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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CONTRACTING ORGANIZATION: UNIVERSITY OF PITTSBURGH
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During the research period, recruitment began, and to date we have 42 patients enrolled/consented into the study. As of October 5, 2017, 27 patients have successfully completed the study. 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-

None listed

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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, 42 subjects have been enrolled/consented. As of this report, 27 subjects have successfully completed the study. Enrollment is on-going, and the study team has developed a Recruitment flyer that will be placed throughout the Pittsburgh VA to help boost enrollment. A study flipcard is currently being developed and is currently submitted for IRB approval in the near future, as another recruitment item that will be available to prospective patients. The study team is also working to gain IRB and public affairs approval to place these two recruitment items at the Erie VAMC as well, to help boost enrollment. All Erie VAMC patients who are scheduled to have their knee or hip replaced, have the actual surgery here at VA Pittsburgh, therefore, the study team feels that by promoting the study at the Erie VAMC, we may be able to help boost enrollment.

Task 3.
Currently data verification is on-going and will continue until all study data has been collected.

We will conduct our first data analysis corresponding with the completion of 25 knee replacement subjects, and 25 hip replacement subjects. We anticipate 25 knee replacement subjects to be completed before 25 hip replacement subjects.

Section 3.3: OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT

Nothing to report

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. Otherwise, nothing to report.

Section 3.5: PLANS DURING THE NEXT REPORTING PERIOD

The study team will continue to enroll patients and look for additional ways to help boost enrollment. We will also add anesthesiologist co-investigators (to only the VA IRB forms) to ensure that any potential study patient will have available anesthesiologist coverage in the setting of simultaneous cases.

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

During this report period, the Pennsylvania Supreme Court ruled that in the state of PA, only study physicians can consent patients for an IND study. The study team has made adjustments to the recruitment procedures to reflect this new ruling.

To date, the local IRB requires a non-descript process where patients must be “invited to say no” to a research pursuit before any study concept is discussed with them. This IRB-based non-starter is illogical in our study since 80% of research-consenting patients would receive our nerve block institutional standard of care, while the other 20% still receive an active control (non-placebo) nerve block. We sense that this IRB-driven semantic separation from reality has been the primary cause of recruitment delays behind original projections. We are now working to revise our recruitment strategy to help boost enrollment. We have received IRB approval for recruitment posters, patient recruitment flip-cards are currently at the IRB for approval and we are looking into the option of using recruitment letters (by US mail).

Section 5.3: CHANGES THAT HAD A SIGNIFICANT IMPACT ON EXPENDITURES

During this report period, the responsibility of data verification was transferred from the statisticians (StatCore team) to the University of Pittsburgh-hired physical therapists. The hired University physical therapists had time available, which was already underwritten,; therefore, it was logical that they could assume this responsibility. This in turn freed up extra funds that were previously needed to pay StatCore for this duty.

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 Adminstration
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

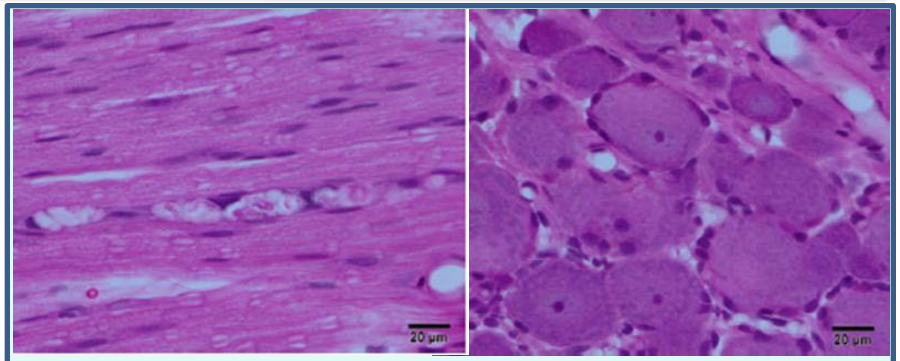
PI: Brian A. Williams, MD, MBA **Org: The University of Pittsburgh** **Award Amount:** $1,950,591

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
- 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 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.



In previous DoD-funded in vivo *rat studies, the 4-drug nerve block was equally safe to the nerve as was plain bupivacaine*

After due diligence in rat studies *in vitro* and *in vivo*, we have gained FDA approval of our IND application, and IRB approval, to evaluate the 4-drug single-injection nerve block (bupivacaine-clonidine-buprenorphine-dexamethasone) in Veterans.

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**	**$557**	**$262**

Updated: Pittsburgh, PA; 05 October 2017

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 10/05/2017, 42 participants enrolled)
☐ Data integrity, interim safety analysis, regulatory updates (underway)
CY18 Goals – Same as for CY 17
CY19 Goal – Finish study enrollment, scholarly output
☐ Submit manuscripts for peer-reviewed publication

Comments/Challenges/Issues/Concerns

- Preparing IRB amendment to gain approval of recruitment advertising flipcard, to help boost enrollment.
- Working with Erie and Pittsburgh public affairs to allow us to promote our study at the Erie VAMC (hang flyer, and make flipcards available).
- Preparing for early data analysis, mantaining study blinding.

Budget Expenditure to Date (as of 05 October 2017)
24-month Budget: $1,131,541
24-month Actual Expenditure:$859,919