BMJ Open

AnAnkle Trial study protocol: a randomised trial comparing pain profiles after peripheral nerve block or spinal anaesthesia for ankle fracture surgery

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016001
Article Type:	Protocol
Date Submitted by the Author:	17-Jan-2017
Complete List of Authors:	Sort, Rune; Herlev Hospital, Dept. of Anaesthesiology Brorson, Stig; Herlev Hospital Gögenür, Ismail Møller, Ann; Herlev Hospital
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery, Patient-centred medicine
Keywords:	Anaesthesia in orthopaedics < ANAESTHETICS, Pain management < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Clinical trials < THERAPEUTICS

Title

AnAnkle Trial study protocol: a randomised trial comparing pain profiles after peripheral nerve block or spinal anaesthesia for ankle fracture surgery.

Rune Sort[1], Stig Brorson[2], Ismail Gögenur[3], Ann Merete Møller[1]

[1]Department of Anaesthesiology, Herlev and Gentofte University Hospital, Denmark.

[2]Department of Orthopaedic Surgery, Herlev and Gentofte University Hospital, Denmark.

[3]Department of Surgery, Centre for Surgical Science, Zealand University Hospital, Denmark.

Corresponding Author:

Rune Sort

Department of Anaesthesiology I65N9

Herlev and Gentofte University Hospital

Herlev Ringvej 75

2730 Herlev, Denmark

sort@dadlnet.dk

Tel: +45 38 68 60 30

Keywords: Peripheral nerve block, regional anaesthesia, ankle fracture, postoperative pain, rebound pain

Word count: 3930 words

Abstract

Introduction: Ankle fracture surgery is a common procedure but the influence of anaesthesia choice on postoperative pain and quality of recovery is poorly understood. Some authors suggest a benefit of peripheral nerve block (PNB) in elective procedures, but the different pain profile following acute fracture surgery and rebound pain upon cessation of the PNB remain unexplored. We present an ongoing randomised study aiming to compare primary PNB anaesthesia with spinal anaesthesia for ankle fracture surgery regarding postoperative pain profiles and quality of recovery.

Methods and analysis: AnAnkle Trial is a randomised, dual centre, open label, blinded analysis trial of 150 adult patients undergoing primary internal fixation of an ankle fracture. Main exclusion criteria are habitual opioid use, impaired pain sensation, other painful injuries or cognitive impairment. The intervention is ultrasound guided popliteal sciatic (20 ml) and saphenal nerve (8 ml) PNB with ropivacaine 7.5 mg/ml and controls receive spinal anaesthesia (2 ml) with hyperbaric bupivacaine 5 mg/ml. Postoperatively all receive paracetamol, ibuprofen and patient controlled i.v. morphine on demand. Morphine consumption and pain scores are registered in the first 27 hours and reported as an integrated pain score (IPS) as the primary endpoint. Pain score intervals are three hours and we will use the area under curve to get a longitudinal measure of pain. Secondary outcomes include rebound pain upon cessation of anaesthesia, opioid side effects (opioid related symptom distress score, OR-SDS), quality of recovery (QoR-15 score) and pain scores and medication day 1-7 (diary).

Ethics and dissemination: The study has been approved by the Regional Ethics Committees in the Capital Region of Denmark, the Danish Data Protection Agency and the Danish Health and Medical Authority. We will publish the results in international peer-reviewed medical journals.

Registration details: AnAnkle Trial is registered in The European Clinical Trials Database (EudraCT 2015-001108-76).

Strengths and limitations of this study

- This is the first trial to thoroughly investigate the postoperative pain profile and directly compare the most commonly used regional anaesthesia techniques for ankle fracture surgery.
- The trial is randomised and designed with attention to allocation concealment and stratification to prevent selection bias.
- The primary endpoint is a composite measure of pain and morphine consumption, which holds more statistical power than when analysing either of the two components alone.
- Blinding of participants and investigators is not feasible, thus the trial is open labelled with blinded data analysis.

Introduction

Peripheral nerve blocks (PNB) are getting increasingly popular for both primary anaesthesia and postoperative pain control in orthopaedic limb surgery, but its suitability for acute fracture surgery is not well established.

Ankle fracture is a common acute condition, which often requires surgery.[1,2] There is no evidence based consensus regarding the best choice of anaesthesia modality for this high volume procedure and the influence of this choice on the postoperative pain profile is poorly understood. Spinal anaesthesia (SA) is most common, but PNBs are becoming widely implemented, as they provide long lasting pain control and are regarded very safe.[3–7] There is some evidence that PNBs used in elective surgical procedures on knee, ankle and foot are effective in reducing pain, opioid consumption, and related side effects such as nausea and vomiting, as well as potentially reducing length of hospital stay and increasing patient satisfaction.[4,8–16] However, PNBs can represent a logistical challenge in the acute setting and, moreover, the pain profile following fractures and fracture surgery is naturally different from that of conditions requiring elective surgery.

Very few studies have investigated the efficacy and possible benefits of PNBs in this context and results are incongruous. One randomised study of postoperative pain scores in ankle fracture surgery showed initial benefit with PNB added to general anaesthesia but also revealed a sizeable "rebound pain" upon cessation of the PNBs, which could challenge the overall benefit on the postoperative pain profile.[17] Another randomised study of bimalleolar fracture surgery patients showed a longer postoperative effect of PNB anaesthesia compared with SA measured as time to first analgesic request, but pain levels were not measured.[18] At our centre, a large retrospective study of postoperative opioid consumption in ankle fracture surgery has suggested that the largest benefit of the regional anaesthesia modalities is obtained with PNBs.[19] However, in a prospective exploratory pilot study investigating primary PNB anaesthesia for ankle fracture surgery we also found a clear indication of rebound pain in relation to cessation of the PNB effect, especially in younger individuals (abstract published).[20]

We hypothesise that:

A. PNB anaesthesia for ankle fracture surgery reduces overall postoperative pain, opioid use and opioid related side-effects compared to SA.
B. Rebound pain following cessation of PNB anaesthesia is more pronounced than rebound pain following cessation of SA after ankle fracture surgery.
C. Patient experienced quality of recovery after ankle fracture surgery is better following PNB anaesthesia than following SA.

We therefore aim to assess the postoperative pain profile and quality of recovery after acute ankle fracture surgery in a randomised setting comparing primary PNB anaesthesia with SA.

Methods and analysis

Trial design

AnAnkle Trial is a prospective, randomised, parallel group, dual centre, open label, blinded analysis trial designed to assess the postoperative pain profile and quality of recovery following ankle fracture surgery under peripheral nerve block anaesthesia compared with spinal anaesthesia. Trial participants are randomly assigned to either SA or PNB anaesthesia as described below. Primary data are patient reported pain scores and on demand morphine consumption reported as an integrated pain score (IPS).

Participant eligibility and consent:

Treating physicians consecutively identify eligible subjects according to the listed criteria. Eligible subjects receive written and oral information and are included after obtaining informed written consent.

Inclusion criteria:

1. Scheduled for internal fixation of an ankle fracture
2. Age $\geq$ 18 years
3. Ability to read and understand Danish and give informed written consent

Exclusion criteria:

1. Allergy towards NSAID, paracetamol, morphine or local anaesthetics
2. Bodyweight < 52 kg; to avoid toxic doses of local anaesthetics
3. Contraindications for SA
4. Current gastro-intestinal bleeding
5. Proximal fibular fracture or multitrauma / other simultaneous fractures
6. Cognitive or psychiatric dysfunction or alcohol/narcotic substance abuse causing expected inability to comply with study protocol
7. No available anaesthesiologist with PNB capability at scheduled time of operation
8. Neuropathy / neurological dysfunction in the lower extremities
9. Habitual daily use of opioids
10. Pregnancy or breastfeeding
11. Infection at anaesthesia injection site
12. Nephropathy requiring dialysis
13. Acute porphyria

Recruitment period

All legislative and ethical approvals were obtained and the trial registered in The European Clinical Trials Database (EudraCT 2015-001108-76) by June 2015.[21,22] Inclusion was initiated in July 2015 and will continue until 150 patients have been included and their primary outcome data secured in an expected inclusion period of 22-24 months.

