD = bupivacaine–buprenorphine–clonidine–dexamethasone; OME = oral morphine equivalent.

\*By two-tailed  $t$  test, for cumulative OMEs consumed every 24 hours, ending with total time elapsed of 96 hours. Patients receiving BPV-BCD consumed significantly less OMEs, at all cumulative time points, compared with the BPV group.

between these two different definitions of worst pain scores relative to baseline pain score with movement, the Pearson correlation coefficient was  $r = 0.518$  ( $P < 0.001$ ).

The most strongly positive correlations were among “time to no pain relief” and “time until numbness wore off,” along with “time to no pain relief” and “time to worst pain.” Notably, there was no correlation (coefficient = 0.228) (Table 4) between “time to start pain” and “time to first prn opioid.” The other correlations with “time to first prn opioid” were only low positive (0.320–0.420), as were the correlations with the nerve block duration note estimate (0.381–0.456). In other words, the nerve block duration note nurse-charted parameters were equal to, to slightly better than, time to first prn opioid, as far as correlation with patient-reported block duration parameters.

Table 5 shows that the group differences in cumulative opioid consumption were significantly less through each cumulative 24-hour segment up to 96 hours. The most robust opioid-sparing effect was seen on day 1 (i.e., the first 24 hours after surgery, a mean difference of 38 mg oral morphine equivalents,  $P < 0.001$ ).

There was one possibly block-related adverse event. One patient had foot drop after TKA, which resolved spontaneously over the next three to four months. The sciatic block for this patient was placed with ultrasound guidance; the intraoperative tourniquet time was 125 minutes at 300 mmHg. We did not “break the blind” as to the treatment received as we plan on a more thorough analysis of all data from this first cohort in addition to the second cohort which has since been enrolled. Sciatic (specifically, common peroneal) nerve palsy can be common in small studies after knee replacement surgery (0–10%) [21], although the incidence in large consecutive case series ranges from 0.3% to 1.3% [21].

## Discussion

This study is the first of its kind to compare head-to-head multimodal perineural analgesia (MMPNA) with BPV-BCD against plain BPV for patients undergoing knee or hip replacement surgery with dual blocks of L2–4 and L4–S3. Analgesic duration of BPV-BCD was two or more times greater than that of plain BPV. There were no serious complications that could be specifically traced to the

blocks. However, such blocks with motor and sensory involvement may not be as useful as intended when active physical therapy after THA or TKA (including ambulation) is to begin the same day as surgery. Such long-duration blocks may be useful for other indications that do not entail immediate weight-bearing ambulation or for the motor-sparing blocks that have emerged since this study was first designed in 2013 (such as adductor canal and/or IPACK blocks).

The extended analgesic duration of the BPV-BCD block is due to the combination of the four drugs. Meta-analysis reveals that buprenorphine yields 8.6 hours of additional nerve block duration [1] when added perineurally as opposed to systemically (such as intramuscular). Clonidine, in meta-analysis [2], adds two hours to the block duration of bupivacaine (yielding a statistically significant improvement of uncertain clinical significance), but in this meta-analysis, most patients received a perineural dose of 150 mcg (as opposed to 50 mcg in our study). Dexamethasone, in meta-analysis [3], adds four hours to the block duration of bupivacaine (yielding a statistically significant improvement), but only adds two hours to the block duration of ropivacaine (a nonsignificant improvement); the dexamethasone dose in this meta-analysis exceeded 4 mg, whereas our total perineural dose across two blocks was 2 mg. It is difficult to determine if the effects of buprenorphine, clonidine, and dexamethasone as a combination provide additive or synergistic prolongation of analgesic duration. However, clonidine and dexamethasone as dual adjuvants in nerve blocks have been reported to be associated with less postoperative nausea and/or vomiting [22].

