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Peripheral nerve block anaesthesia and postoperative pain in acute ankle fracture surgery: the AnAnkle randomised trial

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Abstract

Background: Peripheral nerve blocks (PNBs) are increasingly popular in acute ankle fracture surgery but rebound pain may outweigh the benefits. The AnAnkle Trial was designed to assess the postoperative pain profile of PNB anaesthesia compared with spinal anaesthesia (SA).

Methods: The AnAnkle Trial was a randomised, two-centre, blinded outcome analysis trial. Eligible adults booked for primary ankle fracture surgery were randomised to PNB or SA. The PNBs were ultrasound-guided popliteal sciatic and saphenous blocks with ropivacaine and SAs were with hyperbaric bupivacaine. Postoperatively, all subjects received paracetamol, ibuprofen, and patient-controlled i.v. morphine for pain. The primary endpoint was 27 h Pain Intensity and Opioid Consumption (PIOC) score. Secondary endpoints included longitudinal pain scores and morphine consumption separately, and questionnaires on quality of recovery.

Results: This study enrolled 150 subjects, and the PNB success rate was >94%. PIOC was lower with PNB anaesthesia (median, −26.5% *vs* +54.3%; $P<0.001$) and the probability of a better PIOC score with PNB than with SA was 74.8% (95% confidence interval, 67.0–82.6). Pain scores and morphine consumption analysed separately also yielded a clear benefit with PNB, despite substantial rebound pain when PNBs subsided. Quality of recovery scores were similar between groups, but 99% having PNB *vs* 90% having SA would choose the same anaesthesia form again ($P=0.03$).

Conclusions: PNB anaesthesia was efficient and provided a superior postoperative pain profile compared with SA for acute ankle fracture surgery, despite potentially intense rebound pain after PNB.

Clinical trial registration: Clinicaltrialsregister.eu, EudraCT number: 2015-001108-76.

Keywords: ankle fracture; peripheral nerve block; postoperative pain; rebound pain; regional anaesthesia

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Editor's key points

- Peripheral nerve blocks (PNBs) are frequently used for ankle fracture surgery, but rebound pain may reduce their benefits by increasing postoperative opioid requirements.
- A randomised trial including 150 subjects was designed to assess the postoperative pain profile of regional anaesthesia provided with PNB *vs* spinal anaesthesia (SA) for ankle fracture surgery.
- The primary endpoint of Pain Intensity and Opioid Consumption score was lower in the PNB group, which also had greater patient satisfaction despite similar quality of recovery scores for both groups.

Acute ankle fracture surgery is common, yet there is currently no evidence-based consensus on the optimal anaesthesia modality for this procedure. Focus on postoperative pain control is paramount as fracture surgery is painful,[1] and opioid analgesia has serious dose-dependent side-effects.[2–4] Spinal anaesthesia (SA) is a commonly used technique and seems superior to general anaesthesia (GA) regarding the postoperative pain profile.[5,6] Recently, peripheral nerve blocks (PNB) have gained interest and are being widely implemented for pain treatment and as primary anaesthesia in both elective and acute orthopaedic limb surgery.[7] PNBs are safe and effective and provide long-lasting postoperative analgesia. In elective knee, ankle, and foot surgery, PNBs are reportedly beneficial regarding postoperative pain scores, morphine consumption, and patient satisfaction.[8–16] However, the pain profile after acute trauma surgery is intuitively different and remains sparsely investigated. Recent studies have raised concern that the ensuing 'rebound pain' when the block effect subsides is clinically relevant and may even outweigh the benefits of PNBs on the postoperative pain profile in acute trauma surgery.[17–19] In a recent exploratory study, we acknowledged this potential problem but also discovered that rebound pain is relatively short lasting.[19]

The aim of this randomised clinical trial, the AnAnkle Trial, was to assess the postoperative pain profile and quality of recovery after PNB anaesthesia compared with SA for acute ankle fracture surgery.

