BIOMEDICAL RESEARCH PROTOCOL
UNIVERSITY OF MISSOURI

Project Title: The Use of Intranasal Calcitonin to Improve Pain and Activity in Elderly Pelvic Ring Injuries
IRB Number: 2013172
Version Number: 2
Version Date: 09/13/2019
Principal Investigator: Brett D. Crist, MD
Funding Source: AOTNA Grant

I. Research Objectives/Background

1. Include primary, secondary, and exploratory objectives.
   Primary Objective: To compare acute pain over a three-month period in geriatric patients with pelvic ring injuries who receive intranasal salmon calcitonin with those who do not receive intranasal salmon calcitonin
   Secondary Objective: To compare function and activity over a three-month period in geriatric patients with pelvic ring injuries who are treated nonoperatively and receive intranasal salmon calcitonin with those who do not receive intranasal salmon calcitonin.
   Exploratory objective: To compare radiographic healing in geriatric patients with pelvic ring injuries who receive intranasal salmon calcitonin with those who do not receive intranasal salmon calcitonin
2. Include background and rationale for initiating the study. Includes pre-clinical and clinical data, current experiences with procedures, drug, or device, and any other relevant information to justify the research.

   It is anticipated that geriatric patients who sustain pelvic ring injuries and are treated nonoperatively will demonstrate decreased pain scores and improved subjective and objective function if they are started on intranasal salmon calcitonin within 5 days of injury compared to patients who do not receive intranasal salmon calcitonin. It is anticipated the decreased pain and improved activity/function will prevent complications associated with extended periods of bedrest.

II. Drugs/Biologics/Devices

1. Include the product, dose, route, and regimen.
   200 IU of ISC(intranasal salmon calcitonin) daily for three months

2. Include the rationale for choosing the drug/biologic and dose, or for choosing the device to be used.
   Intranasal salmon calcitonin (ISC) has been demonstrated to decrease pain and improve the level of activity in patients with acute vertebral osteoporotic compression fractures when administered within the first 5 days of onset of pain/injury. Recently, randomized

clinical trials have demonstrated calcitonin to be superior to NSAIDS in promoting early ambulation and preventing functional deterioration in patients with acute osteoporotic vertebral compression fractures.

2. Include the standard reference therapy against which the study product is being compared, or if the reference is a placebo. Include justification for inclusion of a placebo or non-treatment group. The study product is being compared to geriatric patients who are being treated nonoperatively and receive standard of care that does not include intranasal salmon calcitonin. Many geriatric patients with pelvic ring injuries who are treated nonoperatively. However, all patients will be prescribed calcium and vitamin D supplementation.

III. Recruitment Process

1. Describe the recruitment process; including how and where recruitment will take place. Recruitment will take place in the Emergency Room or at University of Missouri Main Hospital. Patients who have pelvic ring injuries will be screened for enrollment.
2. Describe any screening/baseline procedures.
   Patients will be screened by an attending orthopaedic traumatologist determining the type of pelvic ring injury based on x-rays and CT scans and decide upon operative treatment vs. nonoperative treatment. Patients who are deemed to benefit from nonoperative treatment will be screened for enrollment. Any patients who meet the criteria for age will then be further screened for inclusion and exclusion criteria as outlined below.

IV. Consent Process

1. Describe the consent process; including who will be approached for consent and what type of consent will be obtained from each subject population, if there is more than one. Study personnel will approach patient about research study in the emergency room or on the designated floor where they are admitted. Informed consent will be obtained at that time.

V. Inclusion/Exclusion Criteria

1. List the inclusion and exclusion criteria.
2. Inclusion:
   - Males or females over the age of 65 who sustain isolated pelvic ring injuries via a low-energy mechanism.

   Exclusion:
   - An open pelvic ring fracture
   - Concomitant acetabular fracture
   - They are on ISC prior to enrollment
   - Use of medications for the treatment or prevention of Osteoporosis with the exemption of Vitamin D and Calcium supplementation
   - Allergic or have contraindications to calcitonin or salmon

- Sustain other injuries in their spine (excluding transverse and spinous process fractures) or lower extremities
- Unwilling to participate in the study
- Nonambulatory at baseline
- Neurologic deficit associated with the pelvic ring injury

3. Describe restrictions on participation and appropriate screening procedures to ensure that the restrictions are maintained, including pregnancy testing.
    - All patients meeting inclusion criteria will be screened by study personnel.

