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Pilot Study: Extended regional anesthesia for prevention of chronic pain after traumatic injury

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14. ABSTRACT

The ultimate aim was to systematically test the hypothesis that a 5-day regional ambulatory popliteal nerve block in patients undergoing a defined surgery for traumatic ankle fracture would significantly reduce the development of chronic pain conditions. Ankle fracture surgery was chosen as a proxy for combat injuries because it is a common procedure in our clinical facilities, and because regional anesthesia for 5 days would be acceptable to patients and clinicians, not interfering with rehabilitation. Subjects were randomly assigned to receive 5-day regional block or standard care after ankle fracture surgery in an open-label pilot study. Ankle pain questionnaires (SEFAS) were given 4 times over the year following the surgery, and additional clinical data was obtained from medical records. The primary endpoint was the 12-month SEFAS score; this data will be submitted as an amendment when final data is received. 8 control and 6 regional block subjects were enrolled. The group receiving regional block had significantly improved pain scores 3 months after surgery. The primary difficulties noted were premature discontinuation of the pump due to catheter leakage, and limited recruitment. Data were obtained suggesting possible improvements and changes for a full-scale study.

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TABLE OF CONTENTS

Section

1.0 BACKGROUND

Up to 81% of survivors of severe combat trauma have chronic pain conditions [1]. Traumatic limb injuries are common in modern combat injuries. Chronic pain conditions affecting peripheral limbs include complex regional pain syndrome (CRPS), phantom limb pain, and other neuropathic pain syndromes. Chronic pain conditions are also highly co-morbid with posttraumatic stress disorder [1]. When nerves are injured or transected, abnormal spontaneous activity develops at the injury site and within the cell bodies of the peripheral sensory nerves[2-4]. A wealth of preclinical research studies, using a variety of pain models, shows that blocking this spontaneous activity early after the injury, for 5 – 7 days, strongly reduces or completely prevents development of chronic pain behaviors and other long-lasting cellular abnormalities [5-9]. This literature suggests that pre-emptive analgesia, applied in conditions with a known initiating event such as surgery or trauma, should be highly effective in reducing chronic pain. However, clinical studies of pre-emptive analgesia have had mixed results. We propose that the failures in such studies are in part due to a disconnect between the preclinical and clinical studies. Specifically:

a. Many clinical studies of pre-emptive analgesia have used primarily centrally acting analgesics such as opioids, which preclinical studies suggest would not be effective in blocking the critical changes and spontaneous activity occurring in peripheral sensory nerves.
b. Many clinical studies used pre-emptive analgesics for only 1 – 3 days, while preclinical studies suggest 5 – 7 days may be necessary to block development of chronic pain[5].

Regional anesthesia techniques provide an excellent method for blocking nerve signals where they originate, in the peripheral nerve, which research suggests should be ideal for blocking development of chronic pain, in addition to providing analgesia for surgery, blocking acute pain in the immediate post-operative period, and reducing postoperative opioid use with its concomitant problems. Trauma care, rather than surgical care, has led the way in adopting regional anesthesia methods. Military medicine has been a leader in this regard, improving regional anesthesia and introducing it into field hospitals and enroute care, revolutionizing the care of troops injured in combat in the Iraq and Afghanistan conflicts [10,11]. Military medicine studies have demonstrated the safety and efficacy of regional anesthesia for combat wounds,

especially for managing surgical and acute postoperative pain [12,13]. However, controlled research on the effectiveness of regional anesthesia in preventing development of chronic pain syndromes is difficult in the combat situation. Many wounded troops have had regional anesthesia lasting at least 5 – 7 days, without serious anesthetic complications, but under field conditions the interval between injury and starting regional anesthesia could not be controlled or in some cases even documented, the duration of regional anesthesia was not controlled, and long term follow-up was not always conducted to investigate chronic pain development.

In this pilot study we aimed to establish a clinical research team and determine the feasibility of doing a complete study that would test the hypothesis that 5 day regional block after ankle fracture surgery would reduce the incidence of chronic pain at one year. Ankle fracture surgery was chosen as a proxy for combat injuries because it is a common procedure in our clinical facilities, providing a suitable number of research subjects; and because regional anesthesia for 5 days will be acceptable to patients and clinicians, not interfering with rehabilitation. In addition, ankle fracture results in a relatively high incidence of chronic pain conditions including CRPS, and these conditions have important long term negative effects on quality of life in 20% to 50% of patients [14-16].

2.0 METHODS

Research team: The research team assembled currently consists of the clinical research coordinator, the P.I. and sub-investigator from the research division of the Anesthesiology Department at the University of Cincinnati College of Medicine, two clinical anesthesiologists from that department, and one orthopedic surgeon from the Department of Orthopaedic Surgery. Additional research coordinators from the Department of Surgery provided assisted in execution of study.

Study setting and subject recruitment: The study was conducted in hospitals associated with the University of Cincinnati College of Medicine and associated UC Health hospitals: University of Cincinnati Medical Center, the tertiary care facility of the University of Cincinnati located in Cincinnati OH; Holmes Hospital, an outpatient surgery center on the same campus; and West Chester Hospital, an affiliated suburban hospital located in West Chester, OH. The study was approved by the University of Cincinnati Institutional Review Board (protocol number 2016-

4626), including a HIPAA exemption to examine medical records for the purpose of screening potential subjects, and was also approved by the USAF Human Research Protection Office. The trial was registered at the ClinicalTrials.gov website (ID NCT02950558, brief title "Anesthesia for Pain After Ankle Fracture Surgery"). Patients scheduled for open reduction and internal fixation for traumatic ankle fracture were identified in the electronic surgical schedule and their medical charts screened for inclusion/exclusion criteria. Potentially eligible subjects were approached by the study coordinator prior to their surgery and invited to participate.