One shortcoming of the study was the proportion of patients who were uncertain about the timing of their blocks wearing off. Six of 78 patients did not report a time to “start of pain,” and five of 78 did not report a time until “worst pain.” More notably, 24 of 78 did not report a time to “no pain relief,” and 25 of 78 did not report a time until “numbness resolved.” In our study, it appeared to be more difficult to determine analgesic duration than in the YaDeau et al. study of interscalene block patients undergoing total shoulder arthroplasty (their study showed duration benefits of adding BCD to ropivacaine) [6]. This is likely because in our study patients underwent four separate regional anesthesia procedures (spinal, L2–L4 block, L4–S3 block, periarticular infiltration) that are known to produce varying degrees of numbness, and our patients may have had difficulty distinguishing “one numbness” from “the others.” However, in the study of YaDeau et al. [6], general anesthesia plus interscalene nerve block for shoulder surgery was used; general anesthesia would not be perceived as “numbness resolving,” and the resolving brachial plexus block was more easily detected as “numbness resolving.”

At the time the study was designed in the year 2013, the profound duration of numbness and motor block produced by BPV-BCD was not expected to adversely

affect early rehabilitation efforts on postoperative day 1 after surgery. When the standard of care changed for early rehabilitation after THA and TKA on the day of surgery (at our institution in 2018), we authors were forced to reconstruct the research protocol to incorporate a shorter-duration motor block while still utilizing adjuvants for focal MMPNA. Differences in analgesic duration in this first cohort of patients, compared with our next cohort of patients which has since been enrolled, require further detailed inquiry as to the effects on postoperative physical therapy progress and hospital discharge. Along similar lines, the authors felt it was appropriate to submit this “preliminary report” on analgesic duration (a secondary outcome) ahead of the manuscript with the study’s stated primary aims (outcomes of pain and physical function). This is because the duration of analgesia, which was remarkable in this first cohort, would have been demoted to a lesser outcome in light of the necessary changes in the protocol to enable SDPT, had analgesic duration been reported in a more comprehensive manuscript.

In the context of the clinical assessment of block duration, the nerve block duration note (based on the nursing team recording of the peak postoperative pain score) appears to be as robust an indicator of analgesic duration as time to first “as needed” (prn) opioid. However, both parameters only provide low positive correlations to the other patient-reported block duration parameters “time to start pain,” “time until no pain relief,” “time until numbness wore off,” and “time to worst pain.” Meanwhile, “time until no pain relief” and “time until numbness wore off” indicate a strong correlation between patients’ perception of numbness and perception of pain relief, indicating that perhaps opioid analgesia is a lower tier of analgesia than numbness from a nerve block. The disadvantage of this construct is that the same numbness may prove to inhibit physical therapy efforts after surgery. Finally, we found no significant correlation (coefficient = 0.228) (Table 4) between “time to start pain” and “time to first opioid.” This likely indicates an emerging patient preference to avoid the onset of any pain (let alone worst pain) and to preempt pain with analgesic medication; this finding should caution investigators regarding future study design and selection of end points that entail “time to first opioid.”

There are several other study limitations. First, the study was terminated early after the enrollment and completion of only 51 TKA and 27 THA patients (as opposed to 100 of each type of surgical patient, as originally designed). Next, we presented data on analgesic duration, as opposed to the primary study outcome of pain responses on validated questionnaires. Another limitation is the 4:1 randomization that we used. Our justification at the time the grant application was written was because of BPV-BCD being our institution’s standard of care for nerve block drugs. Critics of unequal allocation enrollment (such as Hey and Kimmelman [23]) point out

that researchers often justify unbalanced enrollment strategies in two-arm trials by invoking issues such as patient demand or preferences of a study site in a multicenter trial. Hey and Kimmelman opine that neither justification is justified ethically or scientifically and declare equal allocation to be the most efficient approach to minimize “certain threats to internal validity.” Therefore, future trials involving prospective comparisons of multimodal nerve blocks should consider these positions in earnest.