Sample size estimation

The target sample size for AnAnkle Trial is 150 participants. This estimation for the primary outcome (IPS) is based on the O'Brien Castello formula by calculating Wilcoxon-Mann-Whitney odds (WMW odds) for sample sizing in non-parametric statistics.[23,24] Prior studies have shown a positive correlation between the two parameters on which the IPS is based, i.e. higher pain scores are associated with a higher opioid consumption and vice versa.[23] Using data from our observational study we designed the trial to be able to detect a simultaneous 30 % difference in both morphine consumption and pain scores as we consider this a clinically meaningful difference.

This results in WMW odds = 1.75. With a power of 80 % (β = 20 %) and two sided significance level α = 5 % the resulting sample size is 141 patients. Adding 6 % to adjust for protocol violations results in a final sample size of 150 (2 x 75) patients to include.

We also conducted sample size estimations for the following key secondary outcomes, which were all found to be covered by the set sample size to include: rebound NRS-AUC for 6 hrs. with 50 % intergroup difference, rebound IPS 6 hrs. 30 % difference, NRS-AUC 0-27 hrs. 30 % difference, morphine consumption 0-27 hrs. 30 % difference, and quality of recovery score 10 % difference. All outcomes are listed below.

Randomisation and allocation concealment

Randomisation is externally managed, computer generated and irreversible. The allocation and participant trial identification number is retrieved via a secured website with an allocation ratio of 1:1 between PNB and spinal anaesthesia. The sequence is stratified by trial centre and patient age group (≤ or > 60 years of age) and performed as block randomisation with variable block sizes that are unknown to the investigators to maintain allocation concealment. We thereby follow the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and minimise possible bias from uneven inclusion between centres and age groups with potentially different pain profiles.

Blinding

The trial is open labelled. Thus, investigators and participants are not blinded, but data will be blinded by an independent consultant before analysis.

The difference in anaesthesia application between the groups (spinal in the lower back and PNB at lower thigh level) combined with the characteristic differences in onset and duration of anaesthesia makes blinding of both participants and physicians administering the anaesthesia effectively impossible. PNBs must be administered well before the surgery to ensure sufficient onset time whereas SA is best administered shortly before surgery to ensure adequate duration. A clear difference in duration of the anaesthesia effect between groups is expected which renders blinding of data collectors ineffective. Data for the main outcomes are registered directly by the participants (pain scores) or electronically (morphine PCA pump). Patients do not need to consult with staff to take morphine. The collected data will be anonymised and blinded by an external consultant, not otherwise involved in the trial, before statistical analysis is performed.

Interventions

Intervention group: PNB as ultrasound guided popliteal sciatic nerve block and mid-femoral saphenal nerve block with ropivacaine hydrochloride 7.5 mg/ml. We use a fixed dose of 20 ml (150 mg) for the sciatic nerve and 8 ml (60 mg) for the saphenal nerve to minimise the risk of toxic reactions. Unsuccessful block of a single nerve (tibial, peroneal or saphenal), defined as no effect on sensory function after 40-45 minutes or insufficient effect after 60 minutes, is supplemented with an additional dose of 5 ml or 10 ml provided the patient is weighing 62-71 kg or $\geq$ 72 kg respectively, thus staying within recommended total dosage of 4 mg/kg of ropivacaine.

Control group: standard SA using hyperbaric bupivacaine 5 mg/ml, 2.0 ml.

Both groups: small doses of midazolam, propofol or similar can be offered on demand during administration of spinal or PNB anaesthesia to help remedy any anxiety. Both groups will be offered light to moderate sedation during the operation with propofol i.v. If necessary, i.v. boluses of short action opioid such as fentanyl or sufentanil can be administered.

Standard postoperative pain medication regimen: tablet paracetamol 1000 mg x 4, tablet ibuprofen 400 mg x 3 and i.v. morphine via a patient controlled analgesia (PCA) pump system delivering 2.5 mg of morphine on demand with a 6 minute lock out period. The morphine is changed to tablets 5-10 mg on demand after 27 hours.

Outcomes:

Primary outcome measure:

- Integrated Pain Score (IPS) for the period 0-27 hours post-anaesthesia. IPS is based on Numeric Rating Scale pain score Area Under the Curve (NRS-AUC) and total morphine consumption. NRS pain score is registered every three hours.

The 27-hour primary study period was defined from experiences gained in the observational pilot study to ensure that we capture the full period of potential rebound pain in both groups. The PNBs lasted a mean of 16.5 hours and rebound pain stabilised and subsided within a maximum of about 6 hours. We chose time of anaesthesia as starting point rather than time of surgery because logistical challenges can result in fairly large variations in time from PNB administration to surgery.

Secondary outcome measures:

- Rebound pain: IPS for a 6-hour period from patient-reported time of cessation of the sensory block (PNB or spinal) in the ankle.
- NRS-AUC pain 0-27 hours post-anaesthesia.
- Morphine use 0-27 hours (PCA pump)
- Opioid adverse effects 0-27 hours = Clinically Meaningful Events (CME) assessed with the composite Opioid-Related Symptom Distress Scale (OR-SDS)[25,26]
- Quality of Recovery (Danish QoR-15 score)[27] 0-27 hours
- "Risk patients" i.e. number of patients with IPS +100 to +200 (= high pain *and* high morphine consumption)
- Peak NRS pain score 0-27 hours
- "High pain patients" i.e. number of patients reaching peak NRS ≥ 7

Tertiary outcome measures:

- NRS pain scores postoperative (PO) days 1-7
- Need for on demand opioids PO day 2-7
- Opioid adverse effects PO day 2 = CMEs assessed by the composite OR-SDS score
- Overall patient satisfaction with anaesthesia form including postoperative pain control, NRS-score
- Adverse events / adverse reactions
- Postoperative nerve related symptoms (PONS) on PO day 7

The OR-SDS questionnaire has been validated in English.[25,26,28] We conducted a Danish translation for AnAnkle Trial using two independent medical doctors, bi-lingual in English and Danish. Disagreements were discussed with the principal investigator and minor adjustments were made in a second round after testing the translated version on 8 patients.

Data management, audit and safety

Only data necessary for evaluation of the stated outcomes, safety parameters and possible confounders are collected and only after inclusion and randomisation upon retrieving informed written consent.

For every included patient a Case Report Form (CRF) is devised for registration of all data except morphine use, which is electronically registered by the PCA pump and saved as patient specific files. Data sources include patient reported pain scores, questionnaires and diary, electronic patient files and the PCA morphine data files. The NRS pain scores are registered directly by the patients on paper. They also note the time of return of sensation to the ankle.

All data are marked and handled according to GCP standards and legislative permission by the Danish Data Protection Agency.

Safety:

Any adverse events or reactions (AEs) within five half-lives of the intervention drugs are registered and classified using the Common Terminology Criteria for Adverse Events (CTCAE)[29]. All severe AEs (SAEs) are reported to the responsible trial sponsor and followed until stabile or resolved. If an SAE meet criteria for reporting it is forwarded immediately to the Danish Medicines Agency and the Ethics Committee.

The trial will be stopped in its entirety in the unlikely event that incidence and severity of adverse events compromise the safety of trial participants as evaluated by the trial group.

AnAnkle Trial is monitored by the independent GCP unit at Copenhagen University Hospital through regular auditing visits to both trial centres.

Protocol violations and participant withdrawal

Protocol violations:

- Failed spinal or PNB (defined as change of anaesthesia modality necessary)
- Glucocorticoids or controlled-release opioids administered on the day of surgery

Participants meeting any one of these criteria will not be excluded and data are collected as planned. Data will be included in an intention-to-treat (ITT) analysis but omitted in per-protocol analyses.

