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Safety and Efficacy of ‘SURGISPRAY’ Compared to Placebo to Prevent Intraoperative and Postoperative Blood Loss and Provide Analgesia in Major Orthopaedic Surgery: A Study Proposal

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1. Purpose and rationale:

Minimizing intraoperative and postoperative blood loss associated with major orthopaedic surgical procedures, avoiding postoperative wound hematoma formations, and enhancing analgesia associated with these procedures has been a major focus of orthopaedic surgeons and researchers over the past half dozen years. [3,10,15]

All patients who undergo major orthopaedic surgical procedures performed at Wayne Memorial Hospital in Honesdale (WMH) by the study investigators (i.e., Dr. Mogerman and Dr. Caucci) receive a multimodal approach to perioperative analgesia, which has become standard at most US institutions performing joint replacement surgery within the last few years. [7.8] Such patients receive Celebrex 400 mg, OxyContin 10 mg, Gabapentin 600 mg, Tramadol 50 mg orally, and application of a transdermal Clonidine 0.1 mg patch. In addition, the patients also receive a postoperative regimen of OxyContin 10 mg and Celebrex 200 mg orally.

The use of an intravenous perioperative protocol of tranexamic acid, which has been well established to reduce blood loss, has also become standard at most US institutions performing joint replacement surgery over this period of time as well. [2,6,14]
Many products have also been developed that can be applied topically to the surgical site to control massive bleeding, although these are very expensive, and basically are only used in catastrophic situations, e.g. intra-operative injury to a major artery. [5,9,12,13]

It should be noted that over the past several years, many orthopaedic services, including that at WMH, have been using various topical solutions intra-operatively to help control hemorrhage and improve analgesia, [1,4,11] in addition to the above-referenced peri-operative standards (i.e., oral Celebrex, OxyContin, Gabapentin, Tramadol, and transdermal Clonidine), post-operative regimen (i.e., oral OxyContin and Celebrex), and tranexamic acid protocol.

However, based on a literature review as well as study investigator professional expertise and procedural knowledge, none of these various topical solutions (in layperson terms, known as a ‘wash’ or ‘spray’ in or on the exposed joint and joint space) have been studied in regard to safety or efficacy, nor has there been any standardization of components or dosage. Rather, there is individual surgeon decision or preference for these procedures, which is arguably a subjective, or at the least an inter-variable, determination across surgeons.

For several years, the study investigators at WMH have routinely applied to the surgical site in essentially all major orthopaedic operations and procedures a ‘surgispray’ solution (i.e., ‘wash’ or ‘spray’) containing Morphine 2 mg, Epinephrine 300 mcg, Naropin 1% 150 mg, and Ketorolac Tromethamine 15 mg diluted in normal saline to make up 120 cc of sterile solution, prepared per physician order by the hospital pharmacy. In the rare patient with documented, reported, or suspected allergy to one of the above components, the ‘surgispray’ is prepared without that component. In the course of hundreds of major orthopaedic procedures (e.g., shoulder, hip, and knee replacements, as well as major fractures) by the study investigators as the operating surgeon, there have been no adverse reactions detected of any kind. Thus, the impression of the study investigators as the operating surgeons is that the usage of this preparation of ‘surgispray’ has been very effective in the vast majority of cases, and at least partially effective in all cases, as well as safe.

The composition of the ‘surgispray’ used by the study investigators at WMH was recently modified in an effort to avoid using Class 1 narcotic and to presumably increase efficacy by: (1) substituting Butorphanol 2mg, a synthetic narcotic agonist with a strong safety profile, for the Morphine 2mg, which are essentially equivalent dosages; (2) increasing Naropin to 300 mg; and (3) increasing Ketorolac Tromethamine to 20 mg. There have been no adverse reactions detected, and efficacy appears to be unchanged.