Another study limitation is the effects of the “opioid epidemic” on postoperative prescribing patterns. For this study, the timing of this public health crisis declaration was approximately half-way through the trial. Fortunately, this did not have any apparent adverse effect on data analysis of first-opioid consumption. Another limitation is that perineural buprenorphine has oral morphine equivalent analgesia, but it is unquantifiable. An additional limitation is that our control patients did not receive systemic (as opposed to perineural) buprenorphine, clonidine, or dexamethasone. Next, our somewhat low enrollment rate (17%) may adversely affect the generalizability and/or representativeness of the study results. Finally, our large number of exclusions after randomization (20/98) was related to study termination or changes in the surgical procedure.

To conclude, BPV-BCD provided 26–39 hours of perineural analgesia in the L2–L4 and L4–S3 nerve distributions after hip/knee replacement surgery, compared with 11–21 hours for plain BPV. These BPV-BCD blocks were opioid-sparing.

## Acknowledgments

The authors would like to acknowledge Samantha Bonant, MS, CCRP, for her extensive regulatory coordination efforts and Shirley Podnar, PharmD, and Meghan Tamburino, BS, for their Investigational Drug Service efforts. We also thank Patrice Price, CRNP, for prerecruiting efforts originating from the Preoperative IMPACT Clinic, VAPHS. We also acknowledge VAPHS team certified registered nurse anesthetists Gail Bader, Laura Barnes, Sally Ollio, Catherine Thompson, Deana Lewis, Angela Jaap, Timothy Shapiro, and Diane Boettger for mixing the study drug injections and coordinating the complex schedules related to this task. We acknowledge Michael Mangione, MD, who served as Chief of Anesthesia and Medical Monitor during the course of the study as described herein. We acknowledge Kathryn Brown, MS, PT, David Wortman, MPT, Deborah Kowatch, DPT, and Visnja King, DPT, who served as physical therapists and data entry/quality control specialists during the course of the trial. We also thank Laurel Koval, MOT, OTR/L, and Brad Krushinski, DPT, for their supervisory efforts of the occupational and physical therapists at VAPHS. We also acknowledge Robert T. Modrak, PA-C, for his contributions related to the

description of the intra- and peri-articular injections and for his team-centered communication throughout the course of the study. We also thank Harvey P. Insler, MD, staff orthopedic surgeon, VAPHS. Finally, we acknowledge Peter Z. Cohen, MD, the Chief of Orthopedic Surgery at VAPHS, during the study as described herein.

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# A Tale of Two Cohorts: The Trials and Tribulations of Ever-Changing Orthopedic / Acute Pain Medicine Hospital Practices During the Execution of Military-Funded Clinical–Translational Research (2013–2021)

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**Funding sources:** This commentary is based on the study underwritten by a grant supported by the Office of the Assistant Secretary of Defense for Health Affairs through the FY14 DoD USAMRMC Broad Agency Announcement under Award No. W81XWH-15-1-0294. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense or the Veterans Health Administration.

**Conflicts of interest:** The authors report no conflicts of interest.

The implementation of the clinical trial reported in the accompanying article by Williams et al. [1] encountered several complications related to regulatory processes and the changing practices of the hospital at which the study was conducted. The present editorial reports on the complexities faced during trial execution, with the hope that this information may be helpful to other clinical researchers.

## Study Time Frame and Military Relevance

In 2013, when we applied for funding for this project, single-injection nerve blocks with plain bupivacaine (BPV) were known to provide 15–20 hours of pain relief. Our institution, however, had used multimodal perineural analgesic with buprenorphine, clonidine, and dexamethasone (BCD) for more than 1,000 patients since 2011 [2]. These nerve blocks seemed to provide analgesia of a longer duration, but the method had not been compared against a known benchmark of plain BPV in a clinical trial. The military motivation for our research was to investigate whether single-injection multimodal perineural BPV-BCD nerve blocks could provide sufficient analgesic benefits to facilitate lengthy transport of lower-extremity polytrauma injured soldiers from the

battlefield to definitive care. The study was awarded funding, with the original dates being October 2015 to September 2019. Unfortunately, we were confronted by several enrollment and timeline challenges, and, despite receiving a study extension, were unable to reach our enrollment milestone.