Methods

The AnAnkle Trial was a randomised, parallel group, dual-centre, open-label clinical trial with blinded outcome analysis. The study was approved by the Committees on Health Research Ethics in the Capital Region of Denmark (H-15004360), the Danish Health Authority (2015033540), and the Danish Data Protection Agency (HEH-2015-034). It was conducted in accordance with the Declaration of Helsinki and externally audited by the Copenhagen Good Clinical Practice (GCP) Unit. Written consent was given by all participants.

Before enrolment, the study protocol was published at Clinicaltrialsregister.eu (EudraCT number: 2015-001108-76) and, before data entry, as an open access article.[20] We adhered to the Consolidated Standards of Reporting Trials (CONSORT) statement and the extension on pragmatic trials.[21,22]

Participants and inclusion criteria

We consecutively screened adult patients scheduled for primary ankle fracture surgery with open reduction and internal fixation (ORIF) in either of two large university hospitals. Candidates were considered eligible if they were adults ≥18 yr, and able to read Danish with a uni-, bi- or trimalleolar fracture without involvement of the proximal fibula. Exclusion criteria were: relevant allergies, body weight <52 kg (to avoid local anaesthetic toxicity), contraindications for SA, current gastrointestinal bleeding, other injuries requiring opioid analgesics, habitual daily opioid use, cognitive or psychiatric dysfunction or substance abuse, logistical reasons, neurological dysfunction in the lower extremities, pregnancy or breastfeeding, infection at the injection site, acute porphyria, or nephropathy requiring dialysis. Subjects were recruited from July 2015 until the required sample size was achieved in May 2017.

Procedure

Intervention group

PNBs were administered following local guidelines by any anaesthesiologist experienced in PNBs for surgical anaesthesia. They were ultrasound-guided popliteal sciatic and saphenous blocks using ropivacaine 7.5 mg ml^{-1} at 20 ml for the sciatic nerve and 8 ml for the saphenous nerve. Popliteal blocks were predominantly lateral approach, subparaneural blocks at the level of the bifurcation. Saphenous blocks were placed mid-thigh, which provides a high success rate.[23] Whenever possible, PNBs were administered in the peri-anaesthesia care unit (PACU) at >1 h before surgery. In case of insufficient effect, evaluated by sense of touch, cold and pinprick, a supplement of 5 ml (patient weight, 62–71 kg) or 10 ml (≥72 kg) was allowed after 45–60 min.

Control group

For the control SA group, neuraxial block was administered in the operation theatre by any anaesthesiologist experienced in SA using hyperbaric bupivacaine 5 mg ml^{-1} 2.0 ml with the patient lying on the injured side and in slight anti-Trendelenburg for 5–20 min until certain effect.

Both groups

Anxiety during PNB or SA administration was mitigated with small doses of midazolam or propofol as needed. Sedation with propofol during surgery was optional. Any light to moderate pain during surgery was remedied on demand with fentanyl or sufentanil. In case of severe pain or inability to cooperate, GA was administered.

Postoperatively, SA patients were observed in the PACU until motor function had returned. PNB patients went directly to the orthopaedic ward. Postoperative pain medication regimens were identical: paracetamol 1000 mg every 6 h, ibuprofen 400 mg every 8 h, and patient-controlled analgesia (PCA) with intravenous (i.v.) morphine providing 2.5 mg per dose with a 6 min lockout interval. Steroids or controlled release opioids were not allowed on the day of the operation.

Data collection

Participants registered current pain on a numeric rating scale (NRS) of 0–10 every 3 h from administration of anaesthesia

