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EFFECTS OF A SURGICAL SITE INJECTION ON PAIN SCORES AND NARCOTIC USE AFTER ORTHOPAEDIC TRAUMA SURGERY

A randomized, single-blind, single-center study of the effects of surgical site injection on pain and narcotic utilization in participants who undergo surgery for lower extremity fractures.

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Study Product:	Bupivacaine, Morphine Sulfate, Ketorolac
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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

ASA	American Society of Anesthesiologist Score
VAS	Visual analog scale
SMFA	Short Musculoskeletal Function Assessment; a questionnaire
APS-POQ	American Pain Society Patient Satisfaction Questionnaire
DVT	Deep vein thrombosis
ER	Emergency room
AE	Adverse event
SAE	Serious adverse event
IV	Intravenous
PO	Taken orally
PRN	Taken as needed
TID	Taken three times per day
Q4h	Taken every four hours
CI	Confidence interval
SD	Standard deviation; a parameter which characterizes a population distribution
SE	Standard error
SSI	Surgical Site Injection
ANOVA	analysis of variance; a linear model
NSAID	Non-steroidal anti-inflammatory drug
LOS	Length of Stay

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Protocol Summary

Title	Effects of a Surgical Site Injection on Pain Scores and Narcotic Use after Orthopedic Trauma Surgery
Short Title	Understanding and Improving post-operative Pain in the Fracture Population
Brief Summary	This is a phase I, randomized, single-blind, placebo-controlled, single-center study of the effects of surgical site injection on pain and narcotic utilization in participants who undergo surgery for lower extremity fractures. 400 participants with lower extremity fractures who are admitted for operative fixation will be included in the study. Participants will be randomized to receive either a pain cocktail injection around the fracture site and surrounding tissues or control (no injection). An analysis of pain scores, rehabilitation progress, length of stay, narcotic utilization, and satisfaction scores will be performed.
Phase	Clinical study phase 1
Objectives	To understand the effect of surgical site injections of post-operative pain control
Methodology	phase I, randomized, single-blind, placebo-controlled, single-center study
Endpoint	10mg change in narcotic utilization daily or 15mm change in VAS
Study Duration	4 years
Participant Duration	3 months
Duration of IP administration	Once during surgery
Population	400 participants with peritrochanteric fractures
Study Sites	NYU Langone (Kimmel, Tisch, Langone Orthopedic Hospital, Lutheran)
Number of participants	400
Description of Study Agent/Procedure	Peri-incisional injection of 40cc 0.25% bupivacaine, 5 mg morphine sulfate (1 mg/cc, 5 cc total), and 30 mg of ketorolac (30 mg/cc, 1 cc total) into soft tissue and musculature surrounding the fracture site and 0.25% Marcaine 10 mL into the subcutaneous tissue surrounding the surgical incision.
Reference Therapy	Reference is a control
Key Procedures	Surgical Site injection
Statistical Analysis	As treated analysis will be performed with mean, t-tests, within and between group ANOVA, linear regression, Mann- Whitney-Wilcoxon tests

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1 Key Roles

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2 Background and Specific Aims

2.1 Background

Lower extremity fractures comprise the majority of orthopedic surgery emergency room admissions at major medical centers across the country. Whether due to blunt or high energy mechanisms, femur and tibia fractures often necessitate surgical intervention and prolonged hospital stays due to the need for medical clearance, surgery, physical therapy, pain control and discharge planning. Pain management directly impacts a patient's ability to mobilize with physical therapy, their desire to go home or to a rehabilitation facility, and their need for narcotic medications which have deleterious side effects such as delirium and addiction. However, given the unpredictable and "non-elective" nature of fracture care there is little infrastructure in place to optimize outcomes for fracture patients with regards to pain control and its sequela.

A multitude of Level 1 evidence in arthroplasty research has demonstrated that multimodal analgesia pre and post-operatively combined with intra-operative surgical site injection (SSI) leads to reduced post-operative pain, narcotic requirements, and length of stay in addition to increased mobility and patient satisfaction scores[1–3]. As a result, the standard of practice in arthroplasty has been to use regimented pain protocols including SSI to improve patient outcomes[4]. While pain control is recognized as one of the single most important factors that impacts a patient's hospital stay and outcomes, there is a dearth of Level 1 research on multimodal pain control in the Orthopedic trauma literature.

Recent studies have found support for the use of surgical site injections in patients with femoral fracture treated with plate fixation, intramedullary nail or arthroplasty. In a randomized control trial, Koehler et al studied patients with femur fractures in all anatomic regions and randomly assigned them to either receive a surgical site injection (SSI) and routine pro re nata (PRN) post-op pain medication or only PRN pain medication[5]. Post-operatively, a visual analog score was employed to assess pain and narcotic

administration which showed a statistically significant difference in pain scores and narcotic usage administration between the two groups on post-operative day one, with those who received SSI having less pain and narcotic usage. What remains to be seen is how these interventions impact rehabilitation and narcotic usage in the long-term.