## Trial Tribulation 1: Inability to Enroll the Target Sample Size

The target sample size for the approved randomized clinical trial was a total of 200 patients, with 100 undergoing total hip arthroplasty and 100 total knee arthroplasty. This target sample size was not obtained because of regulatory challenges, limited collaboration from orthopedic surgeons, and changes in policies that affected surgical eligibility. The regulatory challenges included that the institutional review boards of three institutions had oversight of the protocol: VA Pittsburgh, University of Pittsburgh, and Department of Defense. The most labor-intensive institutional review board requirement involved Food and Drug Administration Investigational New Drug application and approval. To our knowledge, no Food and Drug Administration Investigational New Drug approval was required on any previous or

subsequent study of two or more of the BCD adjuvants combined with local anesthetics. Before the study could begin, the Food and Drug Administration required a clinical safety chart review of our nerve block cases from 2011 to 2014 [3], comprising more than 1,800 patients receiving BCD. These regulatory requirements delayed the study start by 6–8 months; recruitment was originally scheduled for March 2016, but because of the regulatory requirements, the first patient was not actually enrolled until November 2016.

The study was also negatively impacted by limited collaboration from orthopedic surgeons. The recruitment process for this study involved more than 2 weeks of interactions with potential participants to enable sufficient time to mail study information, schedule appointments, and bring participants back to the hospital for screening and baseline procedures ahead of the surgical date. However, the surgeons did not have sufficient time to discuss the study with their patients. Other surgeons scheduled the surgery to occur in less than 2 weeks from initial clinic presentation, for pragmatic reasons. Moreover, the orthopedic practice instituted a policy to not operate electively on patients with positive urine cotinine tests. This was a major hurdle because of the prevalence of veterans' tobacco use. Lastly, patient enrollment required substantial effort and resources: Only 17% of screened patients (98 of 571) were eligible to participate because of these timing complexities and other exclusions, reinforcing that regardless of the trial sponsor, recruitment of patients who meet the requirements of clinical trial protocols can be difficult [4].

### **Trial Tribulation 2: Study Interruption, Protocol Change, and Creation of a Second Study Cohort**

In mid-2018, the VA Pittsburgh adopted the evolving nationwide guideline of same-day physical therapy after elective joint arthroplasty, which was first proposed by the American Academy of Orthopaedic Surgeons in December 2015. Processes shifted from initial patient mobilization occurring on the first postoperative day (POD#1) to instead occurring immediately after surgery (POD#0). As a result, the Data Safety Monitoring Board suspended study enrollment until we diluted the nerve block local anesthetic concentrations to enable patients' safe engagement in same-day physical therapy and gained all necessary re-approvals. At the time of study suspension, 98 veterans (48% of the target sample) had been enrolled in the study.

The Data Safety Monitoring Board recommended that we obtain all regulatory approvals and continue study enrollment under the revised study protocol to obtain valuable preliminary data for this new standard of care of starting physical therapy on POD#0. Because of the differences in drug concentrations, the Data Safety

Monitoring Board also suggested we not combine data from the two study cohorts but rather provide descriptive statistics of the second cohort and visually compare them with the cohort enrolled before study suspension. We used our first cohort data of 98 participants for our first *Pain Medicine* article from this study population, addressing analgesic duration from the described nerve blocks [5].

The regulatory approvals kept the study suspended for nearly 7 months, until late June 2019. Because the original funding period went through September 2019, we proposed a no-cost extension until March 2020 to enroll the new cohort. However, recruitment efforts did not fare much better, resulting in 40 additional participants in the second cohort. As before, challenges included the surgical team scheduling surgery in immediately available time slots created by the negative urine cotinine requirement, very few days after the veteran initially presented to the clinic. On a positive note, unrecruited potential study subjects were routed into same-day mobilization anesthesia clinical pathways, which provided other opportunities to further evaluate BCD nerve blocks, resulting in related publications in *Pain Medicine* [6–9]; these reports inform future research directions in ways we could not have with the prospective randomized trial.

