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

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BACKGROUND

- Acute ankle fracture surgery is common.
- Currently no evidence-based consensus on the optimal anaesthesia modality for this procedure.
- Spinal anaesthesia (SA) is a commonly used technique and seems superior to general anaesthesia (GA) regarding the postoperative pain profile.
- Recently, peripheral nerve blocks (PNB) have gained interest and are being widely implemented for pain treatment and as primary anaesthesia.

BACKGROUND

- PNBs are safe and effective and provide long lasting postoperative analgesia.
- PNBs are reportedly beneficial regarding postoperative pain scores, morphine consumption, and patient satisfaction.
- Peripheral nerve blocks (PNBs) are frequently used for ankle fracture surgery, but rebound pain may reduce their benefits by increasing postoperative opioid requirements.

BACKGROUND

- Rebound pain is relatively short lasting.
- The AnAnkle Trial was designed to assess the postoperative pain profile of PNB anaesthesia compared with spinal anaesthesia (SA) for acute ankle fracture surgery.

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METHOD

- The AnAnkle Trial was a randomised, parallel group, dual centre, open-label clinical trial with blinded outcome analysis.
- Approved by the Committees on Health Research Ethics in the Capital Region of Denmark, the Danish Health Authority, and the Danish Data Protection Agency.
- Written consent was given by all participants.

METHOD

- **Participants**

- Adult patients scheduled for primary ankle fracture surgery with open reduction and internal fixation (ORIF) in either of two large university hospital.

- Subjects were recruited from July 2015 until the required sample size was achieved in May 2017.

METHOD

- **Inclusion criteria**
  - Adults ≥18 yr
  - Able to read Danish with a uni-, bi- or trimalleolar fracture without involvement of the proximal fibula.

METHOD

- **Exclusion criteria**

- Local anesthetic allergies
- Body weight <52 kg (to avoid local anaesthetic toxicity)
- Contraindications for SA
- Current GI bleeding
- Other injuries requiring opioid analgesics
- Habitual daily opioid use
- Cognitive or psychiatric dysfunction or substance abuse
- Neurological dysfunction in the lower extremities

METHOD

- **Exclusion criteria**

- Pregnancy
- Breastfeeding
- Infection at the injection site
- Acute porphyria
- Nephropathy requiring dialysis.

METHOD

- **Procedure**
  - ***Intervention group***

- PNBs were administered following local guidelines by any anaesthesiologist experienced in PNBs for surgical anaesthesia.

- Ultrasound-guided popliteal sciatic and saphenous blocks

- Using ropivacaine 7.5 mg/ml at 20 ml for the sciatic nerve and 8 ml for the saphenous nerve

METHOD

- **Procedure**
  - ***Intervention group***

- ***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.

METHOD

- **Procedure**
  - ***Intervention group***

- PNBs were administered in the perianaesthesia 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 (BW 62-71 kg) or 10 ml (≥72 kg) was allowed after 45-60 min.

METHOD

- **Procedure**
  - ***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 2.0 ml with the patient lying on the injured side and in slight anti-Trendelenburg for 5-20 min until certain effect.

METHOD

- **Procedure**
  - ***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.

METHOD

- **Both groups**
  - Postoperatively, SA patients were observed in the PACU until motor function had returned.
  - PNB patients went directly to the orthopaedic ward.

METHOD

- **Both groups**
  - Postoperative pain medication regimens were identical:
    - Paracetamol 1,000 mg every 6 h
    - Ibuprofen 400 mg every 8 h
    - 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.

METHOD

- **Data collection**
  - Participants registered current pain on a numeric rating scale (NRS) of 0-10 every 3 h from administration of anaesthesia until 27 h
  - PCA morphine was electronically registered.
  - Participants registered block cessation when full sensation had returned to the ankle

METHOD

- **Data collection**
  - At 27 h they answered questionnaires on quality of recovery, overall satisfaction, and opioid side-effects.
  - Repeated on postoperative day (POD) 2

METHOD

- **Endpoints**
  - The main outcome was postoperative pain for the 0-27 h interval after anaesthesia.
    - Pain Intensity and opioid Consumption (PIOC) score
      - Calculated by ranking both the NRS area under the curve (AUC) pain score and total morphine consumption 0-27 h