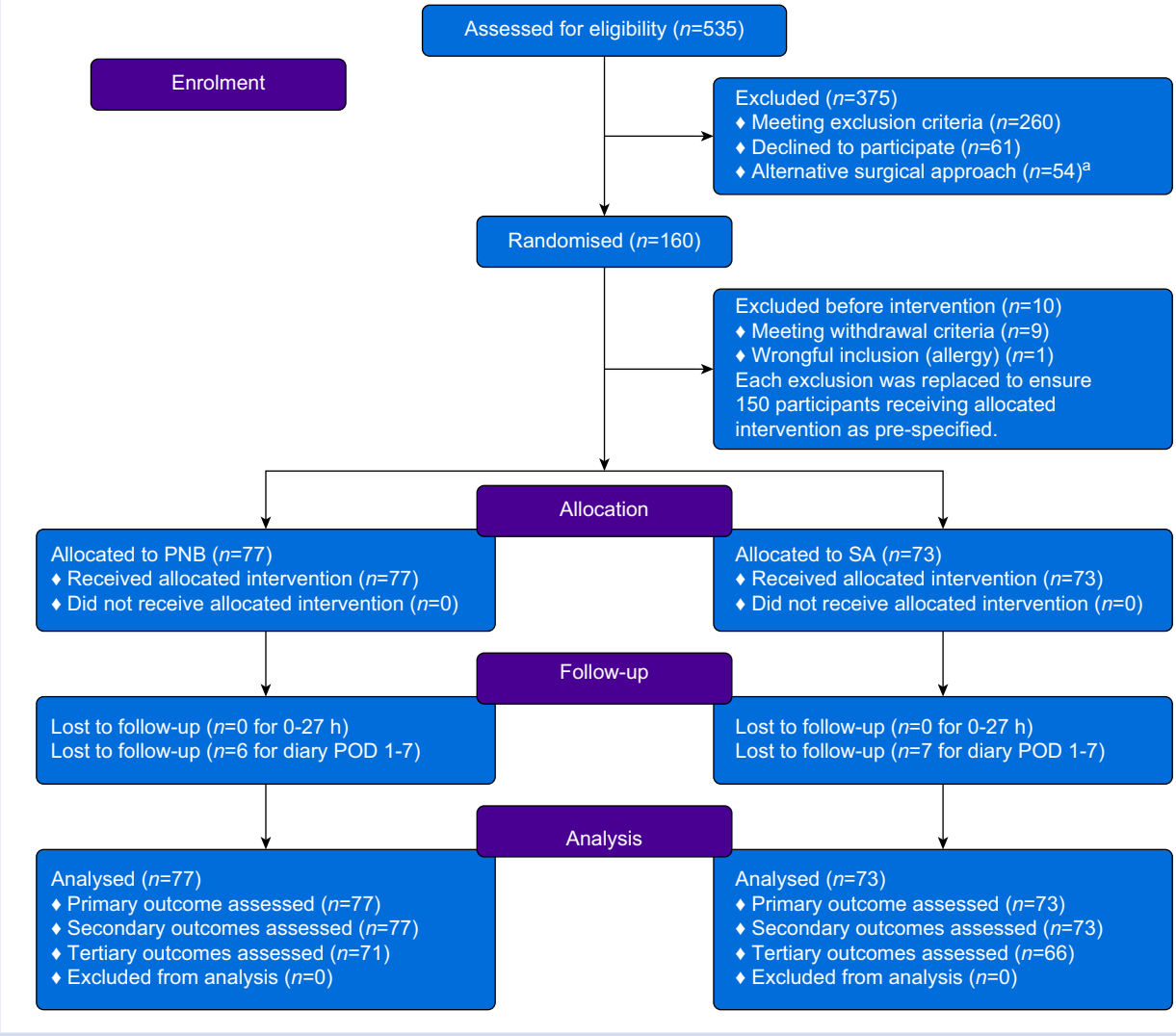

Fig 1. AnAnkle trial flowchart. [a]Described in the second-to-last paragraph of the Discussion section. POD, postoperative day.

until 27 h whereas PCA morphine was electronically registered. The 27 h period was set based on previous experience[19] to include at least 6 h after PNB cessation for any rebound pain.[20] Participants registered block cessation when full sensation had returned to the ankle. At 27 h they answered questionnaires on quality of recovery, overall satisfaction, and opioid side-effects. The latter was repeated on postoperative day (POD) 2 in a patient diary.