### **The Future of MultiModal PeriNeural Analgesia (MMPNA) for Same-Day Mobilization After Elective Joint Replacement**

With the change in nerve block methodology away from the originally planned, potent BPV-BCD (e.g., with 0.25% BPV concentration in the L2–L4 distribution), the next inquiry entails MMPNA interventions (i.e., drugs other than local anesthetics) as proximal nerve/plexus motor-sparing blocks, to better position patients for POD#0 mobilization. Since 2013, a plethora of ultrasound-guided motor-sparing distal-to-plexus block techniques have been described, which are beyond the scope of this editorial and accompanying article [1]. In the meantime, one could consider combined spinal anesthesia with both motor-sparing lumbar plexus psoas compartment and L4–S3 distribution analgesic blocks. Specifically, lumbar plexus analgesia would be with either midazolam or ultra-low-concentration BPV, combined with BCD [7, 9], while L4–S3 analgesia entails midazolam-BCD blocks of the sciatic nerve for total knee arthroplasty, and of the parasacral plexus for total hip arthroplasty. These motor-sparing blocks allow for both analgesia and same-day mobilization, ultimately involving two complex nerve stimulator techniques and three overall injections (with the third injection being the spinal anesthetic). Another option worth considering for total knee arthroplasty is lumbar plexus psoas compartment and sciatic blocks (a two-needle, complex

nerve-stimulator injection technique), entailing a combination of shorter-acting local anesthetics (e.g., mepivacaine with or without dilute BPV) and BCD to promote a surgical block without general or spinal anesthesia and rapid (~4–6 hours from time of block) motor resolution to allow same-day physical therapy [8]. These three described L2–S3 blocks (L2–L4 lumbar plexus/psoas compartment, L4–S3 parasacral plexus, and L4–S3 Labat-approach gluteal sciatic) do not require ultrasound guidance but do require training and experience with landmark-based peripheral nerve stimulation.

The simplest, most motor-sparing answer with effective analgesia may lie in the single-injection spinal anesthetic, with a mixture of surgery-duration local anesthetic and longer-duration preservative-free morphine, for which a meta-analysis has recently been published [10]. Our clinical observations [9] of intrathecal morphine with regard to successful same-day ambulation with a low-burden POD#0 pain/opioid outcome have proved to be quite promising. The new clinical research question now lies in *how many antiemetic categories* should be used to offset the potentially emetogenic intrathecal morphine [6, 10], as opposed to how many MMPNA preservative-free drugs to inject at the level of the plexus or proximal nerve.

### Take-Home Points with Regard to Military Lower-Extremity Polytrauma Analgesia and Same-Day Ambulation After Elective Joint Arthroplasty

Appropriate concentrations of BPV (e.g., 0.25%) combined with the described [1, 2, 5] doses of BCD will provide 24–36 hours of analgesic duration [2, 5], translating to less pain [1]. With regard to anesthesia for elective joint arthroplasty, the described nerve stimulator blocks have likely become an intergenerational lost art since 2013, when we first submitted this grant application. Ultimately, with appropriate multiple-agent antiemetic prophylaxis [6], intrathecal morphine for joint arthroplasty may prove equal or superior to peripheral/plexus blocks with ultrasound and/or nerve stimulation, with lo-

cal anesthetic and/or MMPNA mixtures, with or without local anesthetic infiltration by our orthopedic colleagues.

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# 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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**Funding sources:** This study is underwritten by a grant (to Dr. Williams) from the Department of Defense, United States (DoD Award # W81XWH-15-1-0294). The U.S. Army Medical Research Acquisition Activity (820 Chandler Street, Fort Detrick, MD 21702-5014) is the awarding and administering acquisition office. This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the FY14 DoD USAMRMC Broad Agency Announcement under Award No. W81XWH-15-1-0294. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense or the Veterans Health Administration.