After sustaining hip or other lower extremity fractures, roughly 50% of patients experience persistent pain at the fracture site. Their perception of this pain and the limitations that they suffer because of it may be influenced by their perioperative pain control and expectations regarding their pain and ability to return to normal living[6]. The goal of this study is to not only impact the acute use of narcotics during the inpatient admission but to impact the long term outcome of fracture pain on long-term functional outcomes for these patients.

At our institution pre-op fracture pain management was not standardizedand had been a combination of morphine, fentanyl, dilaudid, and oxycodone given in the emergency and in-patient setting. Post-operatively, oxycodone-acetaminophen 5-325mg and 10-325mg were given for moderate and severe pain every four hours respectively with a dose of oxycodone-acetaminophen 5-325 for breakthrough pain. Adjuncts to these medications such as acetaminophen, tramadol, ketorolac, ofrimev, gabapentin, pregabalin were given inconsistently and often not at all. Starting November 2018 our institution began a new post-op pain medication protocol. In this study a standardized regimen of pain medication will be given to all patients who are enrolled to eliminate this as a potential confounder. The ultimate goal of this study is to diminish the use of post-op narcotics and reduce post-operative pain through the use of an intra-operative SSI.

Rationale for Drug Selection and Route of Administration

In the proposed study, the drugs bupivacaine (marcaine), morphine sulfate (duramorph), and ketorolac (toradol) will be used as a surgical site injection pain "cocktail" as is standard practice in total joint surgery[1–4,7–10]. Orthopedic pain injection cocktail regimens normally include a local amide anesthetic, a NSAID, and an opiate for multimodal therapy (see table 1, taken from Elmallah et al)[10]. Occasionally steroids, antibiotics and other fillers are given. Most commonly ropivacaine or bupivacaine are given as the local anesthetic, morphine sulfate is given as an opiate, and ketorolac is given as the NSAID. Injections are given via tissue infiltration or intramuscular injection and described as "peri-incisional", "periarticular", "extra-articular", and/or "perifracture" injections[1–4,7–13]. In all cases, the injection is placed in the soft tissue around the relevant zone of injury. In published studies and in common practice, patients receive surgical site injections in the deep tissues including the muscle, synovium, capsule, and periosteum, and into the superficial tissues.

As this replicates the standard of care in arthroplasty, this method of injection to the tissue surrounding the fracture site does not significantly increase risk to subjects. The proposed study follows the same injection methods as Koehler et al. where no adverse events were noted from administration. While there is a potential for inadvertent intra-neural or intravascular injection, the injection will be administered away from blood vessels and nerves and under direct visualization to the soft-tissue surrounding the fracture (predominately muscle) and incision. We do not anticipate patients suffering any major complications from receiving the injection.

As for the choice of drugs, at our institution, a peri-incisional analgesic cocktail is injected before closure of all total hip and knee replacements[4,9]. This consists of 40ml 0.25% marcaine, 5mg morphine (5ml), and 30 mg ketorolac (1ml). In an RCT, Koehler et al demonstrated the efficacy of a perifracture cocktail containing 400 mg of 0.75% ropivacaine (53.33 mL), 0.6 mg of 1-mg/mL epinephrine (0.6 mL), and 5 mg of 0.5-mg/mL morphine sulfate (10 mL) for pain control in femur fracture patients[5]. In a study by Kang et al., a multimodal periarticular injection was given to hip fracture patients using a 100-mL cocktail of 300 mg ropivacaine (40 mL), 10 mg morphine sulfate (10 mL), 30 mg ketorolac (1 mL), and 300 mg 1:1000 epinephrine (0.3 mL)[12]. In a study by Jung et al, multimodal periarticular injections were given for high tibial osteotomies using a 50-

mL periarticular injection cocktail of 200 mg bupivacaine (20 mL), 10 mg morphine sulfate (10 mL), and 200 mg 1:100,000 epinephrine (0.2 mL)[13]. In a total joint study by Busch, patients received ropivacaine, ketorolac, epimorphine, and epinephrine[2].

The FDA-approved indications for bupivacaine (marcaine), morphine sulfate (duramorph), and ketorolac (toradol)injection include infiltration and/or intramuscular injection for pain control. Dosing for marcaine infiltration is 0.25% concentration up to 175mg with a further instruction stating "standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of marcaine". Ketorolac tromethamine is approved for intramuscular (IM) administration as: 15 mg in 1 mL (1.5%), 30 mg in 1 mL (3%) , and 60 mg in 2 mL (3%) in sterile solution. Morphine sulfate is approved for intramuscular dosing up to 10mg per 70kg every 4 hours. The peri-incisional injection of these medications is a common prescribed procedure as illustrated in numerous books and studies[1,7,10–12].