METHOD

- **Endpoints**
  - Secondary endpoints
    - The separate PIOC components NRS-AUC pain scores and morphine consumption (PCA pump) 0-27 h after anaesthesia.
    - Quality of recovery (Danish QoR-15 score)
    - Opioid adverse effects by OR-SDS CME (0-27h, POD2)

Date:

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0 All of the time

Please add together the scores given by the patient: Total QoR Day 1 Score:_____

Quality of recovery

(Danish QoR-15 score)

METHOD

- **Endpoints**
  - Secondary endpoints
    - ‘Risk patients’ with a PIOC of +100 to +200 (i.e. high scoring in both pain and morphine consumption)
    - Patient satisfaction with the anaesthesia form
    - Would choose the same anaesthesia type again.

METHOD

- **Randomisation and blinding**
  - Randomisation was generated through a secure website as 1:1 allocation stratified by centre and age group (60 or >60 yr).
  - The AnAnkle Trial was open labelled to participants and investigators but blinded for outcome analysis.

METHOD

- **Sample size estimation and statistical analysis**
  - Required sample size was a final150 participants
  - Withdrawal of consent or surgery indication prompted exclusion and replacement with a new participant.
  - Blinded data were analysed by the intention-to-treat principle using the statistical software SPSS version 25 and R (R Foundation for Statistical Computing, Vienna, Austria).
  - Prespecified age subgroups analysis, as age is a known confounder in pain studies

RESULTS

- This study 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.