The purpose of the proposed study is to determine the safety and efficacy of using this recent novel and inexpensive combination of generic medications diluted in normal saline (referred to as ‘surgispray’), applied topically as a ‘wash’ or ‘spray’ at the time of surgery in or on the exposed surgical site of joint and joint space as compared to placebo of only diluted normal saline, to reduce blood loss and also pain associated with major orthopaedic procedures.

2. Description of human subjects:

The participants for this study will only include adults, and will include males and females aged 18 years and older.
Participants will be persons who volunteer and provide informed consent to participate, and who undergo a study-eligible major orthopaedic surgical procedure at Wayne Memorial Hospital (WMH) by either study investigator Dr. Mogerman or by study investigator Dr. Caucci.

The study-eligible major orthopaedic surgical procedures include: (1) shoulder replacement; (2) hip replacement; (3) knee replacement; and/or (4) major fracture repair.

3. Methods of recruitment:

Participants will be recruited prospectively and in a rolling process upon start of the study.

Patients will be made aware of and offered the opportunity to participate in the study by members of the study team, medical office staff working with the PI, and/or healthcare extension personnel working with the PI in cases and situations where a study-eligible major orthopaedic procedure is already decided upon as a treatment option by the surgeon and patient. Participants will be informed of all viable treatment options and procedures by the PI or his/her designee.

Participants will be informed that their level of treatment or care will not be affected by their choice or decision either way (to participate or not participate in the study), and will not be coerced or pressured to join the study.

Participants will be informed that there is, on average, an equal possibility (i.e., 50/50 chance) that they will receive an active drug (i.e., medicine) or a placebo, ‘sham’, or ‘dummy’ (i.e., sterile salt water) ‘wash’ or ‘spray’ on their joint or into their joint space during the procedure as part of the study, but that they will otherwise receive the same level and caliber of care and medication as if they were not involved in the study. The participants will be informed that one of the major points of the study is to determine if this ‘wash’ or ‘spray’ is helpful or not to the patient and to the patient’s recovery after the procedure, in terms of pain, discomfort, and bleeding.

Participants will be provided the opportunity to ask questions or ask for clarification on any points, will provide informed consent, and will sign the informed consent document for the study before being considered to be officially enrolled as a participant in the study.

4. Research protocol:

The proposed study would be a prospective, randomized, double-blinded, placebo-controlled, single site (WMH) clinical study involving adult patients undergoing major orthopaedic procedures (i.e., shoulder replacement, hip replacement, knee replacement, and/or major fracture repair) performed by the study investigators.

All the participants that consent to and join the study will be randomly designated or assigned in a 1:1 ratio to either the: (1) experimental/intervention group (i.e., surgispray); or (2) control group (i.e., saline spray placebo) at time of enrollment into the study.

The intervention group will receive:

(1) Peri-operative standard WMH regimen
   Celebrex, 400 mg, po
   OxyContin, 10 mg, po
Gabapentin, 600 mg, po
Tramadol, 50 mg, po
Clonidine, 0.1 mg, transdermal patch

(2) Post-operative standard WMH regimen
   OxyContin, 10 mg, po
   Celebrex, 200 mg, po

(3) Transexamic acid protocol regimen

(4) Standard orthopaedic surgical measures for homeostasis

(5) Standard orthopaedic surgical measures for antimicrobial prophylaxis

(6) Surgispray, new formulation (all diluted in normal saline to make 120 cc sterile solution)
   Butorphanol, 2 mg
   Epinephrine, 300 mcg
   Naropin 1%, 300 mg
   Ketorolac Tromethamine, 20 mg

The control group (i.e., placebo group) will receive:

(1) Peri-operative standard WMH regimen
   Celebrex, 400 mg, po
   OxyContin, 10 mg, po
   Gabapentin, 600 mg, po
   Tramadol, 50 mg, po
   Clonidine, 0.1 mg, transdermal patch

(2) Post-operative standard WMH regimen
   OxyContin, 10 mg, po
   Celebrex, 200 mg, po

(3) Transexamic acid protocol regimen

(4) Standard orthopaedic surgical measures for homeostasis

(5) Standard orthopaedic surgical measures for antimicrobial prophylaxis

(6) Sterile Saline solution spray or wash (normal saline only, to make 120 cc sterile solution)

The new 'surgispray' solution will be provided by the hospital pharmacy, prepared either in
house or by a WMH pharmacy-approved outside source, with code numbers.