Endpoints

The main outcome was postoperative pain. The primary endpoint to illustrate this was the composite Pain Intensity and Opioid Consumption (PIOC) score for the 0–27 h interval after anaesthesia. This was calculated by ranking both the NRS area under the curve (AUC) pain score and total morphine consumption 0–27 h across both groups. PIOC is the summation of the deviations from the mean ranks for both parameters and equals −200% to +200% for each patient.[24,25] Effect size was expressed as the probability of having a better (lower) PIOC score with one treatment over the other. PIOC is based on the 'Silverman integrating approach' (SIA),[25,26] but utilises a longitudinal AUC pain measure rather than the original single pain measurement.[24] The PIOC score provides increased statistical strength compared with analysing the inherent endpoints separately, and adds temporality to the pain measure without multiple significance tests increasing the risk of type 1 error.[24]

Secondary endpoints included the separate PIOC components NRS-AUC pain scores and morphine consumption (PCA pump) 0–27 h after anaesthesia and quality of recovery (Danish QoR-15 score)[27] and opioid adverse effects reported as occurrence of clinically meaningful events (CMEs) identified with the Opioid-Related Symptom Distress Scale (OR-SDS) questionnaire.[4] Frequency, severity, and bother of 10 opioid related symptoms were rated on Likert scales. A 'severe' or 'very severe' symptom translates to an adverse 'composite' CME, except for confusion where 'moderate' severity is sufficient.[4] This severity-based CME method is validated to

Table 1 Subject characteristics by study group. IQR, interquartile range; NRS, numeric rating scale.

Variable	Peripheral nerve block (n=77)	Spinal anaesthesia (n=73)
Age, yr; median (IQR [range])	56 (44–66 [18 to 81])	54 (40–67 [19 to 84])
Sex female/male; n (%)	46 (60)/31 (40)	51 (70)/22 (30)
BMI, kg m^{-2}; median (IQR)	26.2 (23.6–29.3)	26.3 (23.7–29.3)
ASA physical status; n (%)		
1	36 (47)	43 (59)
2	37 (48)	27 (37)
3	4 (5)	3 (4)
Fracture type; n (%)		
Unimalleolar	29 (38)	30 (41)
Bimalleolar	18 (23)	23 (32)
Trimalleolar	30 (39)	20 (27)
Preoperative 'average' pain, NRS 0–10; median (IQR [range])	4 (3–5 [0 to 9])	4 (3–5 [0 to 8])
Time from injury to surgery, h; median (IQR)	50 (26–72)	53 (29–94)
Protocol violations; n (%)		
Conversion to general anaesthesia	5 (6)	0 (0)
Steroid or modified-release opioid	4 (5)	7 (10)
Perioperative short-acting opioid	12 (16)	11 (15)

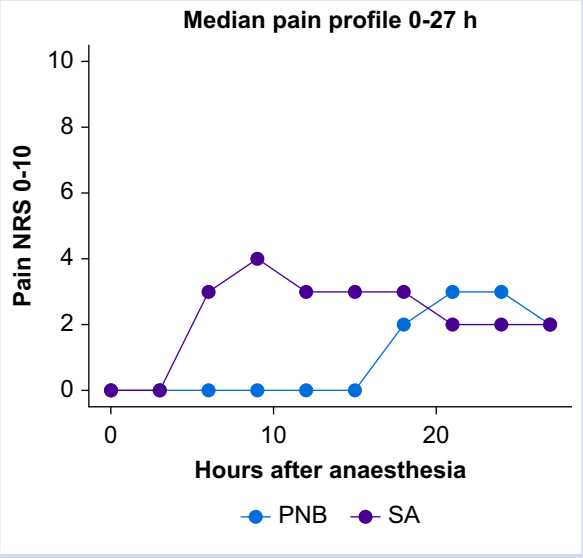

Fig 2. Pain profiles by study group. The median pain score profiles after spinal and peripheral nerve block anaesthesia for ankle fracture surgery. NRS, numeric rating scale; PNB, peripheral nerve block; SA, spinal anaesthesia.

correlate with frequency and bother in a mixed postoperative population.[4] An older version with 12 symptoms has been validated for orthopaedic surgery.[28]

Further endpoints were: proportion of 'risk patients' with a PIOC of +100 to +200 (i.e. high scoring in both pain and morphine consumption), overall patient satisfaction with the anaesthesia form rated on an NRS from −5 (very dissatisfied) to +5 (very satisfied), and proportion of participants who would choose the same anaesthesia type again. We also registered OR-SDS on POD2 and intervention-related adverse events.