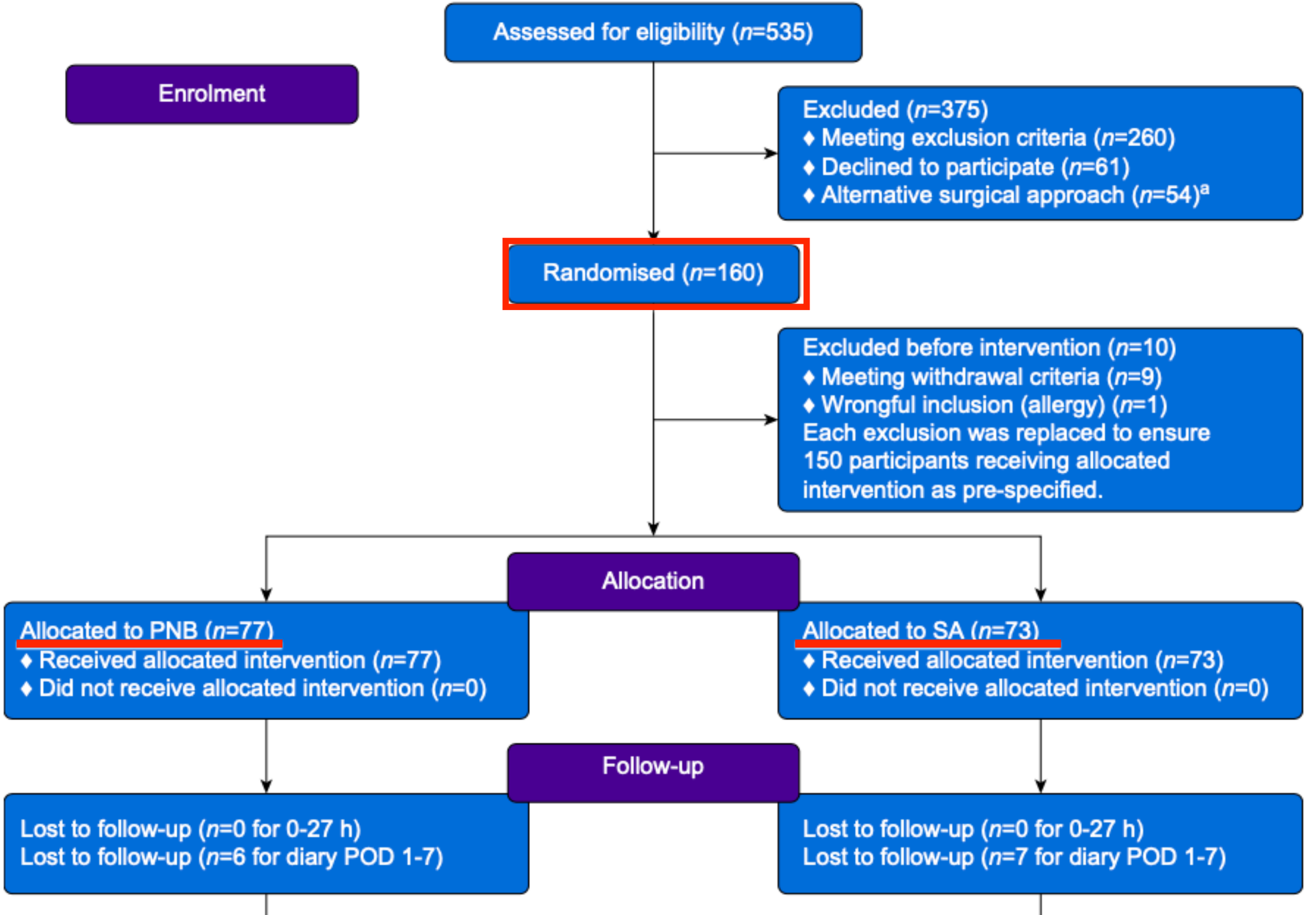

Assessed for eligibility (n=535)
Enrolment
Excluded (n=375)
♦ Meeting exclusion criteria (n=260)
♦ Declined to participate (n=61)
♦ Alternative surgical approach (n=54)a
Randomised (n=160)
Excluded before intervention (n=10)
♦ Meeting withdrawal criteria (n=9)
♦ Wrongful inclusion (allergy) (n=1)
Each exclusion was replaced to ensure 150 participants receiving allocated intervention as pre-specified.
Allocation
Allocated to PNB (n=77)
♦ Received allocated intervention (n=77)
♦ Did not receive allocated intervention (n=0)
Allocated to SA (n=73)
♦ Received allocated intervention (n=73)
♦ Did not receive allocated intervention (n=0)
Follow-up
Lost to follow-up (n=0 for 0-27 h)
Lost to follow-up (n=6 for diary POD 1-7)
Lost to follow-up (n=0 for 0-27 h)
Lost to follow-up (n=7 for diary POD 1-7)

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)

RESULTS

- Five patients in the PNB group required GA during surgery compared with no patients in the SA group (P=0.059)
- ‘Possibly insufficient block’ was stated in three cases(3.9%)
- Whereas two could not cooperate with sedation.
- The mean duration of effect until return of sensation to the ankle
  - **SA :** 3.5 h (95% CI, 3.2-3.9 h)
  - **PNB :** 16.5 h (95% CI, 15.8-17.3 h)