The sterile saline solution or wash (placebo) will be provided by the hospital pharmacy,
prepared either in-house or by a WMH pharmacy-approved outside source, with code numbers.

All study subjects will receive as established standard of care and as described above:
(1) standard multimodal pain relief regimen (i.e., peri-operative WMH regimen); (2) standard
multimodal pain relief regimen (i.e., post-operative WMH regimen); (3) standard protocol of transexamic acid; and (4) standard orthopaedic surgical measures for homeostasis.

The following data will be tracked in determining the results of the study. There will be planned
and scheduled serial assessments on post-operative days (POD) 1, 15, and 30, as appropriate
and applicable, by study personnel:
   1. Date of Form/Assessment
   2. Participant Study ID#
   3. Diagnosis
   4. Description of procedure

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5. Date of procedure
6. Amount of ‘wash’ or ‘spray’ used during the procedure
7. Blood hemoglobin (Hgb) level, pre-operative
8. Blood hemoglobin (Hgb) level, post-operative
9. Estimated Blood Loss (EBL), operative
10. Adverse Reaction or Event description, type, and date, if noted
11. Wound Healing, as determined by the operating surgeon and study team on a Likert scale of 1-9, with 1 = wound dehiscence/infection and 9 = excellent.
12. Participant Pain, as determined by the operating surgeon and study team on a Likert scale of 1-9, with 1 = none and 9 = severe
13. Participant Function, as determined by the operating surgeon and study team on a Likert scale of 1-9, with 1 = poor and 9 = severe
14. Overall Efficacy as determined by the operating surgeon and study team on a Likert scale of 1-9, with 1 = poor/minimally effective and 9 = excellent/very effective
15. Wound Drainage on Dressing as described by operating surgeon and study team on a Likert scale of 1-9, with 1 = minimal drainage on dressing and 9 = large amount of drainage on dressing
16. Number of Transfusions
17. Other Narcotic Analgesics type and amount

Power and Sample Size Calculations, Recruitment, and Enrollment

The study will utilize rolling recruitment and enrollment, and is anticipated to be conducted over a 6 to 18 month period, with 2 to 6 months for final data analysis and publication.

Based on power and sample size calculations to sufficiently power the study for statistical analysis and to limit Type II error, it is estimated that a total of 36 participants (n = 36) will need to be analyzed, with random assignment to either intervention group or control group in a 1:1 ratio. The analysis goal and target will be 18 persons (n1 = 18) in the Intervention Group (i.e., surgispray) and 18 persons (n2 = 18) in the Control Group (i.e., placebo).

There is expected participant attrition and data loss in such a study, however, and thus it is the recruitment and enrollment goal/target of this study is a total of 46 participants (n = 46), with random assignment to either intervention group or control group in a 1:1 ratio. The recruitment and enrollment goal/target will be 23 persons (n1 = 23) in the Intervention Group (i.e., surgispray) and 23 persons (n2 = 23) in the Control Group (i.e., placebo).

The following assumptions and variables were utilized in the power calculations, sample size calculations, and attrition rates to determine recruitment goals and targets for enrollment:
(1) Assumed significance criterion of 0.05
(2) Assumed μ1 = 5.0 on 9 point scale (mean of control group)
(3) Assumed μ2 = 7.0 on 9 point scale (mean of intervention group)
(4) Per 2 and 3 above, assumed magnitude of effect or effect size = 2.0, or = 23%
(5) Assumed σ = 3.0 on 9 point scale, thus 99% of data contained (standard deviation)
(6) Assumed power = 0.80
(7) Assumed data attrition or participant dropout rate = 25%

Data Analysis Plan

The data will be analyzed for 6 distinct study outcomes or end-points, and will be addressed as follows.
**Outcome 1: Analgesia or Pain Control**
This is a discrete variable, expressed as a subjective proxy measurement on a Likert scale of 1-9 for the participant as interpreted and determined by a surgeon and another member of the study team during post-operative and recovery care.