Inclusion/Exclusion criteria:

Inclusion criteria –

- Adult patients of either sex, age 18 to 65
- Referred for surgery for open reduction and internal fixation for ankle fracture
- Agreed to have a single shot local nerve blockade (routinely offered as part of the standard-of-care but declined by some patients)
- Approved by the attending anesthesiologist and orthopedic surgeon (obtained without their having knowledge of whether the subject would be receiving a pump or standard care).

Exclusion criteria:

- patients unable to give informed consent in English
- unable to complete surveys in English
- unable to understand instructions for using the pump in English
- unavailable for follow-up
- Scheduled to enter a rehabilitation facility after the surgery (due to difficulty in conducting the 5 days of safety monitoring phone calls)
- polytrauma, i.e. undergoing other surgeries or having other fractures related to the precipitating cause of the ankle fracture
- infection such as abscess or bacterial infection; mild colds or upper respiratory infections did not require exclusion.
- peripheral vascular disease
- diabetes
- undergoing chemotherapy

- pregnancy (ropivacaine is FDA pregnancy category B; pregnancy test is routine part of the surgical procedure unless the woman signs a waiver; patients who sign such a waiver instead of having a pregnancy test were not eligible for the study, unless their medical record clearly indicated they had had a hysterectomy or tubal ligation.)
- lactating
- have heart disease or heart rhythm disorder or taking anti- antiarrhythmic drugs
- severe renal impairment (Class 3 or worse kidney disease)
- liver disease (cirrhosis or liver failure)
- ever had an allergic reaction to any type of local anesthetic
- taking therapeutic doses of anti-coagulants or anti-platelet therapy (prophylactic doses started because of the hospital admission were not an exclusion)
- taking antidepressants or other psychiatric medications (due to drug interaction risk per the ropivacaine data sheet)
- single shot local nerve block prior to surgery was ineffective (rare)
- selected for neuraxial anesthesia rather than general anesthesia for the open reduction surgery (rare)
- already receiving chronic analgesic therapy for a separate chronic pain condition

Experimental procedure: Eligible subjects who agreed to participate were consented by the study coordinator prior to their ankle surgery. Subjects were randomly assigned to receive either standard-of-care, or to also receive an ambulatory popliteal nerve block for 5 days starting immediately after the surgery was completed. A block-stratified randomization schedule with blocks of sizes 2 and 4 was established. The Cincinnati and West Chester locations had separate randomization schedules as it is thought the two locations provide somewhat different populations, making it desirable to have approximately equal numbers in the control and experimental groups at each site. All ankle surgery patients are currently given the option of popliteal nerve block (single injection of ropivacaine given just prior to surgery), which helps provide pain relief in the immediate postoperative period; the surgery itself is done under general anesthesia. For subjects randomized to receive popliteal ambulatory nerve block, a catheter was placed at the time of the single nerve block injection, immediately after the nerve injection and

taking advantage of the nerve localization procedure (ultrasound and if needed nerve stimulation) used to insert the needle for the single nerve block. An ambIT (Summit Medical Products, Inc., Sandy, UT) portable pump (as currently used in the participating hospitals after some other types of surgeries) was attached to the catheter at the time the block was placed, and continuous block with 0.2% ropivacaine was initiated immediately after surgery in the Post Anesthesia Recovery Unit (PACU). The catheters and pump were placed by attending anesthesiologists or by anesthesia residents under supervision of the attending anesthesiologists. The pumps were programmed to deliver 6 mL/hour with no provision for rescue boluses.

Because 5 day ambulatory block is longer than approved for clinically used ropivacaine preparations, an Investigational New Drug Application (IND) was submitted to the FDA (IND number 133334, Jun-Ming Zhang, sponsor) and approved. In order to avoid having subjects make multiple trips to the clinic for pump refills, the 5-day supply of ropivacaine was provided in 800 mL bags. The infusion pumps and 800 mL bags of ropivacaine were provided by the UC Health Investigational Pharmacy at the University of Cincinnati Medical Center. The ropivacaine 0.2% 800 mL bags were compounded by certified pharmacy technicians and registered pharmacists in a certified ISO Class 5 biologic safety cabinet within an ISO Class 7 buffer room at the University of Cincinnati Medical Center consistent with USP 797 standards and American Society of Health-System Pharmacists (ASHP) guidelines [17]. The bags were prepared by combining four, sterile, preservative-free, commercially available ropivacaine 0.2%, 200 mL bags/bottles[18] into a 1,000 mL empty sterile bag using a single sterile fluid transfer set. Using aseptic technique, the infusion spike of the sterile fluid transfer set was inserted into each commercial bag/bottle to drain completely (including any overfill) into the empty sterile bag via single needle manipulation of the injection port. After the fourth bag/bottle was drained, the needle and transfer set were disconnected from the compounded bag, and the injection port was aseptically covered with a foil seal. Compounded ropivacaine 0.2%, 800 mL bags were dispensed by the inpatient investigational pharmacy following a patient-specific order from a research team anesthesiologist. In order to ensure the sterility of the ropivacaine during the 5 days of use, the following procedure was used: The final ropivacaine 800 mL bags were considered medium-risk compounded sterile products (CSP). In lieu of a separate sterility test, USP 797 guidance indicates medium-risk CSPs should have a beyond use date (BUD) of 30