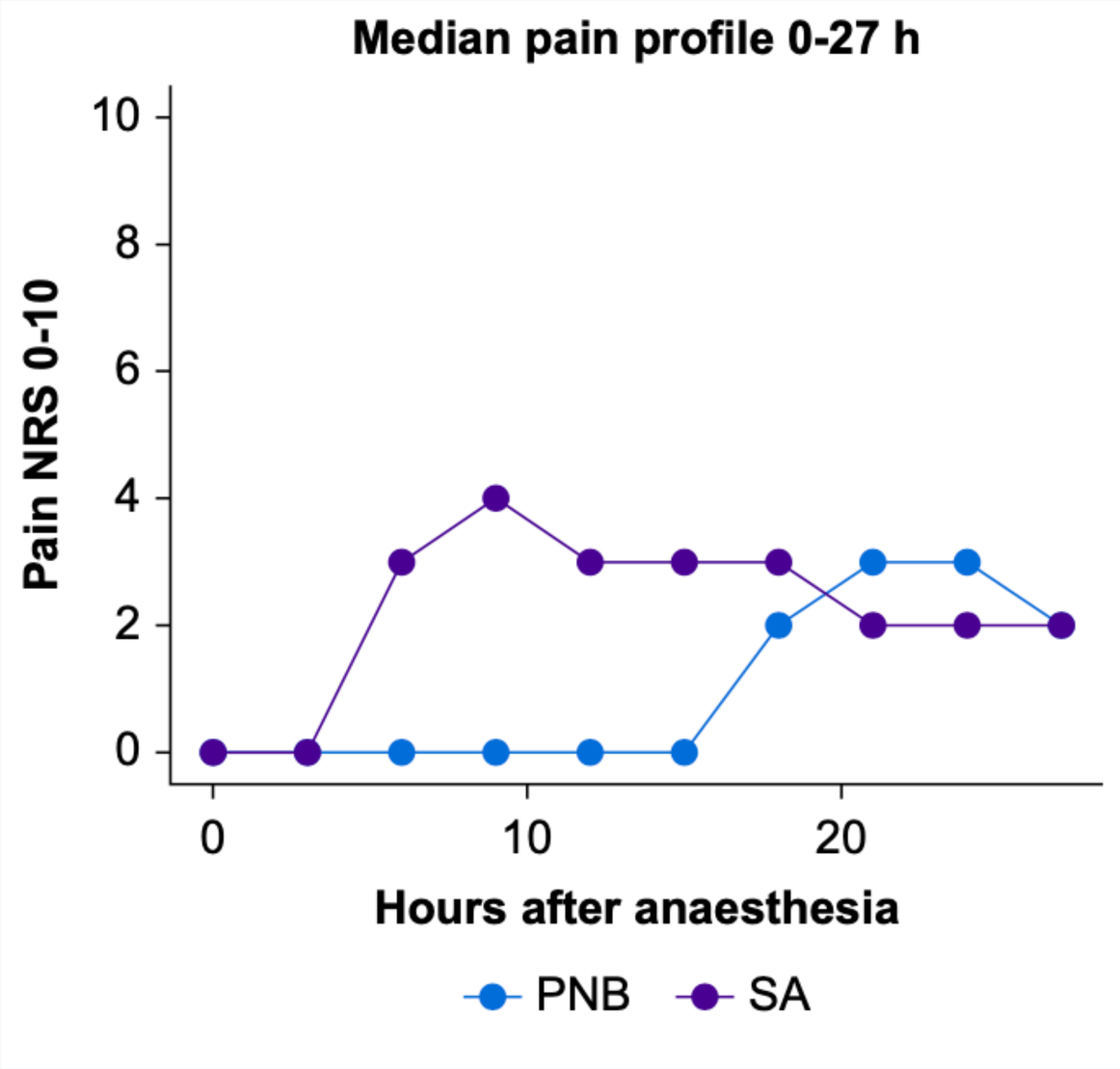
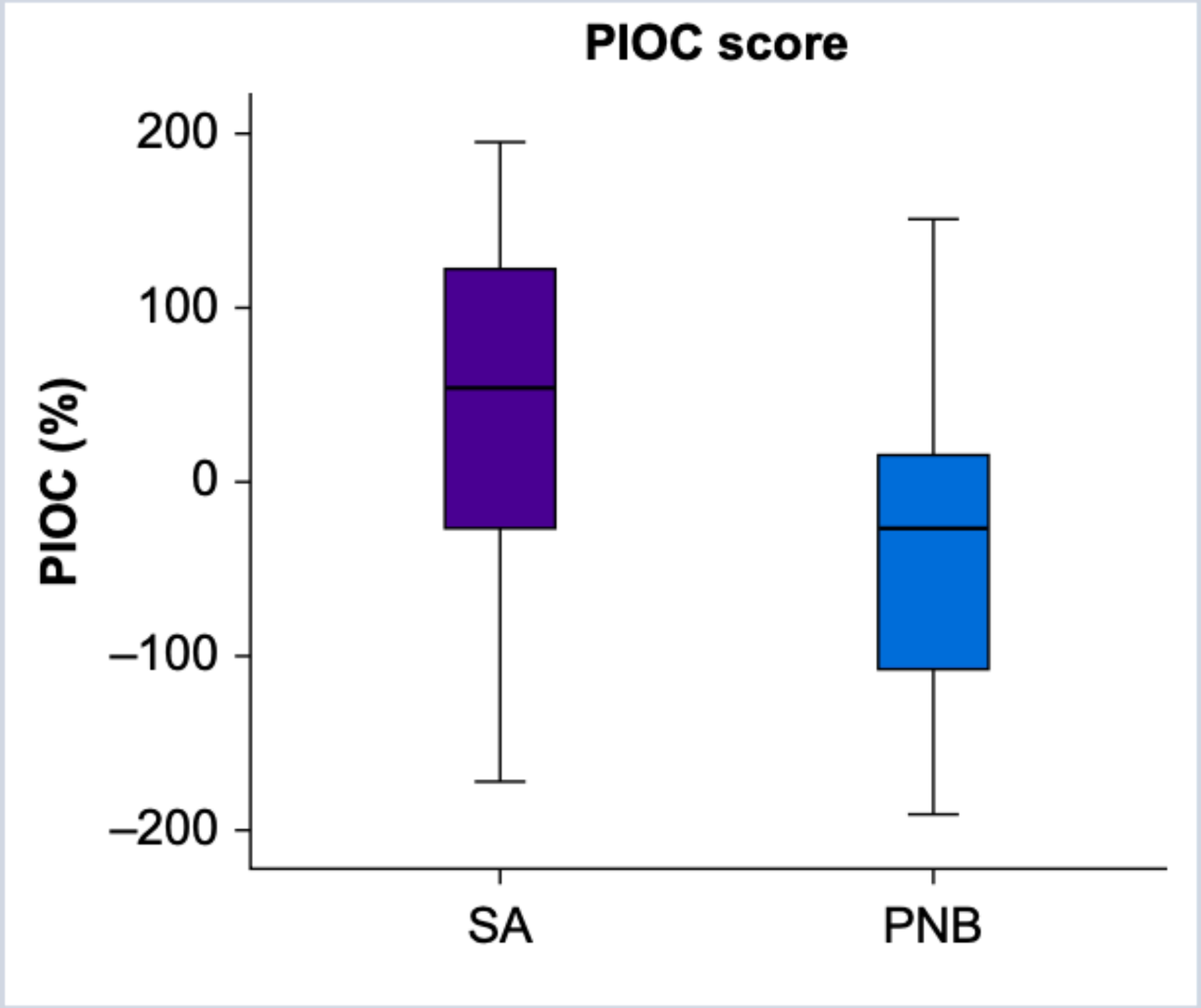