2.2 Specific Aims

AIM 1: To determine if SSI given to during lower extremity fracture surgery reduces post-operative pain. This will be evaluated through the randomizing patients who either receive general or spinal anesthesia into two separate groups, injection or control, and monitoring their pain scores afterwards both in the hospital and outpatient settings. (The type of anesthesia will be determined by the treating anesthesiologist; it is not an experimental variable.)

AIM 2: To determine if SSI given during lower extremity fracture surgery significantly changes post-operative narcotic usage. Using the same groups as above, this will be evaluated through the measurement of narcotic usage both in the immediate post-operative period and for 2 weeks after surgery.

AIM 3: To determine if SSI given during lower extremity fracture surgery alters post-operative function, length of stay, and complications after surgery. This will be measured through rehabilitation documentation, discharge documentation, chart review, and patient interviews.

2.3 Statistical Hypotheses

We hypothesize that SSI given at the time of surgery will reduce post-operative pain and narcotic usage not only during the patients' inpatient hospital stay but also as an outpatient. Furthermore, SSI will improve post-operative function, shorten length, of stay, and reduce complications not limited to but including deep venous thrombosis, delirium, and narcotic dependency. Failing to reject the null hypothesis would signify that SSI has no clinically relevant impact on post-operative outcomes in hip fracture surgery.

2.4 Objectives and Purpose

The ultimate goal of this study is to determine how effective SSI is in reducing post-operative pain in patients with lower extremity long bone fractures and to determine how that reduction in post-operative pain impacts a patient's hospital stay in the short term and their use of narcotics during the treatment period. Primary outcomes measures will be reported and observed pain scores and narcotic use. VAS and APS-POQ will be used to measure pain scores. While it is expected that the greatest benefit of the SSI will be seen in the first day or two after surgery it is possible that there will be in an overall reduction in long-term narcotic use. Secondarily, function/rehabilitation, length of stay, and complications may be impacted by the intervention.

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3 Study Design and Endpoints

Cohort A: Spinal Anesthesia	ARM 1: Experimental	Sample Size: 100	SSI
	ARM 2: Control	Sample Size: 100	No intervention

Cohort B: General Anesthesia	ARM 1: Experimental	Sample Size: 100	SSI
	ARM 2: Control	Sample Size: 100	No intervention

3.1 Description of Study Design

The researchers will use NYU admission records, emergency room records, orthopedic consult records, and immediate care records to identify patients eligible for participation in the study. Orthopedic residents and authorized researchers will consent and enroll patients pre-operatively.

Subjects with a qualifying fracture will be randomized to either the SSI or control group. Subjects in the SSI group will receive a peri-incisional injection of 40cc 0.25% bupivacaine (marcaine), 5 mg morphine sulfate (duramorph) (1 mg/cc, 5 cc total), and 30 mg of ketorolac (30 mg/cc, 1 cc total) into soft-tissue and musculature surrounding the fracture site and 0.25% Bupivacaine (Marcaine) 10 mL into the subcutaneous tissue surrounding the surgical incision. The control group will receive no injection. The injection will be administered by the subjects NYU orthopedic surgeon, all of whom are familiar with the technique. The patient will be blinded to if a medication is being injected. Subjects will not receive ketorolac if they have kidney disease or a history of allergy to NSAIDS or aspirin. The dose of ketorolac will be reduced to 15 mg (30 mg/cc, 0.5cc total) in subjects older than 65 years of age, in subjects with a history of peptic ulcer disease, a CrCl of 30 to 50 ml/min, or subjects with diabetes. These modifications are recommended by the manufacturer and are used in standard practice. A sub group analysis will be done on patients who receive this lower dosage to see if it has an impact on the data.

After initial recruitment, subjects' pain will be assessed via visual analog scale (VAS) by nursing staff on a q4h basis. A standardized regimen of pain medication will be given to all subjects who are enrolled. Pre-operatively subjects will receive acetaminophen 1gm oral (every 6-8 hours, not to exceed 4gm daily) and meloxicam 15mg oral once daily. Post-operatively, subjects will receive acetaminophen 1gm oral (every 6-8 hours, not to exceed 4gm daily), ketorolac 30mg injection, once daily in AM, starting POD 1(15mg for patients >65 years of age and/or renal impairment), and pregabalin (Lyrica) 50mg oral every 8 hours (held for sedation). Ice PRN for mild pain, tramadol 50mg oral every 8 hours PRN for moderate pain, and tramadol 100mg oral every 8 hours PRN for severe pain. Oxycodone 5mg oral every 6 hours PRN will be given for breakthrough pain.

Physical therapy records with regards to ambulation distance and exercise endurance will be examined. Daily assessments of pain via VAS will obtained by the nursing staff as per standard protocol. APS-POQ form will be given on POD1.