Randomisation and blinding

Randomisation was generated through a secure website as 1:1 allocation stratified by centre and age group (≤60 or >60 yr) and arranged in blocks of varying sizes. The AnAnkle Trial was open labelled to participants and investigators but blinded for outcome analysis by having an external consultant encrypt patient ID and group allocation in the data.

Sample size estimation and statistical analysis

Based on pilot study data,[19] we performed a sample size estimation for the primary endpoint using Wilcoxon–Mann–Whitney (WMW) odds with the O'Brien Castello formula.[25,29] We deemed 30% reduction in morphine consumption and pain scores to be clinically relevant. With a power of 80% and a two-sided type 1 error risk of 5%, the required sample size was 141 adjusted to a final 150 participants to accommodate protocol violations. The key secondary endpoints were also covered by this sample size.[20] Withdrawal of consent or surgery indication prompted exclusion and replacement with a new participant.[20]

Blinded data were analysed by the intention-to-treat principle using the statistical software SPSS (version 25; SPSS, Inc., Chicago, IL, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). Data were inspected for normality of distribution and the choice of analysis is shown with each result. PIOC is compared by treatment group with the Mann–Whitney *U*-test and the effect size estimate, called *P′*, is interpreted as the probability of having a better PIOC score in the PNB group.[24] It is tied to WMW odds[25] which equals $P'/(1-P')$. We prespecified age subgroups analysis,[20] as age is a known confounder in pain studies.[30] Handling of missing data is described in the published protocol. For results with <5% missing data, the missing fraction is not stated.

Results

We included 150 of 160 randomised patients for analysis from July 23, 2015 to May 31, 2017. Ten were withdrawn by the predetermined criteria without receiving the intervention (Fig. 1).

The PNB and SA groups were comparable regarding subject characteristics and potentially confounding factors registered and baseline pain scores and protocol violations (Table 1). There were no intergroup differences regarding Charlson comorbidity index, diabetes mellitus, smoking, high alcohol consumption, or duration of surgery. A tourniquet was used in 5% of operations, and an intermittent pneumatic compression system to reduce swelling was used preoperatively in 55% and postoperatively in 5% of cases with no intergroup differences. The median postoperative length of stay in the orthopaedic ward was 46 h (25th–75th percentiles, 28–64 h) with no significant difference between the groups (27 h after anaesthesia was the predefined minimum observation period). Although

not statistically significant, five patients in the PNB group required GA during surgery compared with no patients in the SA group (P=0.059; Fisher's exact test). 'Possibly insufficient block' was stated in three cases, whereas two could not cooperate with sedation. Hence, PNB failure was three out of 77 (3.9%). The mean duration of effect until return of sensation to the ankle was 3.5 h (95% confidence interval [CI], 3.2–3.9 h) for SA and 16.5 h (95% CI, 15.8–17.3 h) for PNB.

Primary endpoint

The median pain score profiles of the two groups are shown in Fig. 2. The PIOC scores, based on both 0–27 h i.v. morphine consumption and AUC pain scores, were significantly lower in the PNB group (median, −26.5% *vs* +54.3%; P<0.001; Mann–Whitney U-test) as shown in Fig. 3. The effect size probability of a subject with PNB having a lower PIOC score than a subject with SA was P'=74.8% (95% CI, 67.0–82.6%).