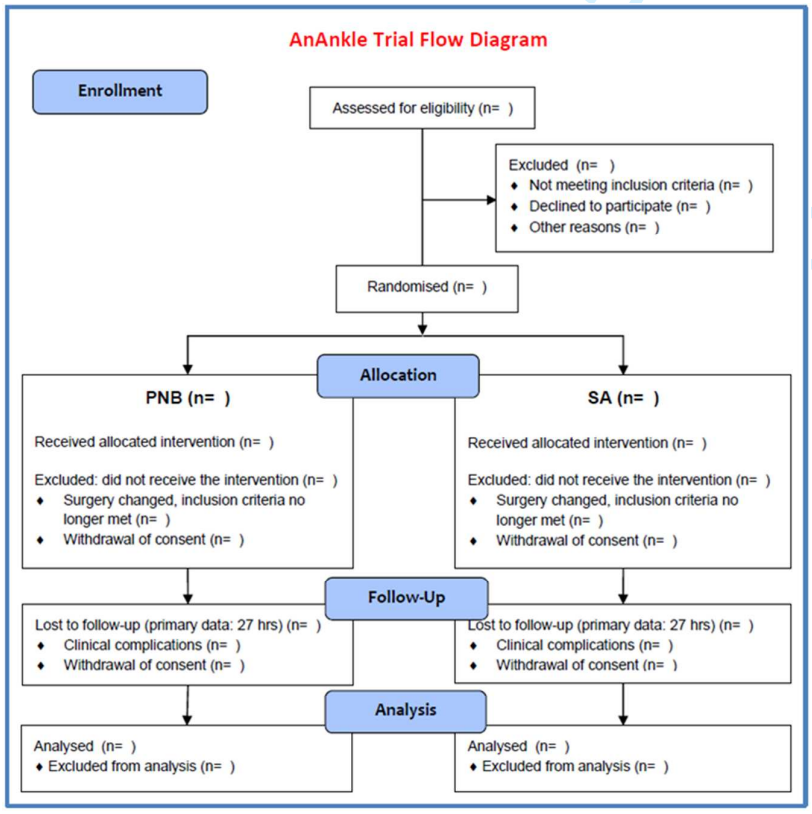
Participant withdrawal:

Participants can be withdrawn / excluded after randomisation if:

- Surgery is cancelled after administration of anaesthesia. The patient can be re-included later if possible.
- Surgery is rescheduled or changed after randomisation and eligibility is no longer upheld according to the in- and exclusion criteria.
- Postoperative complications make the patient unable to comply with study protocol for obtaining primary data (pain scores and PCA-morphine data for 27 hours).
- Withdrawal of consent, before all primary data are obtained (pain scores and PCA-morphine data for 27 hours).

Participants meeting any of these criteria can be excluded from the trial after randomisation. No data will be analysed and they will be replaced by additional inclusion until the calculated sample size is included for ITT analysis. For safety reasons adverse events will be registered for any excluded patients who have received the intervention (anaesthesia). An overview is shown in the flow diagram (figure).

Withdrawal of consent or failure to comply with the protocol after 27 hours postoperatively will not lead to exclusion from analysis of already collected data.



Statistical plan

Primary outcome analysis:

Pain scores and morphine data cannot be expected to follow normal distribution and we expect to handle the primary outcome using non-parametric statistics. The Integrated Pain Score has been validated statistically with this in mind.[23] It is derived from pain scores (NRS-AUC in our trial) and total morphine consumption. Both measures are ranked across both trial groups and the IPS is calculated as deviation from mean rank in pain score added to deviation from mean rank in morphine giving a result for each trial participant between -200 % and +200 %. The groups can be compared for significant difference with a distribution-independent permutation test and/or Mann-Whitney test and effect size can be expressed by Ratio of Mean Rank (RoMR) or WMW-odds.[23]

Analysis of the primary outcome will be performed as "intention-to-treat" analysis including all consenting randomised patients not meeting the defined withdrawal criteria. Additional "per-protocol" analyses will be performed and include only participants who follow the protocol without the defined protocol violations.

Two-sided p-values < 0.05 will be considered statistically significant.

Secondary outcome analyses:

Again, we expect to handle most outcomes using non-parametrical statistics. However, some results such as NRS-AUC measures may prove to resemble a normal distribution which, taken together with the fairly large sample size, warrants the use of parametrical tests in order to obtain confidence intervals on these estimates. In parametric models, we may include adjustment for expected heavy confounders, i.e. age, diabetes and fracture severity (uni-, bi- or trimalleolar), as this can increase the accuracy of the estimate, even though the groups are expected to be comparable due to randomisation.

Subgroup analyses:

Pain experience is known to vary with age and possibly gender.[30] We have stratified randomisation in two age groups (≤ or > 60 years of age) and will perform subgroup analysis on relevant outcomes according to age group and gender.

Accountability procedure for missing data for analysis:

Data for the primary outcome are registered from 0-27 hours from time of anaesthesia. Missing data after this time (till end of participation on postoperative day 7) will not be replaced.

Some missing data are expected in the patient reported NRS pain scores from 0-27 hours. Pragmatically we will fill in a missing measure point with the average of the two adjacent points, in effect drawing a line between them (linear interpolation), and thus allowing for AUC to be calculated. If the missing point is the last one (at 27 hours) the value of the last observation is carried forward. If more than two 0-27 hours NRS scores are missing, the patient will be excluded from per protocol analyses.

The measuring of rebound pain is performed over a period of 6 hours following patient evaluated cessation of the sensory block. Should this period extend beyond the 27-hour-period we will carry forward the last observation to extrapolate data. As the mean effect duration of the PNBs in our observational study was around 16 hours we do not expect that extrapolation will be necessary. When appropriate, we will perform sensitivity analyses to evaluate the impact of data extrapolation.

Ethics and dissemination

Ethical and legislative approvals

AnAnkle Trial is conducted in accordance with applicable regulatory requirements and the study protocol, which is approved by the Regional Ethics Committees in the Capital Region of Denmark, the Danish Data Protection Agency and the Danish Health and Medical Authority. We follow national and international standards for good clinical practice (ICH GCP guidelines) and the recommendations of the CONSORT Statement and extension in reporting randomised clinical pragmatic trials.[31] The protocol was drafted following the SPIRIT guidelines accordingly.[32] The project is monitored by the Copenhagen GCP unit.

Publication plan

We strive to readily publish the results in international peer-reviewed journals and all results will be made public, regardless of whether they come out positive, negative or inconclusive. Due to the complexity of the pain profiles, we intend to publish the results in at least two independent articles with focus on the primary outcome measure and the secondary measure of rebound pain respectively.

All authors must fulfil the criteria of the Vancouver convention.

Discussion

Regional anaesthesia is often preferred in ankle fracture surgery due to the superior safety profile and probably better postoperative pain control compared with general anaesthesia.[17,19,33] To the best of our knowledge, AnAnkle Trial is the first study to thoroughly investigate the postoperative pain profile and

test which one of the most frequently used regional anaesthesia techniques is superior. Postoperative pain studies are often limited by large time intervals between pain registrations. We designed our trial to avoid this issue since it renders evaluation of the clinical significance of rebound pain impossible, because the rebound could be very intense yet completely undetected in-between pain scorings.

AnAnkle Trial constitutes a scientifically strong setup although blinding of the participants and investigators is not practically possible which holds a potential risk of bias; e.g. reported pain scores might be affected by psychological factors influenced by information from the investigators. To minimise this influence, all pain scores used for the primary outcome are registered by the participants, without consulting the staff. Likewise, the morphine data are gathered electronically from the PCA pump, which the patient activates without consulting the staff, thus ensuring a minimal risk of related bias. Finally, data analysis will be blinded. As in most other clinical trials, there remains a risk of sampling bias due to the eligibility criteria, which might impair the overall generalisability of our results.

Among the strengths of the design are randomisation and attention to sequence generation and allocation concealment to prevent selection bias between the two groups. The block randomisation and stratification protect against bias from variability of practice during a relatively long inclusion period on different centres. We have chosen a composite score of pain assessment and opioid consumption as primary outcome. The IPS has been thoroughly tested and proven to hold more statistical power than conventional comparisons of pain scores or morphine alone.[23] There is a natural correlation between the two that can lead to failure in identifying a true effect, or even lead to finding a false positive effect, on either outcome, when not balanced by evaluation of the other. In this study we will use the IPS with a longitudinal pain measurement in the form of AUC pain score rather than a single pain rating. This allows us to illustrate the pain profile over time without letting the results be compromised by statistical mass significance. The individual components of the IPS are separately analysed among various secondary endpoints to provide supplementary details to the composite primary endpoint, as is recommended in the IMMPACT consensus on pain trials.[34]

If AnAnkle Trial yields clear results the implications on clinical practice could be profound. Fracture surgery is very common and optimising the choice of anaesthesia will have a major influence on the postoperative recovery and the overall patient course for a very large group of patients.

Authors' contributions

Rune Sort: Idea development, study planning, writing first draft, revisions, approving final protocol, registering and obtaining legislative and ethical approvals.

Stig Brorson: Idea development, study planning, draft revisions, approving final protocol.

Ismail Gögenur: Idea development, study planning, draft revisions, approving final protocol.

Ann Merete Møller: Idea development, study planning, draft revisions, approving final protocol.