After discharge subjects will receive a 7-10 day prescription for acetaminophen 1000mg every 8 hours, meloxicam 15mg oral once daily, and tramadol 50mg oral, every 4-6 hours, PRN (12 tablets to be dispensed). Subjects will call the provider to request refills as needed.

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After discharge the research staff will call the subjects up to every other day for the first week, twice in the second week, once weekly for the third and 4th weeks and then monthly after discharge to ascertain pain level, reported narcotic usage, and functional status. Research staff will verify documented narcotic refills through epic and pharmacy records. Four to eight weeks after injury subjects will complete a SMFA as well as another APS-POQ form over the phone with a trained interviewer.

	Pre-op	**Post-op: Inpatient**	**Post-op: Discharge**
Standing	Acetaminophen 1gm, oral (every 6-8 hours, not to exceed 4gm daily, review liver function prior to administration) Meloxicam 15mg oral, once daily	Acetaminophen 1gm, oral (every 6-8 hours, not to exceed 4gm daily, review liver function prior to administration) Ketorolac 30mg inj, once daily in AM, starting POD1 (15mg>65 years of age and/or renal impairment) Pregabalin (Lyrica) 50mg, oral every 8 hours (hold for sedation)	Acetaminophen 1gm, oral (every 6-8 hours, not to exceed 4gm daily, review liver function prior to administration) Meloxicam 15mg oral, once daily
Mild		Ice Therapy PRN (alternating 15 min on/off for skin evaluation)	
Moderate		Tramadol 50mg oral, every 8 hours, PRN	
Severe		Tramadol 100mg, oral, every 8 hours, PRN	
Breakthrough		Oxycodone 5mg, oral every 6 hours, PRN	Tramadol 50mg oral, every 4-6 hours, PRN (12 tablets to be dispensed)

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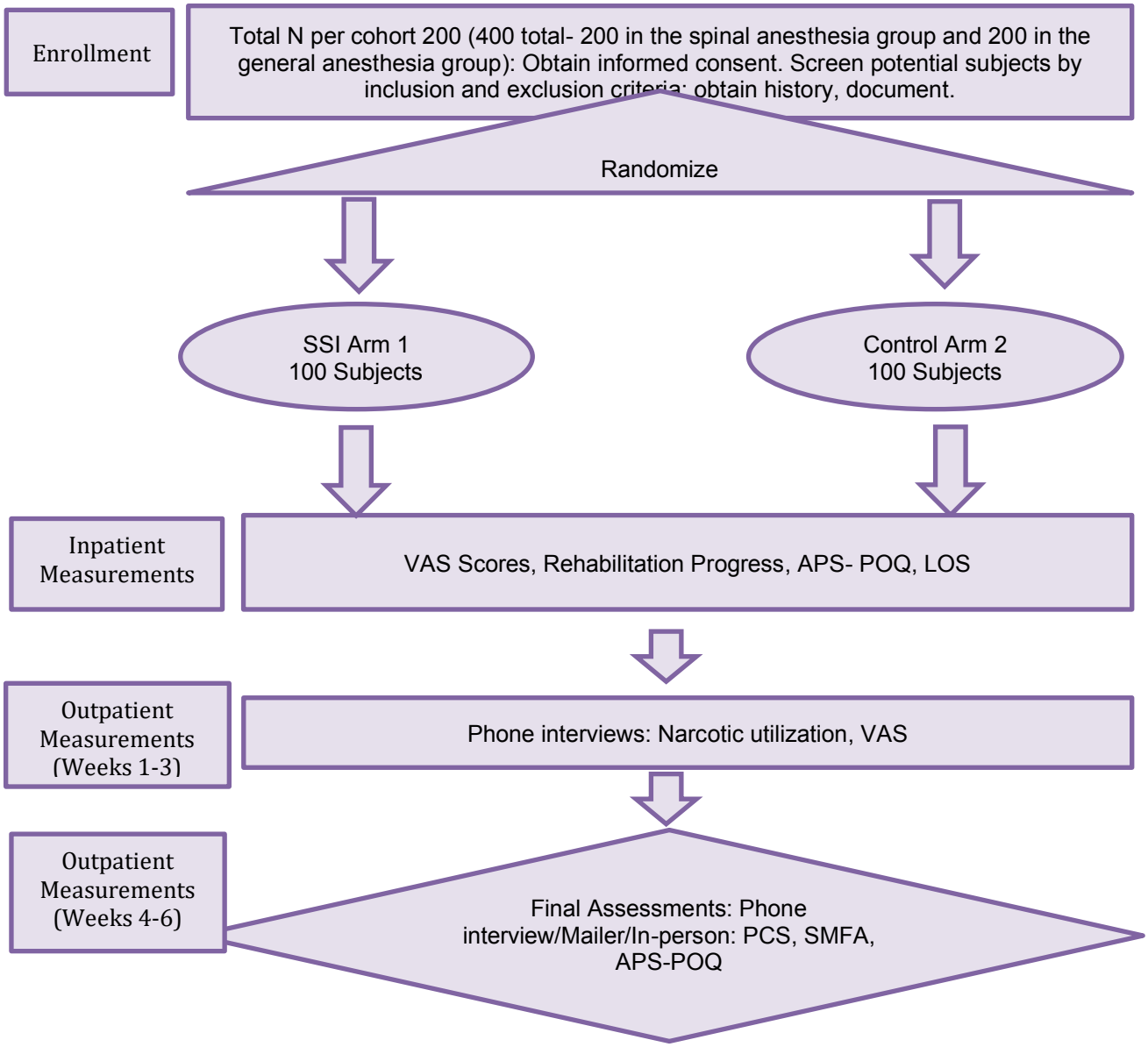
3.2 Schematic of Study Design



