Comparison of Local Anesthetic Infusion Pump Versus Depofoam Bupivacaine for Pain Managemen

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Purpose

We propose a randomized controlled study to compare the effectiveness of a local-anesthetic continuous infusion pump system versus locally injectable FDA approved DepoFoam bupivacaine (Experal) for postsurgical analgesia in patients undergoing unilateral DIEP free flap reconstruction.

Specific Aims

1) Compare the amount of postoperative narcotic use in patients with a local-anesthetic continuous infusion pump system, locally injectable liposomal bupivacaine, and a control cohort by recording the type and amount of narcotic use from a patient's medication records.
2) Examine the incidence of narcotic-related side effects in the experimental groups as compared to the control cohort by documenting incidents of nausea and vomiting, time to first ambulation, and time to first liquid and solid oral intake.
3) Survey patient satisfaction with pain management using a visual analog scale during their hospital stay.

Rationale for the Project

Effective post-surgical pain control in patients undergoing unilateral deep inferior epigastric perforator (DIEP) free flap reconstruction. is critical to patient recovery, and can contribute to faster patient mobilization, shorter hosital stays and reduced health care costs. The admisitration of local anesthetics via wound infiltration is standard of care and an effective practice for postsurgical pain management. However, this method only provides relatively brief analgesia, usually lasting only 12 hours. Other FDA approved delivery systems using an indwelling fusion pump catherter (On–Q pump) are currently being used in our practice and may be used to extend the duration of action of locally adminisisted analgesia by continously infusing anesthetic into the wound. Alternativley, a depot form of bupivicaine has been FDA approved and currently used to deliver a single-dose admistered via wound infiltration for prolonged analgesia by allowing for the diffusion of the drug over an extended period of time. Both of these products are used as standard practice during DIEP free flap reconstructions. However, no studies compare the efficacy of these two methods patients undergoing unilateral DIEP flap reconstructions has been done in a prospective, randomized control manner.

Significance

We would like to compare Clevleland Clinic Foundation's experience with unilateral DIEP flap breast reconstruction to determine if postoperive pain management is improved

with either Depobupivicaine, a local infusion anesthetic pump as comapred to patients given standaad analgesic. We would like to conduct this study to better serve DIEP surgery patients

In a IRB approved pilot study performed by Dr Amir Ghaznavi, at Henry Ford Medical Center in Detroit,MI in 2014 , depoFoam Bupivicaine was compared to Bupivicane alone in patient undergoing breast reconstrcution with transverse rectus abdonius muscle (TRAM) or abdominoplasty procedures.

The primary endpoints were postoperative pain as measured by total postoperative morphine or hydromorphone utilization in a patient controlled analgesia (PCA) and pain scores on visual analog scale (VAS). The VAS was measured while the patients were at rest (VAS-R) and after the patient was asked to cough (VAS-C). Morphine usage was tracked by amount dispensed by the PCA pump. Using the medication chart any rescue medications beyond the PCA usage was also recorded. Patients were also interviewed and asked to rate their postoperative pain on a 10-point scale with 0 being no pain and 10 being the most pain. Other variables recorded were incidents of nausea or vomiting, time to first ambulation, and time to first liquid and solid oral intake. All variable measurements were obtained at 30 minutes, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours postoperatively

A total of twenty patients were randomized into Depofoam bupivacaine group (Exparel, n=15), and continuous infusion pump system (On-Q, n=5) after undergoing abdominoplasty or TRAM flaps. The Exparel group demonstrated higher morphine usage at the 30 minute time point compared to the On-Q group (5.2 mg vs 1.2mg), but a significantly lower volume at all other time points when compared to the On-Q group (6.2 mg vs 16.42 mg at 6 hrs; 5.5 mg vs 14.8 mg at 12 hrs; 5.98 mg vs 14.9 mg at 24 hrs; 5.23 mg vs 11.63 mg at 48 hrs; 2.7 mg vs 12.65 mg at 72 hrs). The VAS scores for the On-Q group were higher at the earlier time points (up to 6 hours) when compared to Exparel group and relatively the same during the remainder of the study (Figure 1 and Figure 2). The remaining variables that were examined revealed that the Exparel group had more nausea and vomiting at earlier time points but that the same group was ambulating, drinking and eating solid food at earlier time points than the On-Q group.