Secondary endpoints

Results for secondary endpoints are listed in Table 2. The separate PIOC components AUC pain scores and 0–27 h morphine consumption were both significantly lower in the PNB group. Opioid side-effects with at least one CME on the OR-SDS were experienced by almost half the participants within the first 27 h. There was an apparent higher incidence in the SA group, which was not statistically significant. From the evening on POD1 to the evening on POD2 there were significantly more subjects experiencing side-effects in the SA group with a relative risk (RR) of 3.56 (95% CI, 1.54–8.20). The number of 'risk patients' (PIOC >100) was significantly higher in the SA group with RR=6.07 (95% CI, 2.20–16.69), and fewer subjects from the SA group would choose the same anaesthesia type again. Satisfaction score and QoR-15 quality of recovery yielded no statistically significant differences between groups. More intervention-related adverse events were reported in the SA group, but the difference was not statistically significant. Intraoperative haemodynamic events were not included in this registration, but records of the need for one or more administrations of vasoactive drugs (ephedrine or phenylephrine) showed a higher incidence in the SA group with 17 subjects (23%) *vs* 5 (6%) in the PNB group, four of whom had GA (P=0.004, χ^2 test; RR=3.59; 95% CI, 1.40–9.22).

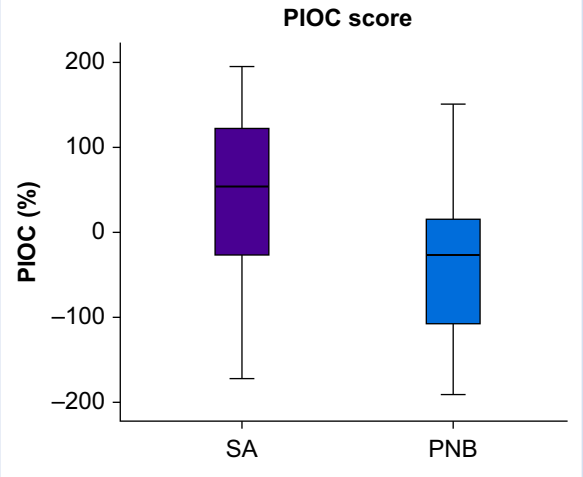

Fig 3. Pain Intensity and Opioid Consumption (PIOC) scores by study group. PIOC scores, based on both 0–27 h morphine consumption and area-under-the-curve pain scores, were significantly lower in the peripheral nerve block group (median, −26.5% *vs* +54.3%, P<0.001; MWU test). The effect size is illustrated by the probability of a patient with peripheral nerve block having a lower PIOC score than a patient with SA, P'=74.8% (95% CI, 67.0–82.6). PNB, peripheral nerve block; SA, spinal anaesthesia; CI, confidence interval; MWU, Mann–Whitney U-test. Bold lines, medians; boxes, 1st–3rd quartiles; whiskers, ranges.

Subgroup analyses

The PNB benefit was somewhat larger, but did not reach statistical significance, in the older patient group with a PIOC effect size probability of P'=82.4% (95% CI, 71.6–93.2%), which was 73.4% (95% CI, 62.9–83.8%) in the younger group. The secondary endpoints yielded generally lower morphine consumption for older subjects across treatment groups, but also proportionally larger reductions in both morphine consumption and pain scores with PNB compared with SA for the older group (Table 2).

Discussion

With this randomised clinical trial, we investigated 150 acute subjects, comparing detailed postoperative pain profiles after ankle fracture surgery under either PNB anaesthesia or SA. We provide novel data by integrating pain scores with opioid consumption, and believe this is the first study sufficiently detailed to show a benefit of PNB compared with SA on postoperative pain in acute fracture surgery despite an evident rebound pain phenomenon upon PNB resolution.