4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age above 18
2. Lower extremity fracture including femoral neck, intertrochanteric, sub-trochanteric, and femoral shaft fracture

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3. English Speaking as primary or native language

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnant women
2. Treatment with Arthroplasty
3. Patients who receive a peripheral nerve block
4. Patients who receive intra-op or post-op ketamine
5. Patients with concomitant TBI or MR
6. Polytrauma patients
7. Pathologic Fractures
8. Patients with a contraindication to any of the medications on the study list due to other medical problems such as renal or liver disease or due to allergy/intolerance
9. Patients with prior extremity weakness resulting from stroke or other neurological condition
10. Prior or current history of narcotic use
11. Patients with advanced dementia
12. NYUMC Students, Residents, Faculty

4.3 Vulnerable Subjects

No vulnerable populations will be intentionally solicited. It is possible that employees, economically disadvantaged persons and students will be solicited in the course of enrollment however no one will be specifically recruited for these reasons and no one with ties to the NYU Orthopedics department or NYU School of Medicine will be eligible for participation.

4.4 Recruitment and Consent

This study will utilize EPIC to identify subjects and redcap to manage and store relevant data. EPIC will be used to identify patients who have been admitted with the injury types described above and who meet the inclusion and exclusion criteria. The PHI that will be seen will include their name, diagnosis, medical record number, age, and telephone number. This is the minimum necessary to identify patients over time and to determine if they are eligible for the study. Approved study team members will handle recruitment efforts. Patients confidentiality will be maintained as all study team members will have gone through CITI training and data will be keep in a secure manner as detailed below. This recruitment search will be done daily.

All orthopedic surgeons at NYU will be notified of the study prior to initiation. If the treating physician has a patient who is recruited and consented they will be notified via sendsafe email.

There will be no recruitment materials used in the study. All recruitment will be done face to face.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

Process of Consent

The consent for participation will be collected during the hospital stay on day one by a study team member. The study team member may or may not be a part of the patients care team. Due the rapid nature of trauma surgery, patients will have a few hours from the time of recruitment to the time of surgery to decide if they want to participate in the study. This will be done in privacy in the patient's hospital room or other private location such as a patient conference room. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant

will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A website (https://nyuorthoresearch.com/) has been created to assist study team members with subject enrollment and consent form access. The website will be updated every six months. Only IRB-approved study documents will be uploaded on the website. The IRB-approved study team members may use this website to download a pdf version of the consent form, which can then be printed and signed by the study subject. The website will altogether be used as a tool for IRB-approved study team members to access clean study documents. A link on the website will also direct the study team member to a redcap survey that will link directly to the redcap project to allow for direct entry of the patient's information for the study. After entering the patient information into the redcap survey, the study team member will not be able to re-download the patient's protected health information from the website and no subject protected health information will be stored on the website. This process is necessary to allow for IRB-approved study team members to enroll subjects while appropriately limiting access to the protected health information in the redcap project as outlined in this protocol. Please see section 10.5 for further information on security of the website.

After obtaining consent, the IRB-approved study team members will either place the consent in a locked research box available at the participating hospitals locked resident room or place it in the locked office of the PI. Signed consents placed in a secure research lockbox will be collected by IRB-approved study team members and placed in the locked office of the PI.

Ultimately, a copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record.

Subject Capacity

All subjects will be assessed for capacity to give informed consent by the study team member, all of whom are physicians. Capacity will be assessed through the subjects' ability to express understanding of the information presented to them, their ability to express a choice, their appreciation of how this is relevant to them, and reasoning about how the study might impact them and others. As specific for capacity testing, the patient must be able to answer the following questions:

- Understanding: "Can you tell me in your own words what I just said about the study?"
- Expressing a choice: "Based on what we've just discussed about the study, what would you choose?"
- Appreciation: "Regardless of what your choice is, do you think that it is possible the medication can benefit you?" and "Regardless of what your choice is, do you think it is possible the medication can harm you?"
- Reasoning: "How could participating in the study affect you?"

