

AWARD NUMBER: W81XWH-15-1-0294

TITLE: 4-Drug Nerve Block Versus plain Local Anesthetic for Knee and Hip Arthroplasty Analgesia in Veterans

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14. ABSTRACT During the research period, recruitment has resumed after being on hold from November 2018 to May 2019. The DSMB requested that the study be placed on a temporary enrollment hold, while the study team updated the protocol to correspond to new standard of care changes within the Pittsburgh VA. Study enrollment was placed on hold for administrative reasons, there were no safety issues. Enrollment into Cohort 2 started in May of 2019, to date we have enrolled 139 patients overall (including Cohorts 1 and 2). It is our hope to enroll 50 patients into Cohort 2, we currently have 41 patients enrolled in Cohort 2. Study enrollment is scheduled to end 1/31/2020. The study continues to be regularly monitored by the University of Pittsburgh Research and Compliance Office, to date, all of the routine monitoring visits have been successful and no major issues have been identified. Team efforts continue for the management of regulatory requirements. These include: (i) Food and Drug Administration Investigational New Drug (FDA-IND) annual review and approval, (ii) University of Pittsburgh and VA Pittsburgh Institutional Review Board (IRB) amendments, annual reviews, and approvals, (iii) University of Pittsburgh Research Conduct and Compliance Office, (iv) VA Pittsburgh Research and Development Quality Assurance, (v) University of Pittsburgh Data Safety Monitoring Board, and ultimately (vi) DOD Human Research Protection Office (HRPO) annual review and approval.					
15. SUBJECT TERMS Bupivacaine, clonidine, buprenorphine, dexamethasone, nerve block, pain, hip, knee					
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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 will evaluate an innovative 36-hour single-injection nerve block that combines a low-concentration local anesthetic with other pain relievers injected near the nerve. In veterans undergoing total hip or knee replacement, we will compare 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 are clonidine-buprenorphine-dexamethasone (CBD). 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 will be measured using both validated and innovative methods. Preoperative baseline survey data will be collected, and patient-follow-up will take place during days 1-4, and at 2 and 6 weeks after surgery. This research is projected to take approximately four years. We project that the 36-hour single-injection 4-drug nerve block will have 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 is now complete, and was 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 recently published in the journal *Pain Medicine*.

- 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) is now complete. 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 are 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. Since enrollment began, 94 subjects have been enrolled/consented. As of this report, 75 subjects have successfully completed the study. Enrollment is on-going, and the study team has developed a Recruitment flyer and flip card that have been approved by the IRB and placed throughout the Pittsburgh VA and the Erie VA to help boost enrollment.

Task 3.

Currently data verification is on-going and will continue until all study data has been collected.

An interim analysis of the Short-Form McGill Pain Questionnaire (SF-MPQ-version 2) was completed on the first 25 knees and the first 27 hips. No statistically significant difference was found between the 4-drug multimodal perineural analgesia (MMPNA) and Bupivacaine groups. Since then, interim analysis of the first studied cohort (n=78) was performed with respect to nerve block duration. Based on the specific question asked, the 4-drug MMPNA group had nerve block durations of 26-39 hr, versus 11-21 hr for plain bupivacaine). These outcomes have been submitted in manuscript form, and the manuscript is currently under revision and review with the journal Pain Medicine.

Section 3.3: OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT

As reported in recent 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' currently- and previously-DoD-funded work comprised a significant portion of the day's curriculum. As soon as a transcript of the public workshop is available, it will be accessible at <https://www.regulations.gov>. or via weblinks originating from the workshop's website at <https://www.fda.gov/Drugs/NewsEvents/ucm571360.htm>. As of January 22, 2020, transcripts are not yet available.

Section 3.4: HOW THE RESULTS WERE DISSEMINATED

As described in the 2016 Annual Report, we consider ourselves fortunate that the peer-reviewed journal *Pain Medicine* was interested in the subject matter that we were required to evaluate for the FDA-IND application. The two manuscripts that were transformed from FDA-IND responses to peer-reviewed manuscripts are listed above. Results from our first interim analysis have been submitted in manuscript form, and the manuscript is currently under revision and review with the journal Pain Medicine.

Section 3.5: PLANS DURING THE NEXT REPORTING PERIOD

During the next reporting period, enrollment will close. Enrollment into the study will close January 31, 2020. At this time, final study clean up and analysis will occur.

4. Impact

See “Presentations” in Section 6 below

“Nothing to Report” applies to the following sections:

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 reporting period.

Section 5.3: CHANGES THAT HAD A SIGNIFICANT IMPACT ON EXPENDITURES

No changes to report for this reporting period.

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.

6. Products (since 2016 Annual Report)

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

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 HAVE 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 has 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 has 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 handles all regulatory submissions, including IRB, FDA, IDSMB and DoD submissions.
Funding Support: Veterans Research Foundation of Pittsburgh, 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 Research Foundation of Pittsburgh, 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 Quad Chart

9. Appendices

- Quad Chart

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

IND 127171: BPV+BCD

Williams et al, unpublished preliminary data

Parameter	BPV-BCD hr (SD)	BPV plain hr (SD)	P value
Time to "Start Pain"	25.7 (11.9)	11.2 (6.3)	<0.001
Time to "No Pain Relief"	32.3 (11.7)	15.3 (8.8)	<0.001
Time to "Numbness Wore Off"	36.6 (12.4)	21.1 (10.6)	<0.001
Time to "Worst Pain"	38.6 (14.3)	19.9 (11.9)	<0.001

THA & TKA patients receiving L2-L4 and L4-S3 blocks preop, combined with bupivacaine spinal anesthesia and postop multimodal analgesia. N=76.
BCD doses: 300+300 mcg, 25+25 mcg, 1+1 mg

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		█	█	█	█
Estimated Budget (\$K)		\$587	\$545	\$550	\$269

Goals/Milestones

CY16 Goal – Regulatory approvals and study enrollment

FDA-IND approval. IRB approvals. Study staff/ infrastructure.

USAMRMC HRPO revisions approved.

Subject pre-screening/enrollment – started 9/26/2016

CY17 Goals – Study enrollment and regulatory updates

Participant screening (As of 11 October 2018, 94 participants enrolled)

Data integrity, interim safety analysis, regulatory updates

CY18 Goals – Same as for CY 17

CY19 Goal – Finish study enrollment, scholarly output

Submit manuscript for peer-reviewed publication

Comments/Challenges/Issues/Concerns

- The study is now off of administrative hold and we are currently enrolling into Cohort-2. Enrollment will end 1/31/2020.

Budget Expenditure to Date (as of 7 January 2020)

Budget: \$1,951,591

Actual Expenditure: \$1,749,062