Funding statement

This study is supported by the non-profit Danish Society of Anaesthesia and Intensive care Medicine "DASAIMs Forskningsinitiativ", the private non-profit foundation "Viggo og Krista Pedersens Fond" and by the public source "Forskningsrådet Herlev Hospital". The first author is the sponsor; the funders have no role in design, conduction or analysis of this trial.

Competing interests statement

None to declare.

Acknowledgements

We would like to thank Jesper Kent Nielsen, M.D., Consultant Anaesthetist, Herlev and Gentofte University Hospital, Herlev, Denmark and Nicolai Bang Foss, M.D., DMSc, Consultant Anaesthetist, Hvidovre and Amager Hospital, Hvidovre, Denmark for valuable input during idea development and drafting of the protocol. We thank biostatistician Tobias Wirenfeldt Klausen, MSc, Dept. of Haematology, Herlev and Gentofte Hospital, Herlev, Denmark for statistical assistance and we thank OPEN, Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark for the secure online randomisation solution.

Data sharing

This is a study protocol so there are no data yet. The trial registration is freely accessible in The European Clinical Trials Database (EudraCT 2015-001108-76).

References

1 Daly PJ, Fitzgerald RH, Melton LJ, *et al.* Epidemiology of ankle fractures in Rochester, Minnesota. *Acta Orthop Scand* 1987;**58**:539–44.

2 Court-Brown CM, McBirnie J, Wilson G. Adult ankle fractures--an increasing problem? *Acta Orthop Scand* 1998;**69**:43–7.

3 Watts SA, Sharma DJ. Long-term neurological complications associated with surgery and peripheral nerve blockade: outcomes after 1065 consecutive blocks. *Anaesth Intensive Care* 2007;**35**:24–31.

4 Klein SM, Nielsen KC, Greengrass RA, *et al.* Ambulatory discharge after long-acting peripheral nerve blockade: 2382 blocks with ropivacaine. *Anesth Analg* 2002;**94**:65–70.

5 Jeng CL, Torrillo TM, Rosenblatt MA. Complications of peripheral nerve blocks. *Br J Anaesth* 2010;**105 Suppl**:i97-107. doi:10.1093/bja/aeq273

6 Capdevila X, Pirat P, Bringuier S, *et al.* Continuous peripheral nerve blocks in hospital wards after orthopedic surgery: a multicenter prospective analysis of the quality of postoperative analgesia and complications in 1,416 patients. *Anesthesiology* 2005;**103**:1035–45.

7 Sites BD, Taenzer AH, Herrick MD, *et al.* Incidence of local anesthetic systemic toxicity and postoperative neurologic symptoms associated with 12,668 ultrasound-guided nerve blocks: an analysis from a prospective clinical registry. *Reg Anesth Pain Med* 2012;**37**:478–82. doi:10.1097/AAP.0b013e31825cb3d6

8 Capdevila X, Barthelet Y, Biboulet P, *et al.* Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999;**91**:8–15.

9 Elliot R, Pearce CJ, Seifert C, *et al.* Continuous infusion versus single bolus popliteal block following major ankle and hindfoot surgery: a prospective, randomized trial. *Foot Ankle Int* 2010;**31**:1043–7. doi:10.3113/FAI.2010.1043

10 White PF, Issioui T, Skrivanek GD, *et al.* The use of a continuous popliteal sciatic nerve block after surgery involving the foot and ankle: does it improve the quality of recovery? *Anesth Analg* 2003;**97**:1303–9.

11 Liu SS, Strodtbeck WM, Richman JM, *et al.* A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. *Anesth Analg* 2005;**101**:1634–42. doi:10.1213/01.ANE.0000180829.70036.4F

12 Grosser DM, Herr MJ, Claridge RJ, *et al.* Preoperative lateral popliteal nerve block for intraoperative and postoperative pain control in elective foot and ankle surgery: a prospective analysis. *Foot Ankle Int* 2007;**28**:1271–5. doi:10.3113/FAI.2007.1271

13 Xu J, Chen X, Ma C, *et al.* Peripheral nerve blocks for postoperative pain after major knee surgery. In: Wang X, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: : John Wiley & Sons, Ltd 2014. CD010937. doi:10.1002/14651858.CD010937.pub2

14 Chan E-Y, Fransen M, Parker DA, *et al.* Femoral nerve blocks for acute postoperative pain after knee replacement surgery. In: Chan E-Y, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: : John Wiley & Sons, Ltd 2014. CD009941. doi:10.1002/14651858.CD009941.pub2

15 Casati A, Cappelleri G, Berti M, *et al.* Randomized comparison of remifentanil-propofol with a sciatic-femoral nerve block for out-patient knee arthroscopy. *Eur J Anaesthesiol* 2002;**19**:109–14.

16 Jankowski CJ, Hebl JR, Stuart MJ, *et al.* A comparison of psoas compartment block and spinal and general anesthesia for outpatient knee arthroscopy. *Anesth Analg* 2003;**97**:1003–9, table of contents.

17 Goldstein RY, Montero N, Jain SK, *et al.* Efficacy of popliteal block in postoperative pain control after ankle fracture fixation: a prospective randomized study. *J Orthop Trauma* 2012;**26**:557–61. doi:10.1097/BOT.0b013e3182638b25

18 Protić A, Horvat M, Komen-Usljebrka H, *et al.* Benefit of the minimal invasive ultrasound-guided single shot femoro-popliteal block for ankle surgery in comparison with spinal anesthesia. *Wien Klin Wochenschr* 2010;**122**:584–7. doi:10.1007/s00508-010-1451-9

19 Christensen KP, Møller AM, Nielsen JK, *et al.* The Effects of Anesthetic Technique on Postoperative Opioid Consumption in Ankle Fracture Surgery. *Clin J Pain* 2016;**32**:870–4. doi:10.1097/AJP.0000000000000335

20 Sort R, Brorson S, Gögenur I, *et al.* Peripheral nerve block in primary ankle fracture surgery - exploring rebound pain. *Eur J Anaesthesiol* 2015;**32**:88.

21 The European Medicines Agency. EudraCT public website. EMA. https://eudract.ema.europa.eu/

22 The European Medicines Agency. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/

23 Dai F, Silverman DG, Chelly JE, *et al.* Integration of pain score and morphine consumption in analgesic clinical studies. *J Pain* 2013;**14**:767–77.e8. doi:10.1016/j.jpain.2013.04.004

24 Noether GE. Sample Size Determination for Some Common Nonparametric Tests. *J Am Stat Assoc* 1987;**82**:645–7. doi:10.1080/01621459.1987.10478478

25 Chan KS, Chen W-H, Gan TJ, *et al.* Development and validation of a composite score based on clinically meaningful events for the opioid-related symptom distress scale. *Qual Life Res* 2009;**18**:1331–40. doi:10.1007/s11136-009-9547-2

26 Yadeau JT, Liu SS, Rade MC, *et al.* Performance characteristics and validation of the Opioid-Related Symptom Distress Scale for evaluation of analgesic side effects after orthopedic surgery. *Anesth Analg* 2011;**113**:369–77. doi:10.1213/ANE.0b013e31821ae3f7

27 Kleif J, Edwards HM, Sort R, *et al.* Translation and validation of the Danish version of the postoperative quality of recovery score QoR-15. *Acta Anaesthesiol Scand* 2015;**59**:912–20. doi:10.1111/aas.12525

28 Apfelbaum JL, Gan TJ, Zhao S, *et al.* Reliability and validity of the perioperative opioid-related symptom distress scale. *Anesth Analg* 2004;**99**:699–709, table of contents. doi:10.1213/01.ANE.0000133143.60584.38

29 National Institute of Cancer. Common Terminology Criteria for Adverse Events (CTCAE). *NIH Publ* 2010;**2009**:0–71. doi:10.1080/00140139.2010.489653

30 Ip HYV, Abrishami A, Peng PWH, *et al.* Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009;**111**:657–77. doi:10.1097/ALN.0b013e3181aae87a

31 Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869.

32 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:e7586.