Additionally, the study team member will assess mental status by asking the patient for their full name, location, and the date. This is a standard practice to ensure a patient is alert and oriented to person place and

time. Capacity testing and the mental status exam will help to reduce the risk of influencing a patient whose judgement may be altered due to opiates or emotional stressors from trauma. As listed in exclusion criteria, those with dementia will be excluded from the study.

All study team members will be physicians, trained in obtaining informed consent.

Subject/Representative Comprehension
The subject themselves will have to clearly state back the basic goals of the study (i.e. to look at the effect of different medications on bone healing) and state that they are willing to participate. This may be done in English or in their primary language with an interpreter.

4.5 Duration of Study Participation

The study will be open for 4 years after beginning enrollment.

4.6 Total Number of Participants and Sites

Recruitment will end when approximately 400 participants are enrolled. It is expected that approximately 400 participants will be enrolled in order to produce 300-350 evaluable participants. There were 350 procedures done on patients matching the inclusion and exclusion criteria in the last year. Based on the simplicity of the intervention and historical enrollment for patients undergoing orthopedic surgery, we anticipate at least 25% participation.

4.7 Participant Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

4.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to participants
    a. Clinical criteria that would meet such risks include, but are not limited to: permanent nerve damage, tissue necrosis, or wound healing complications that are directly related to the injection
2. Demonstration of efficacy that would warrant stopping
    a. If patients receiving the injection require substantially less oral narcotic medication than those in the control group, such that continuing to withhold the medication was not in their best interest, the study may be discontinued.
3. Insufficient compliance to protocol requirements

4. Data that are not sufficiently complete and/or evaluable
5. Determination of futility

5 Risks and Benefits

5.1 Potential Risks

There is no current standard of care in terms of trauma patients receiving these injections. At some institutions it is commonplace to give intra-operative injections for pain control. At NYU it is not standard practice for trauma surgery however this same cocktail of medications is given routinely during surgery to patients undergoing arthroplasty (i.e. total hip and total knee replacement). At this time based on NYU practice there is no risk of being in the control group and not receiving an injection. The risks of receiving and injection are related to the injection site and medication type.

Marcaine is characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation. In this circumstance cardiac arrhythmia, respiratory distress, restlessness, anxiety, and seizure may occur. These risks, however, are minimal as the dosage given in this study is the lowest effective dose and the technique of administration minimizes such an outcome.

Ketorolac is an NSAID and carries a risk GI distress and renal damage. NSAID use will be diminished in patients with poor renal function as described. Post-operative labs are ordered as the standard of care and will allow physicians on the treatment team to identify any renal compromise.

Morphine sulfate (duramorph) is a narcotic medication which carries a risk of constipation, respiratory distress, sedation, and dependence if given in excess or if given over a prolonged period of time. In this study duramorph will be given once, limiting the likelihood of any complication.

Patients are also monitored constantly during surgery by anesthesia and afterwards by physicians and nurses to identify complications. These medications are given during surgery using the lowest effective dose for the shortest duration consistent with patient treatment goals in order to minimize risk.

An injection of these medications given into a blood vessel can cause unintended systemic effects as described above and an injection given into a nerve can cause temporary numbness or weakness. Injections will be performed by trained surgeon under direct visualization to prevent nerve damage and withdraw-inject method will be used to prevent intravascular injection.

All oral and IV medications given after surgery are standard of care and pose no new risk to patients as they would already be receiving them. The only change in this study is adhering to this regimen whereas in practice some medications might get missed.

The potential risks to the research subjects also include possible a loss of confidentiality of sensitive information collected for this study. The risk of loss of confidentiality of the data is negligible under rigorous application of appropriate procedures for data security.

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5.2 Potential Benefits

Some subjects may experience better pain control, improved satisfaction, decreased need for narcotics and decreased side effects. If the study is not inconclusive, the study's results may benefit future patients by helping to confirm the benefits of multimodal regimens in the setting of orthopaedic trauma patients, furthering the case for them to become the standard of care for peri- and postoperative pain control.

6 Statistical Analysis

6.1 General Approach

As treated Sample. The primary analyses will follow the as-treated principle in order to evaluate the true outcome of the intervention as experienced by the patient who is blinded to the intervention.

Missing Data. It is anticipated that the data for some subjects will be incomplete for various reasons: missed clinic visits, refusal to answer a sensitive question on a questionnaire, onset of illness, loss-to-follow-up, etc. All occurrences of incomplete data will be investigated to carefully document the reasons for the missing data.

Sensitivity Analyses. To evaluate the robustness of the main results to reasonable perturbations of the methods and assumptions used, competing statistical methods (those not used in the main analyses) will be relegated to serving as a guide to our confidence in the main results.