hours when stored at room temperature. To extend the BUD, sterility testing was performed on each ropivacaine 800 mL bag, using the QT JuniorTM System (Q.I. Medical, Inc., Grass Valley, CA, USA), which utilizes a 0.22-micron filtration set and fluid thioglycollate growth media[19]. The batched bag remained quarantined before use for 14 days after preparation. On day 14, the QT system being incubated from the tested bag was visually inspected for turbidity per the manufacturer instructions. If no turbidity was seen (i.e., negative growth) at day 14, then the batched bag was released for dispensing for an additional 14 days (i.e., 28 days total from preparation: 14 days quarantined plus 14 days post-release) while being stored at controlled room temperature in the investigational pharmacy until dispensed or expired. Released bags were only dispensed if the BUD did not extend beyond the planned 5-day therapy for a specific subject. Because of the requirement to quarantine ropivacaine and the relatively slow recruitment rate, it was not always possible to assure that ropivacaine would be available for a given subject. Therefore, randomization sometimes deviated from the randomization schedule: a subject scheduled to receive a pump could be placed in the control group if no compounded ropivacaine was available at the time of their surgery, which would be compensated by placing a subsequent subject scheduled to be in the control group into the experimental group when drug was available. On two occasions a subject scheduled to receive a pump was moved to the control group, and on one occasion a subject scheduled for the control group was moved to the pump group. These deviations were not based on subject characteristics. In addition, as the study was just getting underway a national shortage of ropivacaine occurred; in order to start the study the first subjects were moved to the control group.

All subjects were contacted daily for 5 days (duration of planned pump use) using a modified version of a phone script used at our facilities with all patients who have ambulatory pumps. This script was developed as part of obtaining FDA approval and a copy is given in Appendix 1. All subjects were asked for a verbal pain rating (The Verbal Numerical Scale, VNRS, 0 = no pain, 5 = moderate pain, 10 = worst possible pain) and for information about pain medication use on this call, while subjects with pumps were asked additional questions to check for potential complications of pump use. The total amount of ropivacaine used as indicated by the pump screen window was recorded at the time the subject was told to discontinue the pump.

Data: SEFAS: The primary instrument used to capture ankle pain was the Self-reported Foot and Ankle Score (SEFAS), a questionnaire designed to evaluate disorders of the foot and ankle. This patient-centered instrument is very quick to administer [20], and does not require physician input. A study of its use after surgery found it to be a valid, reliable, and responsive patient-oriented outcome measure [21]. It consists of 12 questions focusing primarily on pain and its functional impact on daily life activities[22]. Each response has 5 ordinal response choices scored 0 through 4, with the lowest score (0) representing the most severe disability and the highest total score being 48. If one question was not answered, the scores were renormalized to 48; if more than one was not answered, the score was not used[20]. We established an online copy of this survey which subjects could use to enter their responses, using the REDCap (Research Electronic Data Capture) system for secure web-based capture of questionnaire data with protection of confidentiality of the subjects' data. This service was provided by the Center for Clinical and Translational Science and Training with support from NIH Clinical and Translational Science Award (CTSA) program, grant 5UL1TR001425-04. When completing the questionnaire online, subjects were also asked to indicate what medications they were taking for their ankle pain.

Other clinical data and RAVE database: Additional data was obtained from the subjects' clinical records. These included: demographic information, height, age, and weight; information about the nature of the ankle fracture and duration and complexity of the surgery; information from the PACU stay including duration, VNRS, opioid use, and discharge location; and information from the follow-up appointments (anticipated to occur at 10-14 days, 5-6 weeks, and 3-4 months after surgery) including weight-bearing status, pain medication prescriptions, range of motion, and complications; and information about other medication conditions and prescribed medications. Data (other than the SEFAS) were entered into a Medidata Rave database developed for the study by the Data Management Center at Cincinnati Children's Hospital Medical Center in accordance with Good Clinical Data Management Practices. For privacy reasons, only subject IDs were assigned in the database. Data was cleaned with programmatic queries within Rave.

Clinical trial monitoring was conducted by the Human Research Protection Program of the University of Cincinnati Office of Research Integrity. The monitor conducted 4 on-site visits between October 9 2018 and June 19 2019.

Adverse event monitoring: The protocol incorporated FDA adverse event definitions. Adverse events were recorded by the study coordinator into the RAVE database and reviewed periodically by the medical monitor (a senior anesthesiologist not otherwise associated with the study). In addition to the 5 days of telephone contact noted above, subjects' medical records were examined for the 3 months following the ankle surgery to monitor adverse events.

Data analysis: A statistical analysis plan was developed during database development. The primary outcome was SEFAS scores at one year after the ankle surgery. Additional outcomes were: SEFAS scores at 14 day, 3 month, and 6 month time points. A preliminary analysis of possible confounding effects of the clinical variables obtained was planned, but has not been carried out due to the small enrollment numbers. Differences between the control and experimental groups were tested with the Mann-Whitney test or Fischer's exact test as appropriate. Time-series data were analyzed using two-way repeated measures ANOVA with Holm-Sidak posttest except where noted.

3.0 RESULTS

Enrollment: A total of 14 subjects was enrolled. Table 1 shows demographic information about the subjects. The two groups were well matched in age, BMI, and racial distribution, but the pump group had a much higher proportion of females despite the randomization procedure. This should be borne in mind when examining the preliminary results. Relatively few subjects were recruited at the suburban location (Table 2); recruitment at this site was opened later due to the extra logistics required due to the lack of an on-site Investigational Pharmacy.

Table 1: Demographics

	N	Age*	BMI*	Sex		Race	
Control	8	44.1 ± 3.6	31.2 ± 2.0	Female	2	White	7
				Male	6	Black	1
Pump	6	43.2 ± 6.3	31.5 ± 1.6	Female	5	White	5
				Male	1	Black	1
Total	14	43.7 ± 3.2	31.3 ± 1.3	Female	7	White	12
				Male	7	Black	2

*Mean ± S.E.M.