**Outcome 2: Wound Healing**
This is a discrete variable, expressed as a subjective direct measurement on a Likert scale of 1-9 as determined and recorded by a surgeon and another member of the study team during post-operative and recovery care.

**Outcome 3: Participant Functioning**
This is a discrete variable, expressed as a subjective proxy measurement on a Likert scale of 1-9 for the participant as interpreted and determined by a surgeon and another member of the study team during post-operative and recovery care.

**Outcome 4: Overall Efficacy**
This is a discrete variable, expressed as a subjective direct measurement on a Likert scale of 1-9 for the participant as interpreted and determined by a surgeon and another member of the study team during post-operative and recovery care.

**Outcome 5: Surgical Site Wound Drainage**
This is a discrete variable, expressed as a subjective direct measurement on a Likert scale of 1-9 for the participant as interpreted and determined by a surgeon and another member of the study team during post-operative and recovery care.

**Outcome 6: Percentage (%) of Adverse Reaction or Event**
This is a continuous variable, expressed as a frequency, count, or ratio.

The data will be analyzed primarily in 2 distinct intra-group and inter-group comparisons involving the Intervention Group (surgispray) and the Control Group (placebo), with respective hypotheses or *a priori* assumptions as below:

1. **Intervention Group (surgispray) versus Control Group (placebo)**
   These data for Outcomes 1, 2, 3, 4, and 5 as above will be analyzed utilizing a non-paired T-test. These data will be collected via a 9-point Likert scale (discrete variable, subjective measurement), and will be reported with a Mean, 95% Confidence Interval, and p-value. The average of surgeon and non-surgeon subjective measurements will be utilized for this analysis. In addition, inter-rater variability will be determined to compare surgeon assessment measurements to non-surgeon assessment measurements.

2. **Intervention Group (surgispray) versus Control Group (placebo)**
   These data for Outcome 6 as above will be analyzed utilizing a non-paired T-test.

The null hypothesis (H₀) or *a priori* assumption is no significant difference or no significant change observed for Intervention Group (surgispray) versus Control Group (placebo).

The alternative hypothesis (H₁) is a significant increase or increase in mean change observed for the Intervention Group (surgispray) versus Control Group (placebo).

5. **Compensation and cost:**

Participants will not be compensated in any way for participating in the study.

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There is no anticipated cost to participate in this study per se, above and beyond the cost incurred to the participant as a result of the orthopaedic procedure at WMH and any costs associated or resultant to the procedure, pre-operative, peri-operative, post-operative, and follow-up care costs. The participant will be responsible for any costs incurred as a result of, due to, or associated with surgical procedure complications, complications clinical course, recovery, adverse events, or follow-up.

6. Risks to subjects:

All participants in this study will, as defined above, fit inclusion criteria of persons who undergo a major orthopaedic surgical procedure at Wayne Memorial Hospital (WMH). As such, any and all participants would incur or be subject to the risk commensurate with that procedure or commensurate with any major surgical procedure, peri-operative, and post-operative course, such as but not limited to complications from: anesthesia; pain; bleeding; hemorrhage; stroke; infarction; emboli/clots; infection; disability; and death. The study-eligible major orthopaedic surgical procedures include: (1) shoulder replacement; (2) hip replacement; (3) knee replacement; and/or (4) major fracture repair.

Regarding possible study-related or study intervention-related risks, participants could be subject to risks beyond those mentioned above, including but not limited to: allergic or adverse reaction to components of 'surgispray' – either locally or systemically; swelling; and edema.

The outcome and safety data will be reviewed monthly by a non-blinded study team member (i.e., the study team data monitor) and a report with participants de-identified will be shared with the study team to serve as a study safety monitoring committee. In the event that these periodically evaluated outcome and safety data demonstrate any marked benefit or safety concern of one treatment arm or intervention over another, then termination of the study will be considered, as appropriate and applicable.