6.2 Analysis of Endpoints

Primary Endpoints:
amount (mg) of narcotics (oral morphine mg equivalents) used
duration of narcotic use
patient reported pain scores

Secondary Endpoints:
length of stay
progress with physical therapy: distance ambulated, range of motion, exercises done
reported long-term narcotic use at home/SAR
discharge location: home, acute rehab, skilled nursing facility
documented narcotic refills
falls
adverse events

The analysis of narcotic Use, VAS, APS-POQ, and SMFA scores will rely on a univariate repeated-measures analysis of variance model for mean score. This model is in the class of models commonly known as a unirep-ANOVA models. It assumes that the mean score is a function of elapsed time and the treatment regimen assigned. This model takes into account the fact that the subject's repeated measures are correlated. The fitted model will provide statistical estimates of the mean levels, the treatment-effect differences between mean levels, the standard deviation, the intra-class correlation coefficient, 95% CIs, standard errors (SE), and statistical hypothesis tests. The estimates of means will be used to compute summary criteria such as area under the curve (AUC) for each regimen. All estimates reported will be presented their 95% CIs.

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All endpoints will be evaluated as fits the data set with graphical figures such as scatter plots, box-and-whisker plots, and frequency histograms to visualize the distribution of these outcomes and their relationships to covariates and treatment assignment. When appropriate descriptive graphical and tabular methods, and Kaplan-Meier curves will also be estimated and presented in a graphical figure.

6.2.1 Baseline Descriptive Statistics

The following patient data will be recorded: age, gender, height, weight, date of admission, date of discharge, injury time, injury type, laterality, surgical approach, implants used, duration of surgery, time to union, contamination , ASA, comorbidities (smoking, cardiac history, diabetes, etc.), CBC (WBC, PCV, HGB, RBC, indices, platelet count, differential), and medications.

6.3 Sample Size

In order to have a sufficient N to power the study a minimum of 200 subjects per anesthesia group will be recruited (α=0.05, β=0.2). If the difference in the morphine equivalent consumption, is found to be 15mg daily with a standard deviation between the groups of 25mg, we will need 90 subjects per group in order to reject the null hypothesis with the probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. To allow for within group analyses and accommodate for the poor follow-up rate in fracture patients we will need 400 patients.

6.4 Enrollment/Randomization/Masking Procedures

As per standard of care, an anesthesiologist will determine if subjects receive general or spinal anesthesia. Within these groups subjects will randomized to receive a SSI or no intervention. Randomization will be done via redcapautomated computer randomization After randomization the surgical team will be informed which group the patient has been randomized into.

6.5 Breaking the Study Blind/Participant Code

If there is any adverse event related to the drug this will be disclosed to the patient.

7 Assessment of Safety

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as **non-serious adverse events**.

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

1. **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2. **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs must have their relationship to study agent assessed.. For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

1. **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals.
2. **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal).
3. **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

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4. **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
5. **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Dr. Philipp Leucht will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent. All reportable events that probably to definitely related to the study agent will be reported within 5 days. All nonreportable events will be tabulated and submitted at the time of continuation.

7.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

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7.4 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Dr. Philipp Leucht,, a trained Orthopedic trauma surgeon, will systematically review the study data and events to ensure that the data is collected properly and the subjects are safe. He will review the information gathered from medical records on a weekly basis. Outcomes of the review will be submitted to the IRB no less than annually at the time of continuation review, unless a safety issue is identified that requires prompt monitoring.

8 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries will be printed legibly in black ink.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

9 Ethics/Protection of Human Subjects

9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

9.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be

obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

9.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number with a key to this data being help by the PI. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected in REDCap. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

10 Data Handling and Record Keeping

10.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. All electronic data will be kept in NYU approved REDCap form. All paper data will be kept in a secure locked file drawer in the PIs office.

The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, the original entry will be crossed out with a single line, and then initialed and dated.

10.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication.

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10.3 Protocol Deviations

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5working days of the scheduled protocol-required activity.

Protocol deviations will be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

10.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of the research. This trial will be registered with clinicaltrials.gov as per the ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007.

10.5 Webpage

Material will be hosted on the NYU server and available through the NYU intranet. This requires password access regulated by MCIT. Access will be restricted to people in the orthopedic department with a need to know about current active studies. There will be no patient specific information available on the webpage. Consent forms will be available via direct links to RNAV so that the individual must be on study and log-in with a password in order to open them.

The NYU intranet webpage will be managed by Raj Karia, an Assistant Professor of Research in the Orthopedic Department at NYU. It will be regularly updated no fewer than every 6 months and will be updated with each change that is made to any protocol on the website. The url www.nyuorthoresearch.com will be rerouted to this secure page.

11 Study Finances

11.1 Funding Source

No funding source present.

11.2 Costs to the Participant

There are no expected costs to the subjects. All travel and doctor's visits will occur as a part of routine care.