33 Jordan C, Davidovitch RI, Walsh M, *et al.* Spinal anesthesia mediates improved early function and

pain relief following surgical repair of ankle fractures. *J Bone Joint Surg Am* 2010;**92**:368–74. doi:10.2106/JBJS.H.01852

34 Turk DC, Dworkin RH, McDermott MP, *et al.* Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. *Pain* 2008;**139**:485–93. doi:10.1016/j.pain.2008.06.025

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	1,5
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12-13
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9+fig.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,9+fig.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4,5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

AnAnkle Trial study protocol: a randomised trial comparing pain profiles after peripheral nerve block or spinal anaesthesia for ankle fracture surgery

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016001.R1
Article Type:	Protocol
Date Submitted by the Author:	31-Mar-2017
Complete List of Authors:	Sort, Rune; Herlev Hospital, Dept. of Anaesthesiology Brorson, Stig; Herlev Hospital Gögenür, Ismail Møller, Ann; Herlev Hospital
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Surgery, Patient-centred medicine
Keywords:	Anaesthesia in orthopaedics < ANAESTHETICS, Pain management < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Clinical trials < THERAPEUTICS

Title

AnAnkle Trial study protocol: a randomised trial comparing pain profiles after peripheral nerve block or spinal anaesthesia for ankle fracture surgery.

Rune Sort[1], Stig Brorson[2], Ismail Gögenur[3], Ann Merete Møller[1]

[1]Department of Anaesthesiology, Herlev and Gentofte University Hospital, Denmark.

[2]Department of Orthopaedic Surgery, Herlev and Gentofte University Hospital, Denmark.

[3]Department of Surgery, Centre for Surgical Science, Zealand University Hospital, Denmark.

Corresponding Author:

Rune Sort

Department of Anaesthesiology I65N9

Herlev and Gentofte University Hospital

Herlev Ringvej 75

2730 Herlev, Denmark

sort@dadlnet.dk

Tel: +45 38 68 60 30

Keywords: Peripheral nerve block, regional anaesthesia, ankle fracture, postoperative pain, rebound pain

Word count: 3930 words

Abstract

Introduction: Ankle fracture surgery is a common procedure but the influence of anaesthesia choice on postoperative pain and quality of recovery is poorly understood. Some authors suggest a benefit of peripheral nerve block (PNB) in elective procedures, but the different pain profile following acute fracture surgery and rebound pain upon cessation of the PNB remain unexplored. We present an ongoing randomised study aiming to compare primary PNB anaesthesia with spinal anaesthesia for ankle fracture surgery regarding postoperative pain profiles and quality of recovery.

Methods and analysis: AnAnkle Trial is a randomised, dual centre, open label, blinded analysis trial of 150 adult patients undergoing primary internal fixation of an ankle fracture. Main exclusion criteria are habitual opioid use, impaired pain sensation, other painful injuries or cognitive impairment. The intervention is ultrasound guided popliteal sciatic (20 ml) and saphenal nerve (8 ml) PNB with ropivacaine 7.5 mg/ml and controls receive spinal anaesthesia (2 ml) with hyperbaric bupivacaine 5 mg/ml. Postoperatively all receive paracetamol, ibuprofen and patient controlled i.v. morphine on demand. Morphine consumption and pain scores are registered in the first 27 hours and reported as an integrated pain score (IPS) as the primary endpoint. Pain score intervals are three hours and we will use the area under curve to get a longitudinal measure of pain. Secondary outcomes include rebound pain upon cessation of anaesthesia, opioid side effects (opioid related symptom distress score, OR-SDS), quality of recovery (QoR-15 score) and pain scores and medication day 1-7 (diary).

Ethics and dissemination: The study has been approved by the Regional Ethics Committees in the Capital Region of Denmark, the Danish Data Protection Agency and the Danish Health and Medical Authority. We will publish the results in international peer-reviewed medical journals.

Registration details: AnAnkle Trial is registered in The European Clinical Trials Database (EudraCT 2015-001108-76).

Strengths and limitations of this study

- This is the first trial to thoroughly investigate the postoperative pain profile and directly compare the most commonly used regional anaesthesia techniques for ankle fracture surgery.
- The trial is randomised and designed with attention to allocation concealment and stratification to prevent selection bias.
- The primary endpoint is a composite measure of pain and morphine consumption, which holds more statistical power than when analysing either of the two components alone.
- Blinding of participants and investigators is not feasible, thus the trial is open labelled with blinded data analysis.

Introduction

Peripheral nerve blocks (PNB) are getting increasingly popular for both primary anaesthesia and postoperative pain control in orthopaedic limb surgery, but its suitability for acute fracture surgery is not well established.

Ankle fracture is a common acute condition, which often requires surgery.[1,2] There is no evidence based consensus regarding the best choice of anaesthesia modality for this high volume procedure and the influence of this choice on the postoperative pain profile is poorly understood. Spinal anaesthesia (SA) is most common, but PNBs are becoming widely implemented, as they provide long lasting pain control and are regarded very safe.[3–7] There is some evidence that PNBs used in elective surgical procedures on knee, ankle and foot are effective in reducing pain, opioid consumption, and related side effects such as nausea and vomiting, as well as potentially reducing length of hospital stay and increasing patient satisfaction.[4,8–16] However, PNBs can represent a logistical challenge in the acute setting and, moreover, the pain profile following fractures and fracture surgery is naturally different from that of conditions requiring elective surgery.

Very few studies have investigated the efficacy and possible benefits of PNBs in this context and results are incongruous. One randomised study of postoperative pain scores in ankle fracture surgery showed initial benefit with PNB added to general anaesthesia but also revealed a sizeable "rebound pain" upon cessation of the PNBs, which could challenge the overall benefit on the postoperative pain profile.[17] Another randomised study of bimalleolar fracture surgery patients showed a longer postoperative effect of PNB anaesthesia compared with SA measured as time to first analgesic request, but pain levels were not measured.[18] At our centre, a large retrospective study of postoperative opioid consumption in ankle fracture surgery has suggested that the largest benefit of the regional anaesthesia modalities is obtained with PNBs.[19] However, in a prospective exploratory pilot study investigating primary PNB anaesthesia for ankle fracture surgery we also found a clear indication of rebound pain in relation to cessation of the PNB effect, especially in younger individuals (abstract published).[20]

We hypothesise that:

A. PNB anaesthesia for ankle fracture surgery reduces overall postoperative pain, opioid use and opioid related side-effects compared to SA.
B. Rebound pain following cessation of PNB anaesthesia is more pronounced than rebound pain following cessation of SA after ankle fracture surgery.
C. Patient experienced quality of recovery after ankle fracture surgery is better following PNB anaesthesia than following SA.

We therefore aim to assess the postoperative pain profile and quality of recovery after acute ankle fracture surgery in a randomised setting comparing primary PNB anaesthesia with SA.

Methods and analysis

Trial design

AnAnkle Trial is a prospective, randomised, parallel group, dual centre, open label, blinded analysis trial designed to assess the postoperative pain profile and quality of recovery following ankle fracture surgery under peripheral nerve block anaesthesia compared with spinal anaesthesia. The study is conducted in two university hospitals in the Capital Region of Denmark. Trial participants are randomly assigned to either SA or PNB anaesthesia as described below. Primary data are patient reported pain scores and on demand morphine consumption reported as an integrated pain score (IPS).

Participant eligibility and consent:

Treating physicians consecutively identify eligible subjects according to the listed criteria. Eligible subjects receive written and oral information and are included after anaesthesiologist investigators have obtained informed written consent.

Inclusion criteria:

1. Scheduled for internal fixation of an ankle fracture
2. Age ≥ 18 years
3. Ability to read and understand Danish and give informed written consent

Exclusion criteria:

1. Allergy towards NSAID, paracetamol, morphine or local anaesthetics
2. Bodyweight < 52 kg; to avoid toxic doses of local anaesthetics
3. Contraindications for SA
4. Current gastro-intestinal bleeding
5. Proximal fibular fracture or multitrauma / other simultaneous fractures
6. Cognitive or psychiatric dysfunction or alcohol/narcotic substance abuse causing expected inability to comply with study protocol
7. No available anaesthesiologist with PNB capability at scheduled time of operation
8. Neuropathy / neurological dysfunction in the lower extremities
9. Habitual daily use of opioids
10. Pregnancy or breastfeeding
11. Infection at anaesthesia injection site

12. Nephropathy requiring dialysis
13. Acute porphyria

Recruitment period

All legislative and ethical approvals were obtained and the trial registered in The European Clinical Trials Database (EudraCT 2015-001108-76) by June 2015.[21,22] Inclusion was initiated in July 2015 and will continue until 150 patients have been included and their primary outcome data secured in an expected inclusion period of 22-24 months.