Table 2: Subjects per site

Site	N total	Control	Pump
Holmes	4	2	2
UCMC Main Hospital	7	5	2
West Chester	3	1	2

Screening failures: A total of 111 subjects were screened but not enrolled in the study. 55 were female and 56 were male. Ten (9%) were over age 65 and 1(0.9%) was under 18; these subjects were not screened for additional exclusions. Fourteen (13%) were eligible but declined to participate. Six (5%) could not be contacted or were not able to be invited due to timing issues. Twenty (14%) were excluded by the attending orthopedic surgeon and/or anesthesiologist and/or study coordinator, most often due to substance abuse, psychiatric disorders, other complex medical issues, or due to the nature of the injury. Often these subjects had additional exclusions. Other common exclusions were: polytrauma (32 subjects, 29% of screen failures; of these 13 had additional exclusions); diabetes (12 subjects, 11%; of these 8 had additional exclusions); and use of antidepressants or psychiatric medications (26 subjects, 23%; of these 16 had additional exclusions). A complete list of exclusions observed in the screen failures can be found in Appendix 2.

Pain Surveys: The statistical analysis plan developed for the project listed the SEFAS scores as the key outcomes of interest, with the one-year survey data considered the primary outcome measure. As planned during the initial grant submission, the collection of surveys will continue after the end of the funding period, hence most of the one-year data is not yet available (the most recent enrollments were in June 2019) but will be submitted as an amendment to this report. However, despite the small number of subjects enrolled, the data for the 3 month survey (last time point with complete data) showed a significantly better SEFAS score in the pump group compared to the control group (Figure 1). The difference between the medians was 8 (the full range of SEFAS scores is from 0 to 48). This difference is larger than the minimally important change of 5 determined for this instrument[23]. The surveys at the 14 day time point were often not useable (more than one question omitted), because up to 8 of the 12 questions do not apply to patients who are not weight-bearing, and we found that many subjects were not allowed to bear

weight on the affected ankle at this time. An example of such a question is " For how long have you been able to walk before severe pain arises from the ankle in question?".

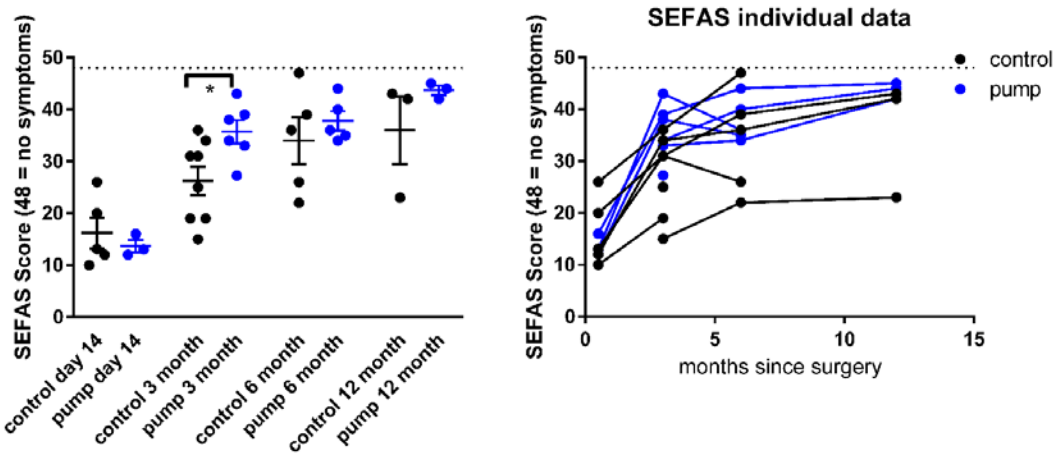

*Figure 1. Left: SEFAS scores at each time point (scatterplot with mean and S.E.M. indicated). *, p<0.05, significant difference between the two groups, Mann-Whitney test. (Repeated measure ANOVA was not used due to the fact that there was so much missing data at some time points but the data will be analylzed with this method once the remaining questionnaire data is received). Dotted line indicates maximum score (normal function); lower scores = higher pain and dysfunction. Right panel shows individual subject trajectories.*

The current status of the questionnaire responses is shown in table 3. An additional 8 surveys are still due to come in; data will be updated in an amended report.

Table 3: Survey response status

	Control (n = 8)			**Pump (n=6)**		
	Completed	**Missing**	**Not due yet**	**Completed**	**Missing**	**Not due yet**
14 day	7	1	0	6	0	0
3 month	8	0	0	6	0	0
6 month	5	2	1	5	1	0
12 month	3	1	4	3	0	3
Total	23	4	5	20	1	3
Response rate to date:		89.6%				

Other pain measurements: Because verbal pain scores were collected in the PACU at varying times and intervals from the subjects, they were summarized as area-under-the-curve. As shown in Figure 2, this measure did not differ significantly between the groups although the pump

group average was lower. Time spent in PACU also did not differ significantly between the groups although the average was lower in the pump group.

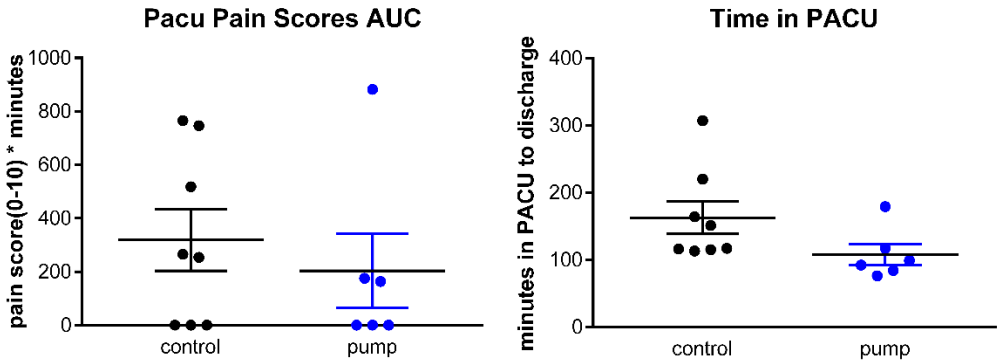

Figure 2. PACU pain-related variables. Verbal pain scores (0 - 10) were recorded periodically during the PACU stay and summarized as area-under-the-curve for each subject. Time from admission to discharge was also recorded for each subject. Differences between the groups were not significant (Mann-Whitney test).