11.3 Participant Reimbursements or Payments

Participants will not receive any financial compensation for participation in this study.

12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way

that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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14 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

14.1 Narcotic Equivalents

Notes from Lamplot(2013)

Narcotic and Route		Dose (mg)		Conversion Factor
Morphine IM/IV	10		1.0	
Hydromorphone IM/IV	1.67		6.0	
Hydrocodone oral		30		0.3
Tramadol oral		100		0.1
Oxycodone oral	20		0.5	
Vicodin 5/500 oral		6 tabs		1.7

Equianalgesic Doses of Opioids[28]

Opioid	Oral Equianalgesic Dose (mg)
Buprenorphine	0.3
Oxymorphone	1.5
Butorphanol	2
Hydromorphone	2
Oxycodone	7
Hydrocodone	10
Morphine	10
Methadone	10-20
Tramadol	40
Propoxyphene	43-45
Codeine	80
Meperidine	100

14.2 VAS

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14.3 APS-POQ Subscales

Affective Subscale
- How much the pain caused you to feel anxious
- How much the pain caused you to feel depressed
- How much the pain caused you to feel frightened
- How much the pain caused you to feel helpless

Pain Severity and Sleep Interference Subscale
- Least pain in 24 hours
- Worst pain in 24 hours
- Estimate of percentage of time in severe pain
- Pain interfered or prevented you from falling asleep
- Pain interfered or prevented you from staying asleep

Perceptions of Care Subscale
- Pain relief in the first 24 hours
- Were you allowed to participate in decisions about pain treatment?
- How satisfied are you with the results of your pain treatment?

Activity Interference Subscale
- Pain interfered or prevented you from activities in bed
- Pain interfered or prevented you from activities out of bed

Adverse Effects Subscale
- Severity of nausea
- Severity of drowsiness
- Severity of itching
- Severity of dizziness

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14.4 SMFA

Difficulty you may be having this week with your daily activities because of your injury or arthritis.

Not at All Difficult
A Little Difficult
Moderately Difficult
Very Difficult
Unable To Do

1. How difficult is it for you to get in or out of a low chair?
2. How difficult is it for you to open medicine bottles or jars?
3. How difficult is it for you to shop for groceries or other things?
4. How difficult is it for you to climb stairs?
5. How difficult is it for you to make a tight fist?
6. How difficult is it for you to get in or out of the bathtub or shower?
7. How difficult is it for you to get comfortable to sleep?
8. How difficult is it for you to bend or kneel down?
9. How difficult is it for you to use buttons, snaps, hooks, or zippers?
10. How difficult is it for you to cut your own fingernails?
11. How difficult is it for you to dress yourself?
12. How difficult is it for you to walk?
13. How difficult is it for you to get moving after you have been sitting or lying down?
14. How difficult is it for you to go out by yourself?
15. How difficult is it for you to drive?
16. How difficult is it for you to clean yourself after going to the bathroom?
17. How difficult is it for you to turn knobs or levers (for example, to open doors or to roll down car windows)?
18. How difficult is it for you to write or type?
19. How difficult is it for you to pivot?
20. How difficult is it for you to do your usual physical recreational activities, such as bicycling, jogging, or walking?
21. How difficult is it for you to do your usual leisure activities, such as hobbies, crafts, gardening, card-playing, or going out with friends?
22. How much difficulty are you having with sexual activity?
23. How difficult is it for you to do light housework or yard work, such as dusting, washing dishes, or watering plants?
24. How difficult is it for you to do heavy housework or yard work, such as washing floors, vacuuming, or mowing lawns?
25. How difficult is it for you to do your usual work, such as a paid job, housework, or volunteer activities?

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How often you are experiencing problems this week because of your injury or arthritis.

None of the Time
A Little of the Time
Some of the Time
Most of the Time
All of the Time

26. How often do you walk with a limp?
27. How often do you avoid using your painful limb(s) or back?
28. How often does your leg lock or give-way?
29. How often do you have problems with concentration?
30. How often does doing too much in one day affect what you do the next day?
31. How often do you act irritable toward those around you (for example, snap at people, give sharp answers, or criticize easily)?
32. How often are you tired?
33. How often do you feel disabled?
34. How often do you feel angry or frustrated that you have this injury or arthritis?

How much you are bothered by problems you are having this week because of your injury or arthritis.

Not at All Bothered
A Little Bothered
Moderately Bothered
Very Bothered
Extremely Bothered

35. How much are you bothered by problems using your hands, arms, or legs?
36. How much are you bothered by problems using your back?
37. How much are you bothered by problems doing work around your home?
38. How much are you bothered by problems with bathing, dressing, toileting, or other personal care?
39. How much are you bothered by problems with sleep and rest?
40. How much are you bothered by problems with leisure or recreational activities?