Sample size estimation

The target sample size for AnAnkle Trial is 150 participants. This estimation for the primary outcome (IPS) is based on the O'Brien Castello formula by calculating Wilcoxon-Mann-Whitney odds (WMW odds) for sample sizing in non-parametric statistics.[23,24] Prior studies have shown a positive correlation between the two parameters on which the IPS is based, i.e. higher pain scores are associated with a higher opioid consumption and vice versa.[23] Using data from our observational study we designed the trial to be able to detect a simultaneous 30 % difference in both morphine consumption and pain scores as we consider this a clinically meaningful difference. We did not plan any interim analyses.

This results in WMW odds = 1.75. With a power of 80 % (β = 20 %) and two sided significance level α = 5 % the resulting sample size is 141 patients. Adding 6 % to adjust for protocol violations results in a final sample size of 150 (2 x 75) patients to include.

We also conducted sample size estimations for the following key secondary outcomes, which were all found to be covered by the set sample size to include: rebound NRS-AUC for 6 hrs. with 50 % intergroup difference, rebound IPS 6 hrs. 30 % difference, NRS-AUC 0-27 hrs. 30 % difference, morphine consumption 0-27 hrs. 30 % difference, and quality of recovery score 10 % difference. All outcomes are listed below.

Randomisation and allocation concealment

Randomisation is externally managed, computer generated and irreversible. The allocation and participant trial identification number is retrieved via a secured website with an allocation ratio of 1:1 between PNB and spinal anaesthesia. The sequence is stratified by trial centre and patient age group (≤ or > 60 years of age) and performed as block randomisation with variable block sizes that are unknown to the investigators to maintain allocation concealment. We thereby follow the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and minimise possible bias from uneven inclusion between centres and age groups with potentially different pain profiles.

Blinding

The trial is open labelled. Thus, investigators and participants are not blinded, but data will be blinded by an independent consultant before analysis.

The difference in anaesthesia application between the groups (spinal in the lower back and PNB at lower thigh level) combined with the characteristic differences in onset and duration of anaesthesia makes blinding of both participants and physicians administering the anaesthesia effectively impossible. PNBs must be administered well before the surgery to ensure sufficient onset time whereas SA is best administered shortly before surgery to ensure adequate duration. A clear difference in duration of the anaesthesia effect between groups is expected which renders blinding of data collectors ineffective. Data for the main outcomes are registered directly by the participants (pain scores) or electronically (morphine PCA pump). Patients do not need to consult with staff to take morphine. The collected data will be anonymised and blinded by an external consultant, not otherwise involved in the trial, before statistical analysis is performed.

Interventions

Intervention group: PNB as ultrasound guided popliteal sciatic nerve block and mid-femoral saphenal nerve block with ropivacaine hydrochloride 7.5 mg/ml. We use a fixed dose of 20 ml (150 mg) for the sciatic nerve and 8 ml (60 mg) for the saphenal nerve to minimise the risk of toxic reactions. Unsuccessful block of a single nerve (tibial, peroneal or saphenal), defined as no effect on sensory function after 40-45 minutes or insufficient effect after 60 minutes, is supplemented with an additional dose of 5 ml or 10 ml provided the patient is weighing 62-71 kg or $\geq$ 72 kg respectively, thus staying within recommended total dosage of 4 mg/kg of ropivacaine.

Control group: standard SA using hyperbaric bupivacaine 5 mg/ml, 2.0 ml.

Both groups: small doses of midazolam, propofol or similar can be offered on demand during administration of spinal or PNB anaesthesia to help remedy any anxiety. Both groups will be offered light to moderate sedation during the operation with propofol i.v. If necessary, i.v. boluses of short action opioid such as fentanyl or sufentanil can be administered.

Standard postoperative pain medication regimen: tablet paracetamol 1000 mg x 4, tablet ibuprofen 400 mg x 3 and i.v. morphine via a patient controlled analgesia (PCA) pump system delivering 2.5 mg of morphine on demand with a 6 minute lock out period. The morphine is changed to tablets 5-10 mg on demand after 27 hours.

Outcomes:

Primary outcome measure:

- Integrated Pain Score (IPS) for the period 0-27 hours post-anaesthesia. IPS is based on Numeric Rating Scale pain score Area Under the Curve (NRS-AUC) and total morphine consumption. NRS pain score is registered every three hours.

The 27-hour primary study period was defined from experiences gained in the observational pilot study to ensure that we capture the full period of potential rebound pain in both groups. The PNBs lasted a mean of 16.5 hours and rebound pain stabilised and subsided within a maximum of about 6 hours. We chose time of anaesthesia as starting point rather than time of surgery because logistical challenges can result in fairly large variations in time from PNB administration to surgery.

Secondary outcome measures:

- Rebound pain: IPS for a 6-hour period from patient-reported time of cessation of the sensory block (PNB or spinal) in the ankle.
- NRS-AUC pain 0-27 hours post-anaesthesia.
- Morphine use 0-27 hours (PCA pump)
- Opioid adverse effects 0-27 hours = Clinically Meaningful Events (CME) assessed with the composite Opioid-Related Symptom Distress Scale (OR-SDS)[25,26]
- Quality of Recovery (Danish QoR-15 score)[27] 0-27 hours
- "Risk patients" i.e. number of patients with IPS +100 to +200 (= high pain *and* high morphine consumption)
- Peak NRS pain score 0-27 hours
- "High pain patients" i.e. number of patients reaching peak NRS ≥ 7

Tertiary outcome measures:

- NRS pain scores postoperative (PO) days 1-7
- Need for on demand opioids PO day 2-7
- Opioid adverse effects PO day 2 = CMEs assessed by the composite OR-SDS score
- Overall patient satisfaction with anaesthesia form including postoperative pain control, NRS-score
- Adverse events / adverse reactions

- Postoperative nerve related symptoms (PONS) on PO day 7

The OR-SDS questionnaire has been validated in English.[25,26,28] We conducted a Danish translation for AnAnkle Trial using two independent medical doctors, bi-lingual in English and Danish. Disagreements were discussed with the principal investigator and minor adjustments were made in a second round after testing the translated version on 8 patients.

Data management, audit and safety

Only data necessary for evaluation of the stated outcomes, safety parameters and possible confounders are collected and only after inclusion and randomisation upon retrieving informed written consent.

For every included patient a Case Report Form (CRF) is devised for registration of all data except morphine use, which is electronically registered by the PCA pump and saved as patient specific files. Data sources include patient reported pain scores, questionnaires and diary, electronic patient files and the PCA morphine data files. The NRS pain scores are registered directly by the patients on paper. They also note the time of return of sensation to the ankle.

All data are marked and handled according to GCP standards and legislative permission by the Danish Data Protection Agency.

Safety:

Any adverse events or reactions (AEs) within five half-lives of the intervention drugs are registered and classified using the Common Terminology Criteria for Adverse Events (CTCAE)[29]. All severe AEs (SAEs) are reported to the responsible trial sponsor and followed until stabile or resolved. If an SAE meets criteria for reporting it is forwarded immediately to the Danish Medicines Agency and the Ethics Committee.

The trial will be stopped in its entirety in the unlikely event that incidence and severity of adverse events compromise the safety of trial participants as evaluated by the trial group or by the Danish Medicines Agency.

AnAnkle Trial is monitored by the independent GCP unit at Copenhagen University Hospital through regular auditing visits to both trial centres, thus ensuring adherence to GCP guidelines as well as proper handling and reporting of AEs.

Protocol violations and participant withdrawal

Protocol violations:

- Failed spinal or PNB (defined as change of anaesthesia modality necessary)
- Glucocorticoids or controlled-release opioids administered on the day of surgery

Participants meeting any one of these criteria will not be excluded and data are collected as planned. Data will be included in an intention-to-treat (ITT) analysis but omitted in per-protocol analyses.

Participant withdrawal:

Participants can be withdrawn / excluded after randomisation if:

- Surgery is cancelled after administration of anaesthesia. The patient can be re-included later if possible.
- Surgery is rescheduled or changed after randomisation and eligibility is no longer upheld according to the in- and exclusion criteria.
- Postoperative complications make the patient unable to comply with study protocol for obtaining primary data (pain scores and PCA-morphine data for 27 hours).
- Withdrawal of consent, before all primary data are obtained (pain scores and PCA-morphine data for 27 hours).