From this pilot study we concluded that with the use of a depot form of bupivicaine (Exparel), more effective postsurgical pain control was achieved in patients undergoing abdominoplasty or TRAM flap reconstruction than those that used an indwelling fusion pump catherters (On–Q pump). Further studies are necessary to enroll more participants undergoing these specific procedures in which this type of post surgical pain control may be most effective.

Our goal in this study is to expand the finding based from our pilot study by observing only those that undergo breast reconstruction with a DIEP flap.

Figure 1

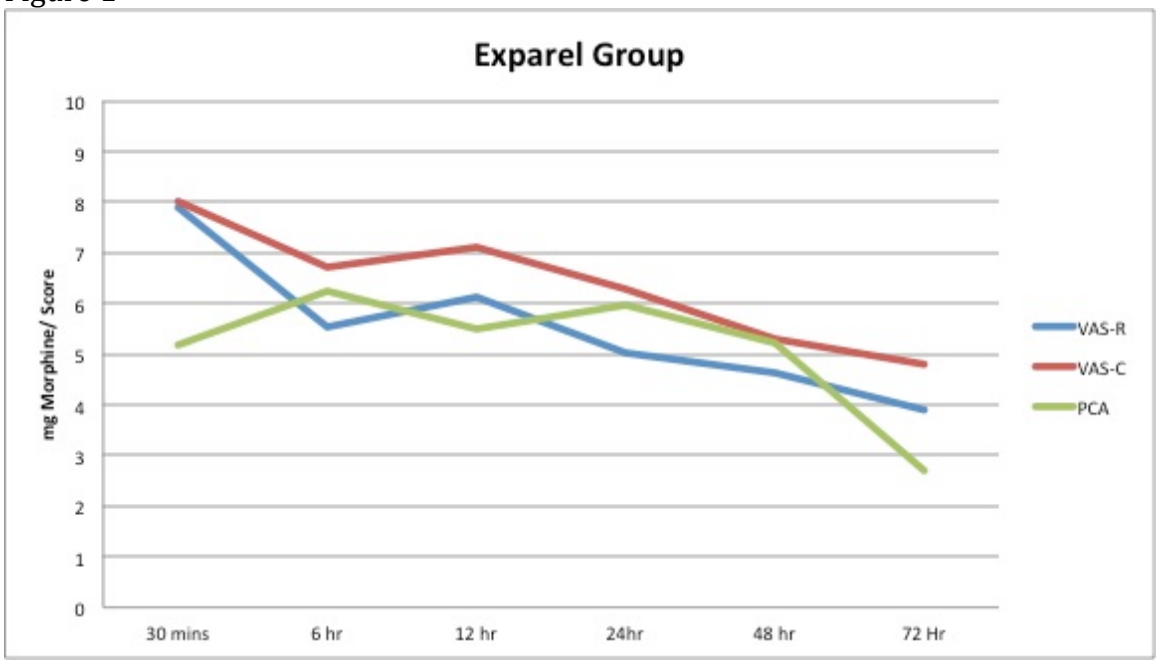
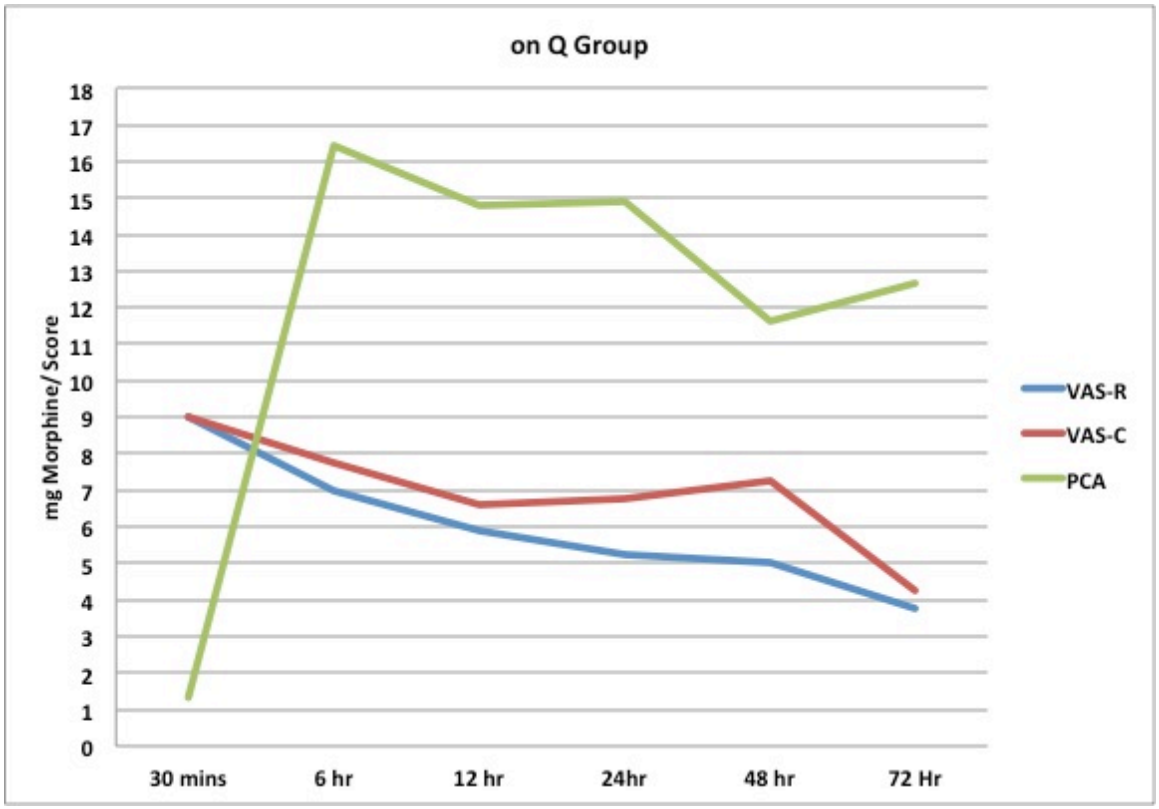