Pain scores were also obtained daily from subjects during the 5 days of follow-up phone calls made as part of subject safety monitoring during the period of planned pump use. Subjects (including control subjects) were asked to rate their ankle pain on the 0-10 verbal pain scale. As shown in Figure 3, pain scores declined over the 5 days, but did not differ significantly between the two groups (2 way repeated measures ANOVA, p=0.0011 for time factor, p = 0.61 for group factor).

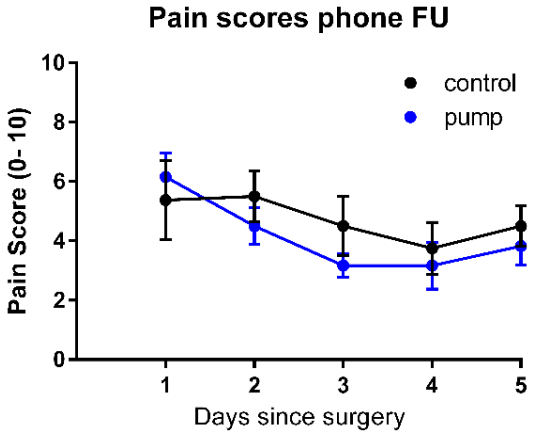

Figure 3 Verbal pain scores reported daily for the 5 days after surgery.

Use of medication for ankle pain was also reported along with each SEFAS survey. Most medications reported were NSAIDS and Tylenol; overall only 2 subjects reported opioid use at any time point and 2 reported using other categories of pain medication at any time point. As shown in Figure 4, the overall percentage of subjects reporting any analgesic use declined with

time but did not differ markedly between the groups. This data is incomplete at the 6 month and 12 month time points as noted above.

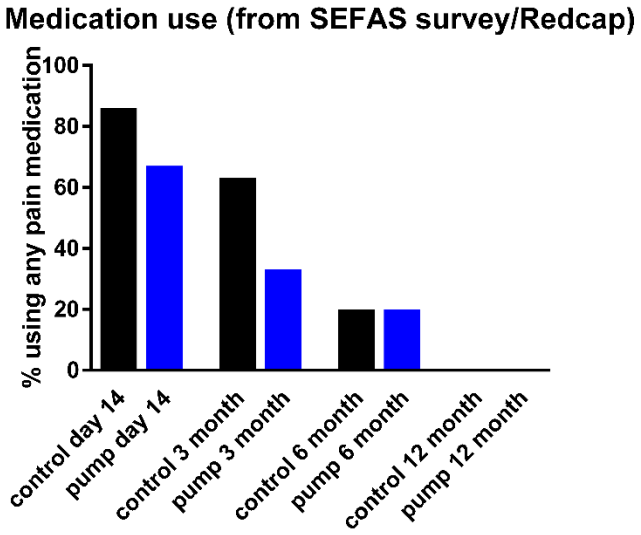

Figure 4. Percent of subjects reporting any use of medication for ankle pain at the time of the 4 SEFAS surveys. Data at 6 and 12 month time points is not yet complete.

Data obtained from orthopedic follow-up appointments: The study was designed to obtain data from the clinical records of follow-up orthopedic appointments that are part of the standard clinical care. Appointments at 10-14 days, 5- 6 weeks, and 3-4 months were programmed into the database, and information about pain status, weight-bearing status, range of motion, wound complications was to be entered from the clinical records. Of the 42 appointments for the 14 subjects, 4 did not occur or were not in the record, and data for 1 has not been entered yet. Most appointments occurred within the assumed range or close to it. The weight-bearing status was readily obtained from the medical charts. However, information about pain status was missing in 20 of 37 records, and information about range-of-motion status was missing in 25 of 37 records. Examining the records of the follow-up appointments also contributed to adverse event monitoring; the only event observed was wound dehiscence, in 1 subject in the control group, at the 5-6 week time point. Weight-bearing status was classified as non-weight-bearing, assisted (cane, walker, boot), or full weight-bearing. The available data did not suggest that use of the pump had any negative effects on the progression from non- to full weight-bearing (Table 4).

Table 4: Weight-bearing data from clinical follow-up orthopedic appointments

		Weight-bearing status				
Group	**Time of FU**	**Non**	**Assisted**	**Full**	**Missing data**	**N**
Control	10-14 Day	3	5	0	0	8
Pump	10-14 Day	4	2	0	0	6
Control	5-6 Week	2	5	0	1	8
Pump	5-6 Week	1	5	0	0	6
Control	3-4 Month	0	2	3	3	8
Pump	3-4 Month	0	1	4	1	6

Adverse events: No serious adverse events were noted. As noted above, one subject in the control group had mild dehiscence of the wound at 5 – 6 weeks that was not considered study related. One subject in the pump group reported abdominal pain with diarrhea and vomiting 2 days after surgery that was not considered study related. One subject in the pump group reported lightheadedness, nausea, and headache on day 3 that was not considered study related. The main problem encountered was that only one of the 6 subjects in the pump group received the full 5 days of treatment. The others had to discontinue early, primarily due to problems with catheter dislodgement or leakage. These are summarized in Table 5. As specified in the statistical analysis plan, these subjects were all analyzed with intent-to-treat protocol and are included in the pump group data presented above.