VI. Number of Subjects

1. Include anticipated enrollment number in this study. Include a break-down in numbers if there is more than one subject population.
    - 60 patients; 25 each group; 10 screen fails
2. Include statistical analysis or other justification for the number of subjects enrolled.

VII. Study Procedures/ Design/Treatment Plan

1. Include study procedures/design/plan; include the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care). Include study duration and number of study visits required.
   After obtaining informed consent, the following will be obtained:

   Baseline: Treatment group will be prescribed 200IU of ISC daily for a period of 3 months. The control group will not be prescribed calcitonin. Participants will complete research only Iowa pelvis score questionnaire, SF-36 questionnaire and visual analogue scale (VAS) to assess subjective pain and function. Two-week follow up visit post discharge: participants will complete Iowa pelvis score questionnaire, SF-36 questionnaire and VAS to assess subjective pain and function. Participants will be referred for a standard of care DEXA bone density scan if they have no previous diagnosis of osteoporosis and no history of previous scan within a year. Six weeks post discharge: participants will complete Iowa pelvis score questionnaire, SF-36 questionnaire and VAS to assess subjective pain and function. Participants will undergo standard of care radiographic analysis of pelvic ring injury with AP/inlet and outlet pelvic x-rays 4. Twelve weeks post discharge: Participants will complete Iowa pelvis score questionnaire, SF-36 questionnaire and VAS to assess subjective pain and function. Participants will undergo standard of care radiographic analysis of pelvic ring injury with AP/inlet and outlet pelvic x-rays - Participants will perform a timed up and go (TUG) test.

2. Blinding, including justification for blinding or not blinding the trial. Describe un-blinding procedures.

After informed consent is obtained, all patients who meet eligibility criteria will be randomized into one of two groups. Randomization will be achieved by numbering 50 sealed white envelopes (25 control, 25 treatment). There is no blinding to the randomization. It would be difficult to blind the participants, or the research personnel. We do not believe there will be any significant bias that can be corrected with blinding.

Treatment: 200IUof ISC daily for a period of 3 month

Control: Will not be prescribed calcitonin (ISC)

3. Justification of why participants will not receive routine care or will have current therapy stopped.
   Patients will receive routine care during this study.
4. Definition of treatment failure or participant removal criteria.
   Patients will be removed if they do not return to their follow-up visits or do not complete the study specific tasks.
5. Description of what happens to participants receiving therapy when study ends or if participation in the study ends prematurely.
   Routine care will continue per the physician's standard of care treatment.
6. Include sub-studies or banking information (correlative/special studies)
   None

VIII. Potential Risks/Adverse Events

1. Describe reasonably foreseeable risks or discomforts to the subjects and steps to minimize risks. This study is expected to have minimal risk to the patient since we are using the FDA approved dosage for this study. This risk will be minimized by going over the purpose of the study with the patient before obtaining consent, and allowing withdrawal from the study at any time.

2. Describe any stopping rules. Stopping rules would include any reactions or side effects to ISC or per the provider's discretion.

3. Include the plan for reporting unanticipated problems or deviations. This plan must include a five-day reporting requirement to the IRB once becoming aware of an event.

IX. Anticipated Benefits

1. Include both direct and indirect benefits for either the individual or society.
   The benefit to society is to provide data that will eventually lead to decrease pain in patients with pelvic ring fractures by using intranasal Calcitonin within 5 days of injury.

No direct benefits will be promised. Subjects can expect to help add to public knowledge about the effect of pelvic rings fractures in elderly patients.

X. Compensation

1. Describe the amount, method, and timing of disbursement. Compensation can include checks, cash, gifts, extra/course credit, etc.
   Subjects will be paid $10 for each visit they complete but will only receive one check once they finish their 12 week visit. Subjects will be paid $30 at their final visit.