**Conflicts of interest:** The authors report no conflicts.

Received on 11 August 2021; revised on 13 October 2021; Accepted on 21 October 2021

## 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<sup>2</sup> 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 ( $\leq 69$ ,  $>69$  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  $\mu$ g fentanyl, 4 mg midazolam, and/or 40  $\mu$ g 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  $\mu$ g, clonidine 25  $\mu$ g, 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  $\geq 100$  kg) of 0.5% bupivacaine, 300  $\mu$ g 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

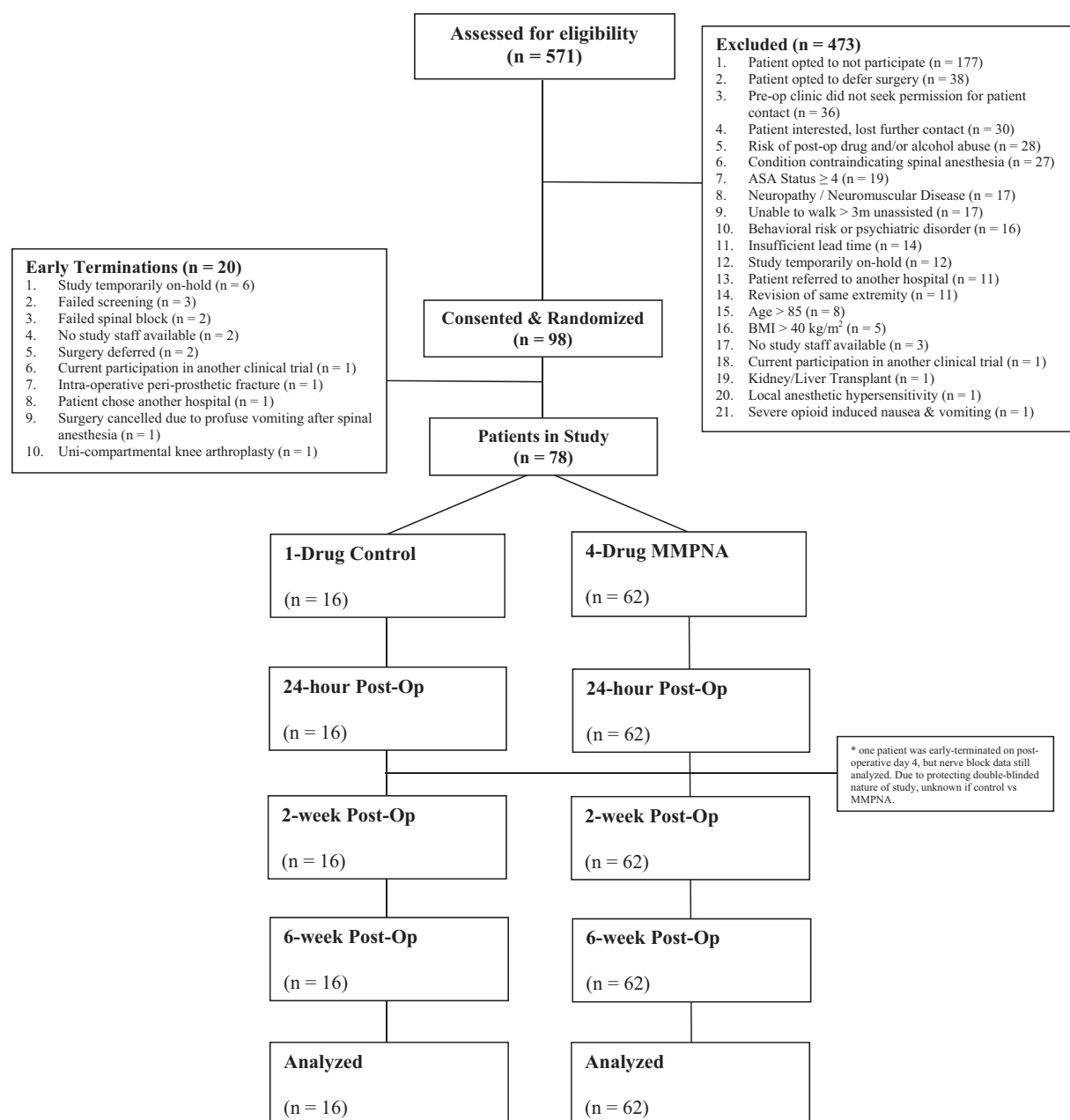


**Figure 1.** CONSORT diagram: first cohort. Reproduced, with permission, from Williams BA, Ibinson JW, Ritter ME, et al. Extended perineural analgesia after hip and knee replacement when buprenorphine-clonidine-dexamethasone is added to bupivacaine: Preliminary report from a randomized clinical trial. *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

