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

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

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.

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) VA Pittsburgh Research and Development Quality Assurance, (IV) University of Pittsburgh Data Safety Monitoring Board, and ultimately (V) 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, 138 subjects have been enrolled/consented. Enrollment is now complete, 112 subjects successfully completed the study.

Task 3.
Data verification is complete. The study is currently in data analysis.

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 February 22, 2021, transcripts are not yet available; we do not anticipate any transcripts at this point in time after the event.

Section 3.4: HOW THE RESULTS WERE DISSEMINATED

Since the last report, we have continued our data analysis and have submitted 2 new manuscripts (described further below). A total of 138 patients were enrolled into this study (Cohort 1: 98, Cohort 2: 40). During this review period, the study team has begun data analysis and manuscript submission of preliminary data; our earlier-submitted manuscript is now published online (*Pain Medicine;* https://doi.org/10.1093/pm/pnaa229). The preliminary data showed positive results towards the BPV-BCD (MMPNA) treatment arm. The block duration data presented in previous quad charts/quarterly reports showed these differences. Please also note that block duration was a secondary outcome, not a key/primary outcome. However, as a secondary outcome, it carries important clinical relevance to our original military medicine application of analgesia for long transport.

We have undergone preliminary data analysis of our primary outcome, and found that continuous pain is less on postoperative day 1 for pooled total knee and total hip data after BPV-BCD treatment. This satisfies our primary outcome, as disclosed on Clinicaltrials.gov.

We have also undergone some exploratory data analyses, and found that hip replacement patients receiving BPV-BCD nerve blocks had less pain at 6 weeks after surgery than did patients receiving plain BPV nerve blocks. This was true both in our first cohort and our second cohort. This 6-week outcome after hip surgery was an unexpected but paradigm-shifting finding.

Two manuscripts were submitted very recently with these and other findings. First was "Pain and Physical Function the Day-of and Day-after Primary Hip and Knee Replacement when Buprenorphine-Clonidine-Dexamethasone is added to Bupivacaine for Lower Extremity Nerve/Plexus

Blocks: Exploratory Outcomes from a Two-Cohort Randomized Clinical Trial." This is catalogued as PME-ORR-Feb-21-169. Second was "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)." This is catalogued as PME-ED-Feb-21-168. We were certainly honored when the journal (*Pain Medicine*) editor invited us to submit an editorial simultaneously with our core manuscript. We submitted these 2 manuscripts on 24 February 2021.

In late 2020, we also submitted two grant applications that leveraged this new 6-week pain relief finding: (i) a study of total knees and total hips that has as its primary outcome pain at 6 weeks after surgery (VA Merit Review application), and (ii) a study of carpal and cubital tunnel surgery patients undergoing various nerve block mixtures to determine pain 2 weeks after surgery (DoD-CPMRP-200008).

Section 3.5: PLANS DURING THE NEXT REPORTING PERIOD

During the next reporting period, we will continue with data analysis.

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 in our studies.

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

- 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.

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

BPV+BCD vs. Plain BPV

Williams et al, unpublished preliminary data, FDA-IND 127171

At 6-week follow-up, THA patients after BPV-BCD nerve blocks had less neuropathic pain than did patients who had plain BPV, based on difference-from-baseline scores of the SF-MPQ.

Parameter	BPV-BCD (n=21)	Plain BPV (n=6)	Grp.Diff (95% CI)	P value
Neuropathic Pain	-11 (11)	-2 (5)	-10 (-17, -3)	0.008

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**

Updated: Pittsburgh, PA; 21 January 2021

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
☑ Data integrity, interim safety analysis, regulatory updates
CY18 Goals – Same as for CY 17
CY19-20 Goals – Finish study enrollment, scholarly output
☑ Submit manuscripts for peer-reviewed publication

Comments/Challenges/Issues/Concerns

- Study enrollment is now complete. Total subjects enrolled = 138.

Budget Expenditure to Date (as of 21 January 2021)
Budget: $1,950,591.00
Actual Expenditure:$1,872,933.98