The composite primary endpoint showed a large effect size favouring PNB but has not been previously used in similar study populations. Secondary endpoints also yielded a clear benefit on both morphine consumption and longitudinal pain measures separately, in congruence with studies of elective surgery.[8–16] In acute fracture surgery, RCTs have found that rebound pain may compromise the benefit of PNBs.[17,18] However, these were limited by large intervals between pain scores and inconsistent pain medication regimens, rendering the extent and clinical relevance of rebound pain effectively unknown. We showed that the PNB benefit was also evident in a far lower fraction of 'risk patients' (PIOC >100), who score highly in both pain and morphine consumption. However, the 0–27 h PCA i.v. morphine use in the PNB group was a median 20 mg and up to 97 mg. As PNBs provided about 17 pain-free hours, these substantial morphine amounts were taken within only ~10 h after PNB resolution. This indicates that rebound pain after PNB can be severe and warrants attention in clinical practice.[31] The rapid morphine consumption in the PNB group may explain the similarity in opioid side-effects on POD1 despite a much larger total consumption in the SA group. POD2 yielded a significant difference favouring PNB in accordance with consumption.

The QoR-15 questionnaire revealed only moderate recovery scores[32] with no significant intergroup difference. The questionnaire should reflect the whole postoperative period 0–27 h but reports in the PNB group may be biased by an experience of rebound pain overshadowing the memory of the painless initial hours. The QoR-15 is thoroughly validated,[27,33,34] but not

Table 2 Secondary endpoint data by study group, including subgroup analyses.

Variable	Peripheral nerve block (*n*=77)	Spinal anaesthesia (*n*=73)	P-value	Test
Morphine i.v. 0–27 h total, mg; median (IQR [range])	**20.0 (12.5–38.8 [0 to 97])**	**32.5 (18.1–65.0 [0 to 132])**	**0.001***	MWU
Morphine i.v. 0–27 h, subgroups†				
>60 yr	**12.5 (7.5–22.5 [0 to 53])**	**28.9 (16.0–42.1 [5 to 132])**	**0.001**	MWU
≤60 yr	**32.5 (16.7–47.5 [0 to 97])**	**42.5 (22.5–72.5 [0 to 129])**	**0.038**	MWU
Pain score 0–27 h AUC, NRS h, median (IQR)	**37.5 (20.3–54.0)**	**72.0 (43.5–102.0)**	**<0.001**	MWU
Pain score 0–27 h AUC, subgroups†				
>60 yr	**21.0 (10.5–45.0)**	**54.8 (36.0–96.0)**	**<0.001**	MWU
≤60 yr	**45.0 (25.1–61.5)**	**75.0 (56.2–111.0)**	**<0.001**	MWU
Opioid adverse effects; *n* (%)				
OR-SDS CME 0–27 h ≥1	34 (45)	36 (51)	0.469	χ^2
OR-SDS CME on POD2 ≥1‡	**6 (10)**	**21 (34)**	**0.001**	χ^2
Quality of recovery, QoR-15; mean (95% CI)	107.3 (102.4–112.1)	104.6 (99.1–110.2)	0.466	t-test
'Risk patients' (PIOC >100); *n* (%)	**4 (5)**	**23 (32)**	**<0.001**	χ^2
Patient satisfaction, NRS −5 to 5; median (IQR [range])	5 (4–5 [−1 to 5])	5 (3–5 [−2 to 5])	0.444	MWU
Would choose anaesthesia form again; *n* (%)	**74 (99)**	**64 (90)**	**0.030**	Fisher's exact
Adverse events (number of patients); *n* (%)	7 (9)	14 (19)	0.075	χ^2

AUC, area under the curve; 95% CI, 95% confidence interval; CME, composite clinically meaningful event; IQR, inter-quartile range; MWU, Mann–Whitney *U*-test; NRS, numeric rating scale; OR-SDS, opioid related symptom distress score; PIOC, pain intensity and opioid consumption score; PNB, peripheral nerve block; POD, postoperative day; QoR-15, quality of recovery 15-item score (0–150).

* Data shown in bold are statistically significant ($P<0.05$).

† For age >60 yr: n=59 (PNB 31, SA 28), for age ≤ 60 yr: n=91 (PNB 46, SA 45).

‡ Missing data for 27 questionnaires (18%), 13 not received and 14 incomplete; sample size, n=123 (PNB 62, SA 61).

specifically for PNBs[33] Patient satisfaction was very high with no intergroup difference but with a clear ceiling effect making interpretation difficult. Wanting to 'do well' when studied, known as the Hawthorne effect, may have inflated the scores in both groups. More subjects in the PNB group would choose the same method again (99% *vs* 90%).