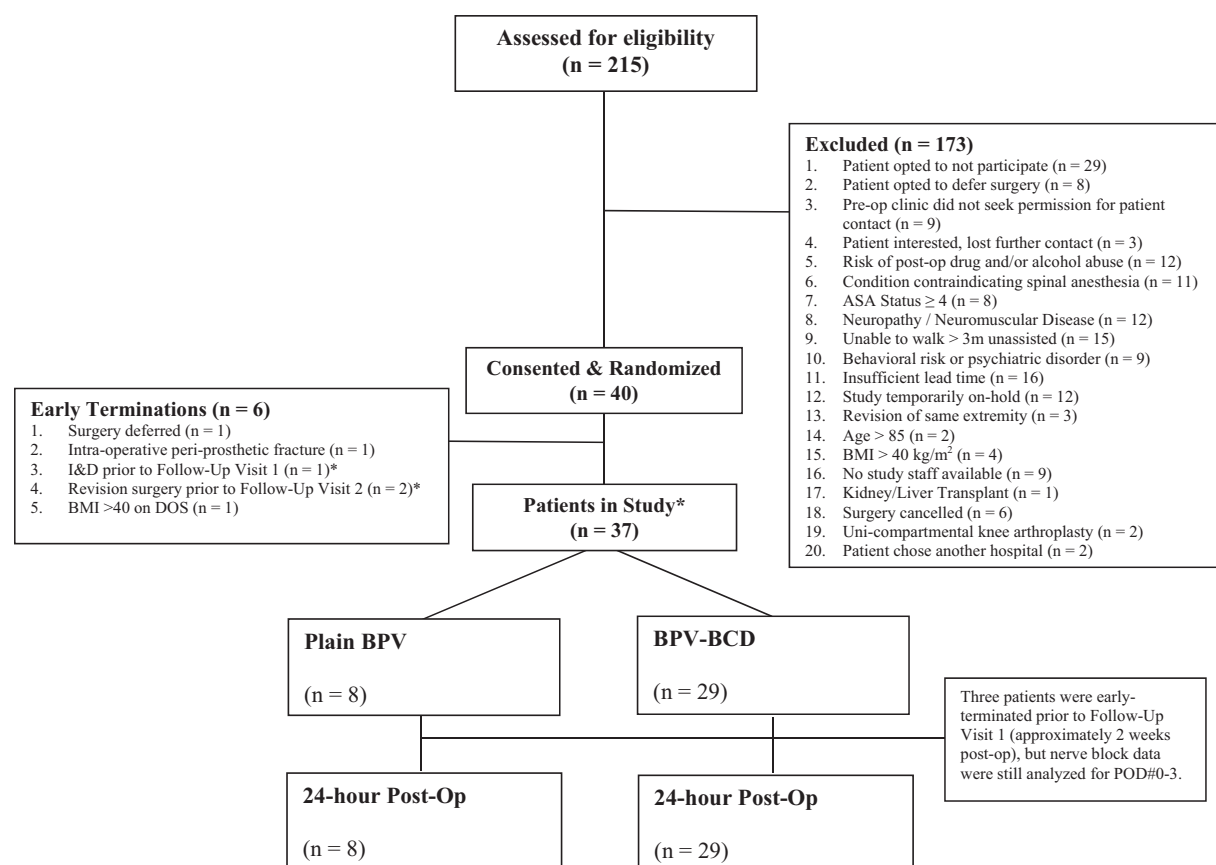


**Figure 2.** CONSORT diagram: second cohort.

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

| Characteristic                                 | Main Cohort (THA and TKA) |                  |           | Second Cohort (THA and TKA, Exploratory Only) |                   |
|------------------------------------------------|---------------------------|------------------|-----------|-----------------------------------------------|-------------------|
|                                                | 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 <sup>2</sup> , 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