Due to the series of subjects with catheter leakage or disconnection problems, this issue was submitted to the IRB as a reportable event on July 12, 2019. The IRB suspended further enrollment until a modification could be submitted addressing this problem. On speaking with the pump manufacturer representative, who also spoke with the last subject listed in Table 5, the problem was likely caused by the catheter being pulled out at the hub. It was discovered that a field safety notice had been sent out indicating that the connecting clamp used at some of the hospital sites was prone to popping open, and required extra taping. A modification to the IRB protocol was submitted describing how the catheter and clamp taping procedure would be modified. This was approved by the IRB on July 17, 2019. This also caused a delay in the

regular annual continuing review, which was approved on Oct 4, 2019 by the IRB and Nov 1 by HRPO. This left little time for additional enrollments, and hence no enrollments occurred after June 20, 2019.

Table 5: Pump discontinuation data

Enrollment order	Days of pump use	Stopped early?	Reason for stopping
1	5.0	No	n/a
2	2.4	Yes	complaint of slight metallic taste around lips
3	3.8	Yes	Catheter leakage
4	3.5	Yes	pulled out catheter while showering (instructions for sponge bath only)
5	1.8	Yes	Catheter leakage
6	1.9	Yes	Catheter leakage - pulled out from clamped connector

4.0 DISCUSSION

Research team: As intended for this pilot study, the project provided an opportunity to assemble a clinical research team and infrastructure based in the department of Anesthesiology. The members of the research division and the participating physicians acquired a great deal of new experience with FDA processes, investigational pharmacy, clinical monitoring, and database development. This experience can be carried forward into future clinical trials.

Primary conclusions: As noted in the Results section, the primary endpoint data (pain score 1 year after surgery, as an indicator of chronic pain development), will not be available until the end of June 2020. The 3-month pain scores were encouraging, supporting the hypothesis that local nerve block in the days after surgery may prevent development of chronic pain. This is tempered by the fact that most subjects were not able to use the ambulatory pump for the full 5 days as originally planned.

Difficulties encountered: The study presented several logistical difficulties. The need to obtain FDA approval was not foreseen and was very time consuming. The requirement to batch and

quarantine the 5 day supply of ropivacaine meant that study drug was not always available, and added additional expenses for compounding and for wasted drug. Because we were recruiting trauma patients, there was for each subject a very narrow window of time, often less than 24 hours, between the initial presentation of the injury and the arrival of the subject in the Pre Op holding area, which was the last point at which subjects could be consented. In addition this meant that some traditional means of recruiting subjects such as advertising or posting on the hospital or university websites were not useful. The national shortage of ropivacaine just as the study was set to start recruiting subjects was also disruptive. Finally, the difficulties in setting up the ambulatory pump to last for 5 days were not anticipated based on our institution's prior successful experience using these pumps for shorter time periods, but limited the effectiveness and duration of the study.

Modifications suggested for a full study:

Screening criteria: It might be best to explicitly exclude people with substance abuse disorders; this became a de-facto exclusion due primarily to the decision of the attending physicians who must approve each subject's enrollment. This seems likely related to a perception that such subjects might not be reliable in providing follow-up or might not give accurate ratings of pain. The exclusion for antidepressant use might be modified in order to increase the pool of potential subjects. This exclusion was based on possible drug interactions, but instead a more specific list of excluded drugs might be obtained, or the FDA might be asked to approve enrollment of antidepressant users on the basis that low plasma levels of ropivacaine observed in pump users makes possible drug interactions less worrisome. The exclusion for diabetes seems difficult to modify given a number of studies showing that this increases the risk for catheter infection. The exclusion for polytrauma could perhaps be refined to allow some injuries that are not considered likely to result in chronic pain conditions. However, it seems scientifically difficult to justify examining the prevention of chronic ankle pain in someone who has had e.g. multiple other fractures as well. Another alternative might be to consider a different type of injury as the proxy condition to be studied; however, this would need to be amenable to ambulatory peripheral nerve block and to have a relatively high incidence of developing into chronic pain conditions. The use of this traumatic injury made recruiting logistically more difficult; there was a narrow

window of time between the subject's injury and the scheduled ankle surgery and this made it more difficult to recruit.

SEFAS: the instrument seemed to capture the desired information, however, it was not very useful for the 2 week time point because many of the questions assume the subject is already bearing weight on the ankle. It might be best to analyze a subset of the questions in order to capture the degree of pain at this time point. Early postoperative pain is an important predictor for developing chronic pain. However, using a subset would mean the use of a non-validated instrument and it would not allow comparison with SEFAS scores obtained at later time points. The response rate was reasonably good (close to 90%).

Study design: Depending on the data still to be obtained, shortening the pump use duration to e.g. 3 or 4 days might be considered, if the pilot data show that even the shorter durations seem to reduce chronic pain. On the other hand, the apparent lack of effect of the pump on the daily verbal pain scores (Figure 3) suggest that a somewhat higher flow rate than the 6 ml/hour used, and/or provision for bolus injection, might be useful. The observational study from the Cleveland Clinic [24] that was cited to justify safety of the procedure to the FDA used an 8 mL/hour with 12 mL bolus-on-demand per hour, with reprogramming allowed if pain control was inadequate. Extra care will need to be taken to ensure the catheter remains in place over the longer-than-usual time course, perhaps including having catheters placed only by study doctors. The attempt to obtain data from standard-of-care appointments was not very successful, in that these did not usually contain all the information elements programmed into the database. However, this did provide an important and useful component of the adverse event monitoring. For a full study, it would be best to have a research appointment at e.g. 6 or 12 months with a study physician to fully evaluate the presence and type of chronic pain conditions that develop. Efficiently testing the hypothesis that the treatment prevents chronic pain requires a relatively high incidence of chronic pain to occur; previous studies cited in our initial application showed ankle fracture resulting in chronic pain in 20% to 50% of patients [14-16]. To date we have only 7 of the 12-month surveys, of which only 1 subject still reported significant pain levels. Depending on how the final data appear, it may be worth considering a different type of injury to serve as a proxy for combat injuries that has a higher incidence of developing into chronic pain.