Figure 2



Subjects in the project

Study participants will include non-pregnant women aged 18 years or older scheduled to have unilateral DIEP flap breast reconstruction. Patients will be required to have an ASA physical status classification of 1, 2, or 3. Patients will be excluded if they have a concurrent or recent medical condition that could interfere with study participation, including history of hepatitis, alcohol/substance abuse, uncontrolled psychiatric disorders, known allergy, or contraindication to amide-type local anesthetics, opioids, or propofol. Patients will also be excluded if they have a body weight of less than 50 kg, have participated in another study involving an investigational medication within the prior 30 days, or are taking analgesics (ie, nonsteroidal anti-inflammatory drugs, acetaminophen, or opioids), antidepressants, or glucocorticoids within the 3 days before surgery.

Describe the control population

Group 3 of our study will compromise the control group for our study. Patients in this arm will receive .25% bupivacaine without epinephrine injected using ultrasound guidance in between the internal oblique and transversus abdominis muscles as well as along incisional lines. This form of local wound infiltration is the current standard of care for post-operative pain management for DIEP reconstructions of the breast.

Support the likelihood of recruiting the number of subjects required

Evidence from our Breast Reconstrcution database using data transferred from Epic/Clarity, in 2014 show fifty four unilateral DIEP breast reconstructions were performed and in 2013 sixty six unilateral DIEP breast reconstructions were performed.

Project Design and Protocol

All patients meeting the inclusion criteria will be randomized using a blocked randomization technique, stratifying patients by the timing of the procedure, and it will be employed to allocate patients in equal numbers to each group. The randomization will be created using the plan procedure within SAS software (version 9.3 or higher; Cary, NC).. Patients will be assigned to one of three groups: Group 1 -DepoBupivicaine Injection; Group 2- OnQ catheter placement, and the control Group 3- 0.25 % Bupivicaine injection.

Bupivacaine is a commonly utilized medicaiton for post-operative pain control with a favorable side-effect profile. The dosages of medications given in the study are within safe limits.

The maximum safety dosage of bupivicaine is 2mg/kg with a half life of 3.5 hours. This means a 70kg adult could receive 150mg (.15g). This calculation does not account for the slow release profile of DepoBupivicaine which would increase the maximum safe dose.

The DepoBupivicaine patients (Group 1) will receive an injection of 166mg of DepoBupivicaine diluted in 60mL, the On Q patients (Group 2) will receive an infiltration via an OnQ soaker catheter of 0.25% bupivicaine at 4mL/hour (ie. .01 gram/hour) and 0.25 % Bupivicaine patients (Group 3) will receive 2mg/kg of 0.25% of bupivicaine.