Subgroup analyses revealed lower pain scores and lower morphine consumption for older patients across treatment groups. Interestingly, the benefit of PNB over SA was somewhat larger in the older group compared with younger subjects. The study was not powered for this comparison and the difference in PIOC effect size probability did not reach statistical significance. Although underpowered, this seems clinically relevant as it indicates less rebound pain and greater benefit with PNB anaesthesia for older patients. Importantly, opioid sparing with PNB was proportionally larger for older subjects, who are more susceptible to opioid-associated adverse consequences including falls, fractures, and delirium.[35]

We chose SA as the comparator to PNB because SA was most commonly used at our centre for ankle fracture ORIF, was associated with lower postoperative opioid consumption than GA in a retrospective study,[5] and had lower pain scores than GA in a prospective study.[6]

The strengths of this study include the large sample size for an RCT of acute fracture cases and the novel approach to illustrating a detailed pain profile including a focus on patient-reported measures. The use of an integrated and clinically meaningful endpoint including a longitudinal measure of pain adds to the internal validity. The PIOC measure is clinically relevant as it takes any opposing effects between opioid consumption and pain scores into consideration. The pragmatic approach of using standard treatments and a broad patient population adds to the external validity and generalisability of the results. Importantly, we ensured clinically meaningful results by using a multimodal pain regimen and i.v. PCA in both groups, which is known to lower pain scores.[36] By reporting the separate PIOC components as secondary endpoints, we adhere to the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) on using composite endpoints.[37] The overall design was strong with good allocation concealment and external GCP audit, and followed the IMMPACT recommendations on clinical trials in acute pain.[38]

The key limitation of the study is the lack of blinding. The marked differences in onset and duration between PNB and SA would make blinding futile, even with sham blocks. Some inadvertent influence on participants by unblinded investigators cannot be ruled out. Secondly, differences in initial postoperative care between the PACU and ward could affect the participants, although pain treatment regimens were identical. We minimised these influences by standardising subject information, by having the subjects register data without the presence of personnel, by electronically registering PCA morphine consumption, and by blinding the data before analysis. The Hawthorne effect may also influence patient-reported data, but probably in both groups similarly. Anxiety questionnaires were omitted, although anxiety is a known predictor of postoperative pain.[30] This should not affect the results because of the random allocation but may affect external validity as the most anxious patients might be more inclined to refuse participation. Recruitment was challenged by a midway change in practice at one centre. Unstable trimalleolar fractures could no longer be included because the surgery method was changed to a posterior approach with longer duration, rendering the set spinal dose insufficient. This slowed recruitment but is unlikely to have influenced the results as the centre-stratified randomisation ensured equal distribution of fracture types in the two treatment groups.

In conclusion, this randomised clinical trial shows a substantial benefit of PNB anaesthesia compared with SA on the postoperative pain profile in acute ankle fracture surgery despite evident rebound pain upon PNB resolution. Both pain scores and morphine consumption were markedly reduced by PNB, and patients having PNB anaesthesia were more likely to choose the same modality again. The benefit of PNB may be greater for older patients, which should be explored in future studies.

Authors' contributions

RS and biostatistician TWK take responsibility for the integrity of the data and the accuracy of the data analysis. RS held primary responsibility for the trial as 'Sponsor' and Principal Investigator. SB, IG, NBF and AMM were senior academic supervisors.
Concept and design: RS, SB, IG, AMM
Study planning: RS, SB, IG, AMM, JKN, NBF, NS, PTT, TWK
Conduction and data acquisition: RS, SH, LLH, JKN
Statistical analysis: RS, TWK
Data interpretation: RS, SB, IG, AMM, NBF
Drafting of the manuscript: RS
Critical revision and approval of the manuscript: RS, SB, IG, AMM, LLH, SH, JKN, NBF, NS, PTT, TWK

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Declarations of interest

The authors declare that they have no conflicts of interests.

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