It might also be worth considering a type of surgery that has more time between initial presentation and surgery, to make recruitment easier, or to consider a condition that requires a longer hospitalization so that pump use could be in-hospital. This might also allow use of standard 200 mL bags of ropivacaine that are replaced, obviating the need for compounding and quarantine. A full size study should include a funding period that includes the year following the final enrollment; in the initial application it was thought that expenses incurred during this period would be minimal, consisting of only subject incentive payments, but because the study evolved into an FDA-regulated study, this final year also incurs more significant costs related to database maintenance and clinical trial monitoring.

5.0 CONCLUSIONS

This pilot study achieved the intended result of establishing a clinical research infrastructure and demonstrating the feasibility of testing extended regional anesthesia after trauma as a possible way to lower the risk of developing chronic pain conditions. The final study data containing the key primary endpoints will be submitted as an amendment after the last pain surveys are submitted in June 2020. Data at the 3 month time point were encouraging, as better pain scores were observed in the group receiving extended regional anesthesia. Several challenges to conducting this type of study were identified and useful information for designing a full-scale study was obtained.

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APPENDIX 1:

Script and data recording for telephone follow-up of study subjects – DOD extended regional nerve block study
Patient name _____ Record number _____Telephone number(s) _____
Date of surgery _____ Date and time on which catheter should be pulled _____
Randomized to receive pump? ☐ yes ☐ no
1st call: Date _____ Time _____ By _____ (print name and title, and sign)
Please check boxes and detail any "yes" answers. **Have subject discontinue pump if any marked * are answered yes.** A. How would you rate the ankle pain you are experiencing today, on a scale of 0 to 10 (where 0 is pain free and 10 is the worst pain imaginable)? _____
B. What pain medications have you used in the past 24 hours? Please give amounts if possible._____
Questions only for subjects with pumps:
*C. Are you experiencing any problems with the infusion pump? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]
D. Are you having any significant numbness☐, tingling☐or painful sensations☐ from your operated ankle?
*E. Do you have any light headedness, ringing in your ears or metallic taste in your mouth? ☐ yes ☐ no
*F. Is there any redness, discharge, or tenderness around the catheter infusion site (other than mild redness just at insertion site)? ☐ yes ☐ no
*G. Are there are leaks from the pump or around the catheter infusion site? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]
H. Do you have any problems with bleeding, irritation or redness from around the wound site? ☐ yes ☐ no

I. Is your foot completely numb ? ☐yes ☐ no
J. Can you move your foot around ? ☐yes ☐ no
K. Please read me the number from the screen on your pump, that shows how much drug has been dispensed. _____ [note: number will have one digit after the decimal point; the decimal point may be hard for subjects to see.
L. Do you have any questions about your pump?_____
☐ Patient told to turn off pump and remove catheter ☐ Patient told to return to the clinic ☐ Patient OK to continue using pump, Other comments:
_____

Script and data recording for telephone follow-up of study subjects – DOD extended regional nerve block study
Patient name _____ Record number _____Telephone number(s) _____
Date of surgery _____ Date and time on which catheter should be pulled _____
Randomized to receive pump? ☐ yes ☐ no
2nd phone call call: Date _____ Time _____ By _____ (print name and title, and sign)
Please check boxes and detail any "yes" answers. **Have subject discontinue pump if any marked * are answered yes.**
A. How would you rate the ankle pain you are experiencing today, on a scale of 0 to 10 (where 0 is pain free and 10 is the worst pain imaginable)? _____
B. What pain medications have you used in the past 24 hours? Please give amounts if possible._____
Questions only for subjects with pumps:
*C. Are you experiencing any problems with the infusion pump? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]
D. Are you having any significant numbness☐, tingling☐or painful sensations☐ from your operated ankle?
*E. Do you have any light headedness, ringing in your ears or metallic taste in your mouth? ☐ yes ☐ no
*F. Is there any redness, discharge, or tenderness around the catheter infusion site (other than mild redness just at insertion site)? ☐ yes ☐ no
*G. Are there are leaks from the pump or around the catheter infusion site? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]
H. Do you have any problems with bleeding, irritation or redness from around the wound site? ☐ yes ☐ no
I. Is your foot completely numb ? ☐yes ☐ no
J. Can you move your foot around ? ☐yes ☐ no
K. Please read me the number from the screen on your pump, that shows how much drug has been dispensed. _____ [note: number will have one digit after the decimal point; the decimal point may be hard for subjects to see.

L. Do you have any questions about your pump?_____
☐ Patient told to turn off pump and remove catheter ☐ Patient told to return to the clinic ☐ Patient OK to continue using pump, Other comments:
_____

Script and data recording for telephone follow-up of study subjects – DOD extended regional nerve block study
Patient name _____ Record number _____Telephone number(s) _____
Date of surgery _____ Date and time on which catheter should be pulled _____
Randomized to receive pump? ☐ yes ☐ no
3rd phone call call: Date _____ Time _____ By _____ (print name and title, and sign)
Please check boxes and detail any "yes" answers. **Have subject discontinue pump if any marked * are answered yes.**
A. How would you rate the ankle pain you are experiencing today, on a scale of 0 to 10 (where 0 is pain free and 10 is the worst pain imaginable)? _____
B. What pain medications have you used in the past 24 hours? Please give amounts if possible._____
Questions only for subjects with pumps:
*C. Are you experiencing any problems with the infusion pump? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]
D. Are you having any significant numbness☐, tingling☐or painful sensations☐ from your operated ankle?
*E. Do you have any light headedness, ringing in your ears or metallic taste in your mouth? ☐ yes ☐ no
*F. Is there any redness, discharge, or tenderness around the catheter infusion site (other than mild redness just at insertion site)? ☐ yes ☐ no
*G. Are there are leaks from the pump or around the catheter infusion site? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]
H. Do you have any problems with bleeding, irritation or redness from around the wound site? ☐ yes ☐ no
I. Is your foot completely numb ? ☐yes ☐ no
J. Can you move your foot around ? ☐yes ☐ no
K. Please read me the number from the screen on your pump, that shows how much drug has been dispensed. _____ [note: number will have one digit after the decimal point; the decimal point may be hard for subjects to see.
L. Do you have any questions about your pump?_____
☐ Patient told to turn off pump and remove catheter ☐ Patient told to return to the clinic ☐ Patient OK to continue using pump, Other comments:
_____