Participants meeting any of these criteria can be excluded from the trial after randomisation. No data will be analysed and they will be replaced by additional inclusion until the calculated sample size is included for ITT analysis. For safety reasons adverse events will be registered for any excluded patients who have received the intervention (anaesthesia). An overview is shown in the flow diagram (figure).

Withdrawal of consent or failure to comply with the protocol after 27 hours postoperatively will not lead to exclusion from analysis of already collected data.

Statistical plan

Primary outcome analysis:

Pain scores and morphine data cannot be expected to follow normal distribution and we expect to handle the primary outcome using non-parametric statistics. The Integrated Pain Score has been validated statistically with this in mind.[23] It is derived from pain scores (NRS-AUC in our trial) and total morphine consumption. Both measures are ranked across both trial groups and the IPS is calculated as deviation from mean rank in pain score added to deviation from mean rank in morphine giving a result for each trial participant between -200 % and +200 %. The groups can be compared for significant difference with a distribution-independent permutation test and/or Mann-Whitney test and effect size can be expressed by Ratio of Mean Rank (RoMR) or WMW-odds.[23]

Analysis of the primary outcome will be performed as "intention-to-treat" analysis including all consenting randomised patients not meeting the defined withdrawal criteria. Additional "per-protocol" analyses will be performed and include only participants who follow the protocol without the defined protocol violations.

Two-sided p-values < 0.05 will be considered statistically significant.

Secondary outcome analyses:

Again, we expect to handle most outcomes using non-parametrical statistics. However, some results such as NRS-AUC measures may prove to resemble a normal distribution which, taken together with the fairly large sample size, warrants the use of parametrical tests in order to obtain confidence intervals on these estimates. In parametric models, we may include adjustment for expected heavy confounders, i.e. age, diabetes and fracture severity (uni-, bi- or trimalleolar), as this can increase the accuracy of the estimate, even though the groups are expected to be comparable due to randomisation.

Subgroup analyses:

Pain experience is known to vary with age and possibly gender.[30] We have stratified randomisation in two age groups (≤ or > 60 years of age) and will perform subgroup analysis on relevant outcomes according to age group and gender.

Accountability procedure for missing data for analysis:

Data for the primary outcome are registered from 0-27 hours from time of anaesthesia. Missing data after this time (till end of participation on postoperative day 7) will not be replaced.

Some missing data are expected in the patient reported NRS pain scores from 0-27 hours. Pragmatically we will fill in a missing measure point with the average of the two adjacent points, in effect drawing a line between them (linear interpolation), and thus allowing for AUC to be calculated. If the missing point is the last one (at 27 hours) the value of the last observation is carried forward. If more than two 0-27 hours NRS scores are missing, the patient will be excluded from per protocol analyses.

The measuring of rebound pain is performed over a period of 6 hours following patient evaluated cessation of the sensory block. Should this period extend beyond the 27-hour-period we will carry forward the last observation to extrapolate data. As the mean effect duration of the PNBs in our observational study was around 16 hours we do not expect that extrapolation will be necessary. When appropriate, we will perform sensitivity analyses to evaluate the impact of data extrapolation.

Ethics and dissemination

Ethical and legislative approvals

AnAnkle Trial is conducted in accordance with applicable regulatory requirements and the study protocol, which is approved by the Regional Ethics Committees in the Capital Region of Denmark, the Danish Data Protection Agency and the Danish Health and Medical Authority. We follow national and international standards for good clinical practice (ICH GCP guidelines) and the recommendations of the CONSORT Statement and extension in reporting randomised clinical pragmatic trials.[31] The protocol was drafted following the SPIRIT guidelines accordingly.[32] The project is monitored by the Copenhagen GCP unit.

Publication plan

We strive to readily publish the results in international peer-reviewed journals and all results will be made public, regardless of whether they come out positive, negative or inconclusive. Due to the complexity of the pain profiles, we intend to publish the results in at least two independent articles with focus on the primary outcome measure and the secondary measure of rebound pain respectively.

All authors must fulfil the criteria of the Vancouver convention.

Discussion

Regional anaesthesia is often preferred in ankle fracture surgery due to the superior safety profile and probably better postoperative pain control compared with general anaesthesia.[17,19,33] To the best of our knowledge, AnAnkle Trial is the first study to thoroughly investigate the postoperative pain profile and test which one of the most frequently used regional anaesthesia techniques is superior. Postoperative pain studies are often limited by large time intervals between pain registrations. We designed our trial to avoid this issue since it renders evaluation of the clinical significance of rebound pain impossible, because the rebound could be very intense yet completely undetected in-between pain scorings.

AnAnkle Trial constitutes a scientifically strong setup although blinding of the participants and investigators is not practically possible which holds a potential risk of bias; e.g. reported pain scores might be affected by psychological factors influenced by information from the investigators. To minimise this influence, all pain scores used for the primary outcome are registered by the participants, without consulting the staff. Likewise, the morphine data are gathered electronically from the PCA pump, which the patient activates without consulting the staff, thus ensuring a minimal risk of related bias. Finally, data analysis will be blinded. As in most other clinical trials, there remains a risk of sampling bias due to the eligibility criteria, which might impair the overall generalisability of our results.

Among the strengths of the design are randomisation and attention to sequence generation and allocation concealment to prevent selection bias between the two groups. The block randomisation and stratification protect against bias from variability of practice during a relatively long inclusion period on different centres. We have chosen a composite score of pain assessment and opioid consumption as primary outcome. The IPS has been thoroughly tested and proven to hold more statistical power than conventional comparisons of pain scores or morphine alone.[23] There is a natural correlation between the two that can lead to failure in identifying a true effect, or even lead to finding a false positive effect, on either outcome, when not balanced by evaluation of the other. In this study we will use the IPS with a longitudinal pain measurement in the form of AUC pain score rather than a single pain rating. This allows us to illustrate the pain profile over time without letting the results be compromised by statistical mass significance. The individual components of the IPS are separately analysed among various secondary endpoints to provide supplementary details to the composite primary endpoint, as is recommended in the IMMPACT consensus on pain trials.[34]

If AnAnkle Trial yields clear results the implications on clinical practice could be profound. Fracture surgery is very common and optimising the choice of anaesthesia will have a major influence on the postoperative recovery and the overall patient course for a very large group of patients.

Authors' contributions

Rune Sort: Idea development, study planning, writing first draft, revisions, approving final protocol, registering and obtaining legislative and ethical approvals.
Stig Brorson: Idea development, study planning, draft revisions, approving final protocol.
Ismail Gögenur: Idea development, study planning, draft revisions, approving final protocol.
Ann Merete Møller: Idea development, study planning, draft revisions, approving final protocol.

Funding statement

This study is supported by the non-profit Danish Society of Anaesthesia and Intensive care Medicine "DASAIMs Forskningsinitiativ", the private non-profit foundation "Viggo og Krista Pedersens Fond" and by the public source "Forskningsrådet Herlev Hospital". The first author is the sponsor; the funders have no role in design, conduction or analysis of this trial.

Competing interests statement

None to declare.

Acknowledgements

We would like to thank Jesper Kent Nielsen, M.D., Consultant Anaesthetist, Herlev and Gentofte University Hospital, Herlev, Denmark and Nicolai Bang Foss, M.D., DMSc, Consultant Anaesthetist, Hvidovre and Amager Hospital, Hvidovre, Denmark for valuable input during idea development and drafting of the protocol. We thank biostatistician Tobias Wirenfeldt Klausen, MSc, Dept. of Haematology, Herlev and Gentofte Hospital, Herlev, Denmark for statistical assistance and we thank OPEN, Odense Patient data Explorative Network, Odense University Hospital, Odense, Denmark for the secure online randomisation solution.

Data sharing

This is a study protocol so there are no data yet. The trial registration is freely accessible in The European Clinical Trials Database (EudraCT 2015-001108-76).

Figure Legends

Figure 1: AnAnkle Trial Flow Diagram

References

1 Daly PJ, Fitzgerald RH, Melton LJ, *et al.* Epidemiology of ankle fractures in Rochester, Minnesota. *Acta Orthop Scand* 1987;**58**:539–44.

2 Court-Brown CM, McBirnie J, Wilson G. Adult ankle fractures--an increasing problem? *Acta Orthop Scand* 1998;**69**:43–7.

3 Watts SA, Sharma DJ. Long-term neurological complications associated with surgery and peripheral nerve blockade: outcomes after 1065 consecutive blocks. *Anaesth Intensive Care* 2007;**35**:24–31.