There is a risk of a potential breach of confidentiality for participants. Precautions will be taken to prevent any breach in confidentiality. While data collection and data analysis is ongoing, participant name will be removed and instead be assigned a specific study identification number or ID as appropriate.

7. Benefits:

It is unknown and unproven at this point if the participants will receive any direct benefit from participating in this study or from the treatment or interventions being studied.

However, it is intended that this study will help to address a current limitation or gap in the medical literature and professional knowledge, which is expected to benefit future patients as well as the participant if undergoing an applicable procedure or surgery in the future.

8. Procedures for obtaining informed consent:

Informed consent will be obtained pre-operatively from all participants involved in the study.

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Patients will be made aware of and offered the opportunity to participate in the study by members of the study team, medical office staff working with the PI, and/or healthcare extension personnel working with the PI in cases and situations where a study-eligible major orthopaedic procedure is already decided upon as a treatment option by the surgeon and patient. Participants will be informed of all viable treatment options and procedures by the PI or his/her designee.

Participants will be informed that their level of treatment or care will not be affected by their choice or decision either way (to participate or not participate in the study), and will not be coerced or pressured to join the study.

Participants will be informed that there is, on average, an equal possibility (i.e., 50/50 chance) that they will receive an active drug (i.e., medicine) or a placebo, sham, or dummy (i.e., sterile salt water) ‘wash’ or ‘spray’ on their joint or into their joint space during the procedure as part of the study, but that they will otherwise receive the same level and caliber of care and medication as if they were not involved in the study. The participants will be informed that one of the major points of the study is to determine if this ‘wash’ or ‘spray’ is helpful or not to the patient and to the patient’s recovery after the procedure, in terms of pain, discomfort, and bleeding.

Participants will not be compensated in any way for participating in the study.

There is no anticipated cost to participate in this study per se, above and beyond the cost incurred to the participant as a result of the orthopaedic procedure at WMH and any costs associated or resultant to the procedure, pre-operative, peri-operative, post-operative, and follow-up care costs. The participant will be responsible for any costs incurred as a result of, due to, or associated with surgical procedure complications, complications clinical course, recovery, adverse events, or follow-up. Participants will be provided the opportunity to ask questions or ask for clarification on any points, will provide informed consent, and will sign the informed consent document for the study before being considered to be officially enrolled as a participant in the study.

9. Confidentiality of the data:

Any data transferred electronically will be stored on a password-protected personal computers belonging to and/or used by study team researchers. There will be no individual identifying data presented or made available outside the research study team that could potentially identify a participant. The data collected will be password protected, and have access limited to study staff and study personnel.

Non-blinded or non-masked data will be available to a study team member (i.e., the study team data monitor), and the pharmacy staff or pharmacist will be non-blinded or non-masked as the preparer of the treatment (i.e., surgispray or saline).

All data and information regarding participants will be treated as confidential in nature, and will only be shared as needed for study purposes and clinical care purposes per all applicable WMH regulations and requirements.

10. Public release of data:

The researchers, investigators, and/or study team may publish collected data and information.
Identifying information will not be reported, and only aggregated and de-identified data will be reported and presented.

The results of the study may be presented at an educational, professional, institutional, quality improvement, or public meeting or conference, as well as published or shared as appropriate.

11. Description and source of secondary data:

No additional or secondary sources of data are anticipated to be utilized, other than any mentioned previously.

The researchers, investigators, and/or study team may compare results to other studies that were similar in the past, and may potentially perform a meta-analysis of pooled data from several studies as appropriate.

12. References:

Addendum: Informed consent will be obtained from participants in the offices or clinics of the study investigators in non-emergent and non-urgent cases only: in cases involving major fractures, informed consent will be obtained in the Emergency Department or on the nursing units, especially emphasizing to this emotionally vulnerable group of patients that their participation decision will not affect their care in any way.