Script and data recording for telephone follow-up of study subjects – DOD extended regional nerve block study

Patient name _____ Record number _____Telephone number(s) _____

Date of surgery _____ Date and time on which catheter should be pulled _____

Randomized to receive pump? ☐ yes ☐ no

4th phone call call: Date _____ Time _____ By _____ (print name and title, and sign)

Please check boxes and detail any "yes" answers. **Have subject discontinue pump if any marked * are answered yes.**

A. How would you rate the ankle pain you are experiencing today, on a scale of 0 to 10 (where 0 is pain free and 10 is the worst pain imaginable)? _____

B. What pain medications have you used in the past 24 hours? Please give amounts if possible._____

Questions only for subjects with pumps:

*C. Are you experiencing any problems with the infusion pump? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]

D. Are you having any significant numbness☐, tingling☐or painful sensations☐ from your operated ankle?

*E. Do you have any light headedness, ringing in your ears or metallic taste in your mouth? ☐ yes ☐ no

*F. Is there any redness, discharge, or tenderness around the catheter infusion site (other than mild redness just at insertion site)? ☐ yes ☐ no

*G. Are there are leaks from the pump or around the catheter infusion site? ☐ yes ☐ no [**discontinue pump unless able to resolve over the phone**]

H. Do you have any problems with bleeding, irritation or redness from around the wound site? ☐ yes ☐ no

I. Is your foot completely numb ? ☐yes ☐ no

J. Can you move your foot around ? ☐yes ☐ no

K. Please read me the number from the screen on your pump, that shows how much drug has been dispensed. _____ [note: number will have one digit after the decimal point; the decimal point may be hard for subjects to see.

L. Do you have any questions about your pump?_____

☐ Patient told to turn off pump and remove catheter ☐ Patient told to return to the clinic ☐ Patient OK to continue using pump, Other comments:

_____

Script and data recording for telephone follow-up of study subjects – DOD extended regional nerve block study

Patient name _____ Record number _____Telephone number(s) _____

Date of surgery _____ Date and time on which catheter should be pulled _____ [try to call close to this time of day if possible]

Randomized to receive pump? ☐ yes ☐ no

5th (final) phone call call: Date _____ Time _____ By _____ (print name and title, and sign)

Please check boxes and detail any "yes" answers. **Have subject discontinue pump if any marked * are answered yes. Have patient discontinue pump at about the same time of day they entered the PACU, pull catheter, and discard pump.**

A. How would you rate the ankle pain you are experiencing today, on a scale of 0 to 10 (where 0 is pain free and 10 is the worst pain imaginable)? _____

B. What pain medications have you used in the past 24 hours? Please give amounts if possible._____

C. Have you had any change in medications since coming home from your surgery? ☐yes ☐ no (If yes, record details: _____)

Questions only for subjects with pumps:

*C. Are you experiencing any problems with the infusion pump? ☐ yes ☐ no

D. Are you having any significant numbness☐, tingling☐ or painful sensations☐ from your operated ankle?

*E. Do you have any light headedness, ringing in your ears or metallic taste in your mouth? ☐ yes ☐ no

*F. Is there any redness, discharge, or tenderness around the catheter infusion site (other than mild redness just at insertion site)? ☐ yes ☐no

*G. Are there are leaks from the pump or around the catheter infusion site? ☐yes ☐ no

H. Do you have any problems with bleeding, irritation or redness from around the wound site? ☐ yes ☐ no

I. Is your foot completely numb ? ☐ yes ☐ no

J. Can you move your foot around ? ☐ yes ☐ no

K. Please read me the number from the screen on your pump, that shows how much drug has been dispensed. _____ [note: number will have one digit after the decimal point; the decimal point may be hard for subjects to see.

L. Do you have any questions about your pump?

M. Please turn off your pump, and remove the catheter. [Refer patient to instructions that come with the pump regarding how to remove catheter.]

☐ Patient told to return to the clinic ☐ Patient told to turn off pump and remove catheter – 5 days completed.

Other comments: _____

Appendix 2:

Complete list of reasons for screen failures. A total of 111 subjects were screened but did not enroll. Most subjects have more than one exclusion.

Reason not enrolled	number of subjects
Eligible but declined	14
surgeon declined or non UC health orthopedic dept. surgeon	15
anesthesiologist declined	1
age >65 (not screened for further exclusions)	10
age <18 (not screened for further exclusions)	1
unable to give consent in English	6
unable to answer surveys in English	5
Not available for follow-up	7
polytrauma	31
talus injury	2
infection	0
peripheral vascular disease	1
diabetes	13
receiving chemotherapy	0
pregnant	0
lactating	1
heart disease, anti-arhyth drugs, renal impairment	7
liver disease	7
local anesthetic allergy	3
taking therapeutic blood thinners	2
taking anti-depressants/psychiatric meds	22
on meds for chronic pain condition	11
unable to meet with Pt	3
timing issue	3
not planned to discharge to home	2
study coordinator's judgement	5
not having general anesthesia	1