Consent

All patients will sign an informed consent that will be presented to them during a pre-operative visit with their attending surgeon.

Pre-operative Protocol

No preemptive morphine was given to patients. Patients at high risk for post-operative nausea and vomiting will be given Dexamethasone 4mg and Reglan 10 mg. Anesthesia will be given according to Table 1.

Table 1:

Induction	Propofol
Intubation (muscle relaxation)	Succinylcholine
Maintenacnce	Sevoflourane
Muscle relaxation	Rocuronium
Analgesia	Fentanyl 2-7 mcg/Kg
Prophylactic Analgesia	Toradol 30- 60 mg
Reversal	Glycopirolate + Neostigmine
Anti-emetic	Zofran 4 mg

Operative Technique

Surgeons for patients randomized to Group 1(DepoBupivicaine) will be given a schematic for injection of DepoBupivicaine. One 20 cc vial of EXPERAL (266 mg) will be diluted with 60 cc preservative-free normal sterile saline for a total volume of 80 cc. The infiltration technique for the DepoBupivicaine (See Baxter et al, and Hivelin et al) will be 20 cc of injected with a 25-gauge needle on either side of the suture line, (Figure 2 and Figure 3) injected directly into the fascia. The injections will be done in between the internal oblique and transversus abdominus muscles as determined via ultrasound.

Another 20 cc of will be injected on the outside edge of the surgical site where the sensory nerves branch up from the fascia to the skin flap. () The final 20 cc will be injected along the length of the incision where the skin will be anchored down with care to inject the product near the ileoinguinal nerve to ensure appropriate analgesic coverage . Once again, the DepoBupivicaine will be injected directly into the fascia above the muscle layer. All patients will have two closed-suction drains placed at the inferior aspect of the donor site, oriented horizontally and remote from the any infusion catheter..

For patients assigned to the Group 2 (OnQ) the surgeons will be given an instruction sheet with specific placement of catheter (See Bulter et al). All patients in the group will have two ON-Q soaker catheters installed into the abdominal donor site before donor-site closure. The catheters will be inserted through 3-mm stab incisions in the suprapubic area and 3 cm caudal to the donor-site incision. One catheter will be placed directly in the plane between the internal oblique and the transversus abdominus (see Hebbard et al) , and the second catheter will be placed subcutaneously, superficial to the anterior rectus sheath along the superior aspect of the donor site (Figure 1). At the conclusion of surgery, a 4-ml/hour infusion 0.25% Bupivicaine % solution will be delivered continuously by the continuous infusion
pump system (2 ml/hour through each catheter). All patients will have two closed-suction drains placed at the inferior aspect of the donor site, oriented horizontally and remote from the any infusion catheters.

Patients assigned to the control Group 3 (0.25 % Bupivicaine) will be given 0.25% bupivacaine without epinephrine. A dose of 2mg/kg will be given. Thus, a 80 kg patient will be given 80 cc of 0.25% Bupivacaine . The infiltration technique for the Maracine will be identical to the EXPERAL injection whereby 20 cc of will injected with a 25-gauge needle on either side of the suture line (Figure 2 and Figure 3) directly into the fascia above the muscle layer. The injections will be done in between internal oblique and transversus abdominus muscles as determined via ultrasound. Another 20 cc of will be injected on the outside edge of the surgical site where the sensory nerves branch up from the fascia to the skin flap (Figure 3). The final 20 cc will be injected along the length of the incision where skin will be anchored down; care will be taken to inject the product near the ileoinguinal nerve to ensure appropriate analgesic coverage (Figure 4). Once again, the 0.25% Bupivacaine will be injected directly into the fascia above the muscle layer. All patients will have two closed-suction drains placed at the inferior aspect of the donor site remote from the any infusion catheters and oriented horizontally.