Second Cohort<sup>†</sup>

\*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 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

<sup>5</sup>The DVPRS is a graphic pain rating scale on which patients can rate their pain on a scale of 0–10, with 0 being the worst possible pain; it includes four questions on how the prior 24 hours' pain has affected the patient's ac-

Downloaded from <https://academic.oup.com/painmedicine/advance-article/doi/10.1093/pm/pnab325/6420267> by VA Pittsburgh Healthcare System user on 10 December 2021

**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

| Outcomes of Quality of Recovery, Physical Function, and Range of Motion | Main Cohort*       |                 | Second Cohort†         |                                             |                    |                 |                        |                                     |
|-------------------------------------------------------------------------|--------------------|-----------------|------------------------|---------------------------------------------|--------------------|-----------------|------------------------|-------------------------------------|
|                                                                         | 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 <sup>‡</sup> total                                                  | -                  | -               | -                      | 13 (-5 to 32)<br>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)<br>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 <sup>§</sup>                                      | -                  | -               | -                      | -0.5 (-1.4 to 0.4)<br>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 <sup>¶</sup>                                            | -                  | -               | -                      | -0.08 (-0.27 to 0.11)<br>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 <sup>  </sup>                                           |                    |                 |                        |                                             |                    |                 |                        |                                     |
| Knee flexion (°)                                                        | -                  | -               | -                      | -17 (-31 to -3)<br>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)<br>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)<br>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)<br>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).

<sup>‡</sup>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").<sup>§</sup>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.<sup>¶</sup>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.<sup>||</sup>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.

## Acknowledgments

The authors acknowledge and thank Shirley Podnar, PharmD, and Meghan Tamburino, BS, Veterans Health Foundation, Pittsburgh, PA, USA, for their Investigational Drug Service efforts. We also thank Patrice Price, CRNP, for pre-recruiting efforts originating from the Preoperative IMPACT Clinic, VAPHS (Pittsburgh, PA, USA), during the main study cohort, and Ms. Price along with Rebecca Durian, CRNP, Rachael Baber, CRNP, Mary Jayne Nick, CRNP, and Kimberly Cehic, CRNP, during the second cohort. We also acknowledge and thank VAPHS team certified registered nurse anesthetists Gail Bader, Laura Barnes, Sally Ollio,

Catherine Thompson, Deana Lewis, Angela Jaap, Timothy Shapiro, and Diane Boettger for mixing the study drug injections and coordinating the complex schedules related to this task. We acknowledge and thank Michael P. Mangione, MD, who served as Chief of Anesthesia, VAPHS, and Medical Monitor during the main cohort, and Todd M. Oravitz, MD, who served as Medical Monitor during the second cohort. We acknowledge and thank Hulimanagala R. Rakesh, MD, for the anesthesia care of some study patients at VAPHS during the main cohort. We acknowledge and thank Kathryn Brown, MS, PT, David Wortman, MPT, Deborah Kowatch, DPT, and Visnja King, DPT, who served as physical therapists (University of Pittsburgh, Department of Physical Therapy, Pittsburgh, PA, USA) and data entry/quality control specialists during the course of the trial. We also thank Laurel Koval, MOT, OTR/L, and Brad Krushinski, DPT, both from VAPHS, for their supervisory efforts of the occupational and physical therapists at VAPHS. We also thank Robert T. Modrak, PA-C, VAPHS, for his contributions related to the description of the local anesthetic infiltration injections and for his team-centered communication throughout the course of the study. We also thank Harvey P. Insler, MD, staff orthopedic surgeon, VAPHS. We acknowledge Peter Z. Cohen, MD, the Chief of Orthopedic Surgery at VAPHS, Pittsburgh, PA, USA, during the main cohort, and Patrick J. McMahon, MD, Chief of Orthopedic Surgery at VAPHS, during the second cohort.

## Supplementary Data

Supplementary Data may be found online at <http://pain-medicine.oxfordjournals.org>.

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