4 Klein SM, Nielsen KC, Greengrass RA, *et al.* Ambulatory discharge after long-acting peripheral nerve blockade: 2382 blocks with ropivacaine. *Anesth Analg* 2002;**94**:65–70.

5 Jeng CL, Torrillo TM, Rosenblatt MA. Complications of peripheral nerve blocks. *Br J Anaesth* 2010;**105 Suppl**:i97-107. doi:10.1093/bja/aeq273

6 Capdevila X, Pirat P, Bringuier S, *et al.* Continuous peripheral nerve blocks in hospital wards after orthopedic surgery: a multicenter prospective analysis of the quality of postoperative analgesia and

complications in 1,416 patients. *Anesthesiology* 2005;**103**:1035–45.

7 Sites BD, Taenzer AH, Herrick MD, *et al.* Incidence of local anesthetic systemic toxicity and postoperative neurologic symptoms associated with 12,668 ultrasound-guided nerve blocks: an analysis from a prospective clinical registry. *Reg Anesth Pain Med* 2012;**37**:478–82. doi:10.1097/AAP.0b013e31825cb3d6

8 Capdevila X, Barthelet Y, Biboulet P, *et al.* Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999;**91**:8–15.

9 Elliot R, Pearce CJ, Seifert C, *et al.* Continuous infusion versus single bolus popliteal block following major ankle and hindfoot surgery: a prospective, randomized trial. *Foot Ankle Int* 2010;**31**:1043–7. doi:10.3113/FAI.2010.1043

10 White PF, Issioui T, Skrivanek GD, *et al.* The use of a continuous popliteal sciatic nerve block after surgery involving the foot and ankle: does it improve the quality of recovery? *Anesth Analg* 2003;**97**:1303–9.

11 Liu SS, Strodtbeck WM, Richman JM, *et al.* A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. *Anesth Analg* 2005;**101**:1634–42. doi:10.1213/01.ANE.0000180829.70036.4F

12 Grosser DM, Herr MJ, Claridge RJ, *et al.* Preoperative lateral popliteal nerve block for intraoperative and postoperative pain control in elective foot and ankle surgery: a prospective analysis. *Foot Ankle Int* 2007;**28**:1271–5. doi:10.3113/FAI.2007.1271

13 Xu J, Chen X, Ma C, *et al.* Peripheral nerve blocks for postoperative pain after major knee surgery. In: Wang X, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: : John Wiley & Sons, Ltd 2014. CD010937. doi:10.1002/14651858.CD010937.pub2

14 Chan E-Y, Fransen M, Parker DA, *et al.* Femoral nerve blocks for acute postoperative pain after knee replacement surgery. In: Chan E-Y, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: : John Wiley & Sons, Ltd 2014. CD009941. doi:10.1002/14651858.CD009941.pub2

15 Casati A, Cappelleri G, Berti M, *et al.* Randomized comparison of remifentanil-propofol with a sciatic-femoral nerve block for out-patient knee arthroscopy. *Eur J Anaesthesiol* 2002;**19**:109–14.

16 Jankowski CJ, Hebl JR, Stuart MJ, *et al.* A comparison of psoas compartment block and spinal and general anesthesia for outpatient knee arthroscopy. *Anesth Analg* 2003;**97**:1003–9, table of contents.

17 Goldstein RY, Montero N, Jain SK, *et al.* Efficacy of popliteal block in postoperative pain control after ankle fracture fixation: a prospective randomized study. *J Orthop Trauma* 2012;**26**:557–61. doi:10.1097/BOT.0b013e3182638b25

18 Protić A, Horvat M, Komen-Usljebrka H, *et al.* Benefit of the minimal invasive ultrasound-guided single shot femoro-popliteal block for ankle surgery in comparison with spinal anesthesia. *Wien Klin Wochenschr* 2010;**122**:584–7. doi:10.1007/s00508-010-1451-9

19 Christensen KP, Møller AM, Nielsen JK, *et al.* The Effects of Anesthetic Technique on Postoperative Opioid Consumption in Ankle Fracture Surgery. *Clin J Pain* 2016;**32**:870–4. doi:10.1097/AJP.0000000000000335

20 Sort R, Brorson S, Gögenur I, *et al.* Peripheral nerve block in primary ankle fracture surgery -

exploring rebound pain. *Eur J Anaesthesiol* 2015;**32**:88.

21 The European Medicines Agency. EudraCT public website. EMA. https://eudract.ema.europa.eu/

22 The European Medicines Agency. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/

23 Dai F, Silverman DG, Chelly JE, *et al.* Integration of pain score and morphine consumption in analgesic clinical studies. *J Pain* 2013;**14**:767–77.e8. doi:10.1016/j.jpain.2013.04.004

24 Noether GE. Sample Size Determination for Some Common Nonparametric Tests. *J Am Stat Assoc* 1987;**82**:645–7. doi:10.1080/01621459.1987.10478478

25 Chan KS, Chen W-H, Gan TJ, *et al.* Development and validation of a composite score based on clinically meaningful events for the opioid-related symptom distress scale. *Qual Life Res* 2009;**18**:1331–40. doi:10.1007/s11136-009-9547-2

26 Yadeau JT, Liu SS, Rade MC, *et al.* Performance characteristics and validation of the Opioid-Related Symptom Distress Scale for evaluation of analgesic side effects after orthopedic surgery. *Anesth Analg* 2011;**113**:369–77. doi:10.1213/ANE.0b013e31821ae3f7

27 Kleif J, Edwards HM, Sort R, *et al.* Translation and validation of the Danish version of the postoperative quality of recovery score QoR-15. *Acta Anaesthesiol Scand* 2015;**59**:912–20. doi:10.1111/aas.12525

28 Apfelbaum JL, Gan TJ, Zhao S, *et al.* Reliability and validity of the perioperative opioid-related symptom distress scale. *Anesth Analg* 2004;**99**:699–709, table of contents. doi:10.1213/01.ANE.0000133143.60584.38

29 National Institute of Cancer. Common Terminology Criteria for Adverse Events (CTCAE). *NIH Publ* 2010;**2009**:0–71. doi:10.1080/00140139.2010.489653

30 Ip HYV, Abrishami A, Peng PWH, *et al.* Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009;**111**:657–77. doi:10.1097/ALN.0b013e3181aae87a

31 Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:c869.

32 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:e7586.

33 Jordan C, Davidovitch RI, Walsh M, *et al.* Spinal anesthesia mediates improved early function and pain relief following surgical repair of ankle fractures. *J Bone Joint Surg Am* 2010;**92**:368–74. doi:10.2106/JBJS.H.01852

34 Turk DC, Dworkin RH, McDermott MP, *et al.* Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. *Pain* 2008;**139**:485–93. doi:10.1016/j.pain.2008.06.025

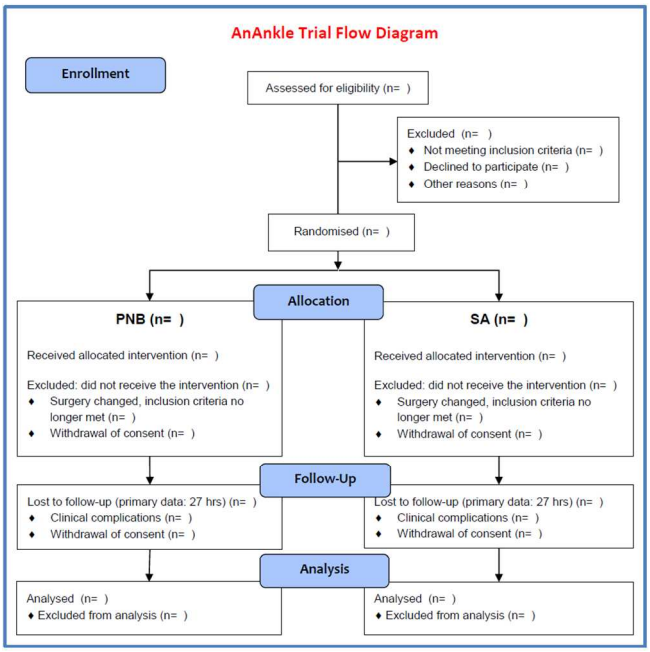


Figure 1: AnAnkle Trial Flow Diagram

123x80mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	1,5
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12-13
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9+fig.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5,9+fig.
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4,5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5-6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8-9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.