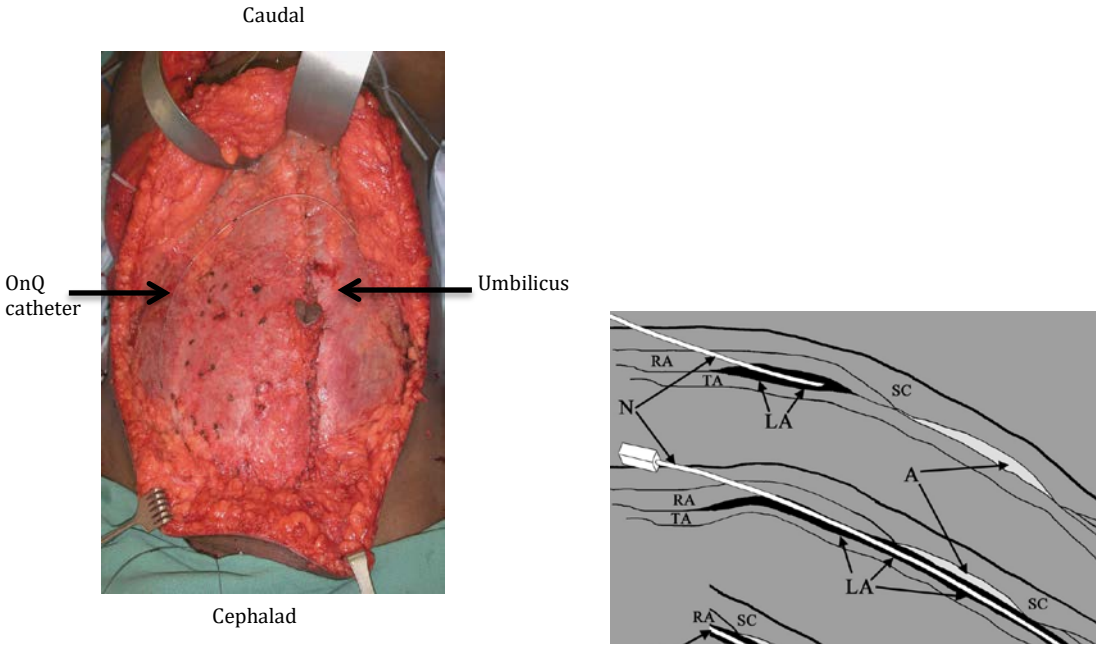
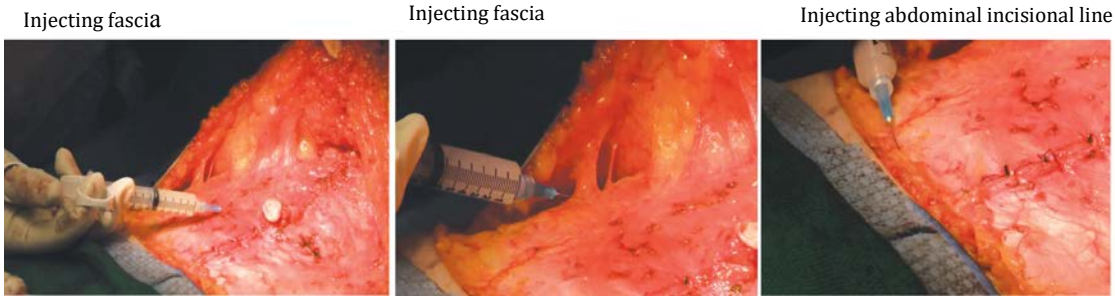


Figure 1. A. OnQ catheter *in vivo* prior to closure of open abdomen (See Haller et al) B. Schematic of OnQ catheter place in a plane above the Tranversus Abdominus (TA) (see Hebbard et al)



A. B. C.

Figure 2. Injecting bupivacaine into fascia and along incisional lines (C) prior to closure(Baxter et al).

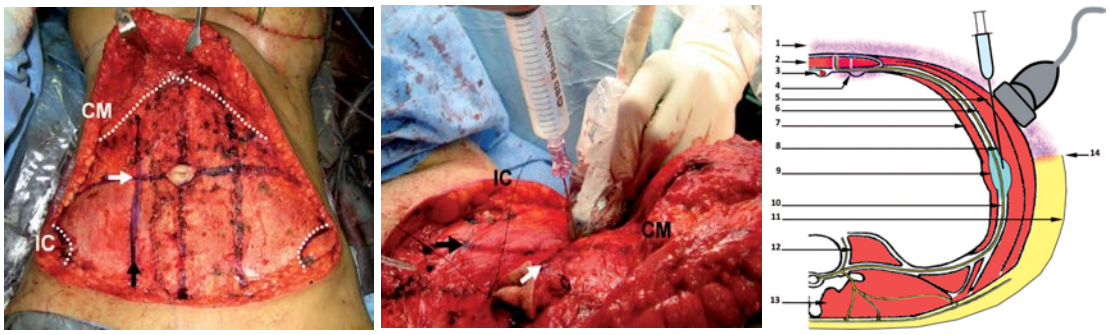


Figure 3 A. Open abdomen prior to closure marking site of injection of either DepoBupivicaine or 0.25 % Bupivicaine (White Arrow) B. Using ultrasound probe in vivo C. Schematic of plane between the Internal Oblique and Transversus Abdominus