XI. Costs

1. Detail costs of study procedures, drugs, biologics, or devices and identify who will cover the cost. All costs are being covered by the AOTNA grant. No additional costs to the participants for being enrolled in the study. Participants will pay for all standard of care costs.

   Cost:
   $1,800 – Calcitonin Costs ($72 per participant x 25 participants)
   $1,500 – Participant Stipend ($30 per participant x 50 participants)
   $6,500 – Study Coordinator (0.7 calendar months, 5.9% effort, of assistance, covering salary and benefits for this effort)
   Total: $9,800

XII. Data Safety Monitoring Plan

Describe the plan to monitor the data, if necessary. A plan is required for treatment and/or intervention studies, sensitive data are being collected, there is a possibility for subjects to experience adverse events, etc. Adverse events will be reported to the IRB as necessary within 5 days of becoming aware of the event.

1. The plan should include when something needs to be reported
2. The frequency of the monitoring, such as points in time or after a specific number of participants are enrolled
3. Who will conduct the monitoring, such as a data board, medical monitor, investigator, independent physician; the specific data to be monitored
4. Procedures for analysis and interpretation of the data
5. Actions to be taken upon specific events or end points
6. Procedures for communication from the data monitor to this site.

XIV. References/Appendices

1. Include findings from a literature search or pilot study must be outlined including appropriate detailed references to earlier studies and data.

1. Karponis A, Rizou S, Pallis D, Zafeiris CP, Georgiou DF, Galanos A, Giannoulis F, Lyritis GP. Analgesic effect of nasal salmon calcitonin during the early post-fracture period of the distal radius fracture. J Musculoskelet Neuronal Interact. 2015 Jun;15(2):186-9.
2. Knopp JA, Diner BM, Blitz M, Lyritis GP, Rowe BH. Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. Osteoporos Int. 2005 Oct;16(10):1281-90.
3. Lyritis GP, Paspati I, Karachalios T, Ioakimidis D, Skarantavos G, Lyritis PG. Pain relief from nasal salmon calcitonin in osteoporotic vertebral crush fractures. A double blind, placebo-controlled clinical study. Acta Orthop Scand Suppl. 1997 Oct;275:112-4.
4. Lyritis GP, Tsakalakos N, Magiasis B, Karachalios T, Yiatzides A, Tsekoura M. Analgesic effect of salmon calcitonin in osteoporotic vertebral fractures: a double-blind placebo- controlled study. Calcif Tissue Int. 1991 Dec;49(6):369-72.
5. 5. Hoch A, Ozkurtul O, Pieroh P, Josten C, Bohme, J. Outcome and 2-Year Survival Rate in Elderly Patients With Lateral Compression Fractures of the Pelvis. Geriatr Orthop Surg Rehabil. 2017 Mar;8(1):3-9.
6. Leslie MP, Baumgaertner MR. Osteoporotic pelvic ring injuries. Orthop Clin North Am. 2013 Apr;44(2):217-24. Review.
7. Henriksen K, Byrjalsen I, Andersen JR, Bihlet AR, Russo LA, Alexandersen P, Valter I, Qvist P, Lau E, Riis BJ, Christiansen C, Karsdal MA; SMC021 investigators. A randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy and safety of oral salmon calcitonin in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D. Bone. 2016 Oct;91:122-9.
8. Endo N, Fujino K, Doi T, Akai M, Hoshino Y, Nakano T, Iwaya T. Effect of elcatonin versus nonsteroidal anti-inflammatory medications for acute back pain in patients with osteoporotic vertebral fracture: a multiclinic randomized controlled trial. J Bone Miner Metab. 2017 Jul;35 (4):375-384.
9. Ito A, Yoshimura M. Mechanisms of the analgesic effect of calcitonin on chronic pain by alteration of receptor or channel expression. Mol Pain. 2017 JanDec;13:1744806917720316.
10. Yoshimura M, Furue H, Ito A. Anti-nociceptive effect of calcitonin on chronic pain associated with osteoporosis. Clin Calcium. 2001 Sep;11(9):1153-7.
11. Ito A, Furue H, Yoshimura M. Recent insights into mechanisms for analgesic effect by calcitonin. Nihon Rinsho. 2007 Nov 28;65 Suppl 9:386-90.