Post-operative Protocol

No short-acting analgesics, such as Fentanyl, will be given post-operatively. All patients will receive a narcotic intravenously through a patient-controlled analgesia pump programmed for demand-only mode (no basal rate). The patient-controlled anesthesia will be filled with morphine or hydromorphone (if patient sensitivity to morphine). Oral narcotics will be offered when the patient's diet is advanced as tolerated, typically post-operative day 1. Patients will be encouraged to ambulate on post-operative day 1. The continuous infusion pump catheters will be removed by the surgeon when the pump is empty. Drains will be removed when output is less than 30mL in a consecutive 24 hour period.

Our primary endpoints will be postoperative pain as measured by total postoperative morphine or hydromorphone utilization from a patient controlled anesthesia pump (PCA) and pain scores on visual analog scale (VAS). The VAS will be measured while the patient is at rest (VAS-R) and after the patient is asked to cough (VAS-C). For each patient, the area under the curve (AUC) of the VAS-R will be calculated. Morphine usage will be tracked by patient controlled analgesia (PCA) dispensed. Using the medication chart, any rescue medications beyond the PCA will also be recorded. Patients will be interviewed and asked to rate their postoperative pain on a 10-point scale with 0 being no pain and 10 being the most pain. Another variables recorded will include incidents of nausea or vomiting, time to first ambulation, and time to first liquid and solid oral intake. All measurements for variables were obtained at 6 hrs, 12 hrs, 24 hrs, 48 hrs, 72 hrs. Nursing staff on our designated breast reconstruction floor will be instructed on how to interview patients and collect data for the 6 and 12 hour timepoints. This information will be stored on Epic EMR in a stardard note and nurses will be given a smart text to use in order to appropriately ascertain all information. The 24, 48, and 72 hour time points will be collected by the co-investigators. Any pain medications given by PCA, IV or PO will recorded and converted to morphine as diagramed below:

Equianalgesic Potency Conversion
TABLE A

Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone	NA	20
Hydrocodone	NA	30-45
Oxymorphone	1	10
Meperidine	75	300
Codeine	130	200

Discuss limitations and difficulties

The limitations of our study include potential confounding pain from the mastectomy site, the subjectivity in patient perception of pain, and differences in patient threshold to request patient- controlled anesthesia and oral narcotics

Provide the tentative schedule for completion

Our schedule for the study will be 6 months continuous enrollment and experimentation from September to February, or until our groups are filled. .

Data collection
The data fields will be: Birth date, sex, type of surgery, utilization of mesh, number of mg on PCA, VAS at rest and VAS with cough, number of rescue pain medications given, number of incidents of nausea/vomiting, time to first ambulation, time to first liquid and solid intake post surgery.

Planned Data Analysis

The data will be examined with an analysis of variance (ANOVA) procedure with repeated measures. The design will have one between factor, (group (3), and one within factor, time (6). The analysis will test for a group effect, a time effect and a group by time interaction. We anticipate that the three groups will be comparable at the start. This implies the likelihood of a significant interaction term. If this happens, our primary analysis will focus on the ANOVA for the 72-hour time point. This will show us if a differential effect has occurred. All assumptions of the test will be examined and data transformations or nonparametric methods used if indicated.

We will not be utilizing QHS, rather, one of the plastic surgery residents, Steven Rueda, will serve as our statistician.

Sample Size Justification

We propose to randomly assign individuals recruited during the recruitment period into 3 equal groups. With three groups this translates to a difference between groups of 5 for total morphine used on day 3 and 0.7 for the VAS. This assumes standard deviations of 4.9 for morphine and 0.7 for VAS. Effects of these sizes represent clinically important differences in the range that we believe will happen.

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