Fig 2. Pain profiles by study group. The median pain score profiles after spinal and peripheral nerve block anaesthesia for ankle fracture surgery. NRS, numeric rating scale; PNB, peripheral nerve block; SA, spinal anaesthesia.

The median pain score profiles

- **SA :** 3.5 h (95% CI, 3.2-3.9 h)
- **PNB :** 16.5 h (95% CI, 15.8-17.3 h)



Primary endpoint

- PIOC scores were significantly lower in the PNB group (median, -26.5% vs +54.3%; P<0.001)
- 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 endpoint

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

Secondary endpoint

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RESULTS

- **secondary endpoints**
  - Intraoperative haemodynamic events were not included in this registration
  - 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.

Subgroup analysis

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†				
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DISCUSSION

- Acute fracture surgery, RCTs have found that rebound pain may compromise the benefit of PNBs.
- This study showed that the PNB benefit was also evident in a far lower fraction of ‘risk patients’ (PIOC >100).
- However, the 0-27 h PCA i.v. morphine use in the PNB group was a median 20 mg and up to 97 mg.
- PNBs provided about 17 pain-free hours, these substantial morphine amounts were taken within only ~10 h after PNB resolution.

DISCUSSION

- The QoR-15 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.
- Subgroup analyses revealed lower pain scores and lower morphine consumption for older patients across treatment groups.
- The study was not powered for this comparison and the difference in PIOC effect size probability did not reach statistical significance.

STRENGTHS

- The large sample size for an RCT of acute fracture cases
- A detailed pain profile including a focus on patient reported measures
- Using a multimodal pain regimen and i.v. PCA in both groups

LIMITATIONS

- Lack of blinding
    - Marked differences in onset and duration between PNB and SA
- Differences in initial postoperative care between the PACU and ward could affect the participants.
- Although pain treatment regimens were identical.

LIMITATIONS

- Minimised these influences by
  - standardising subject information
  - having the subjects register data without the presence of personnel
  - electronically registering PCA morphine consumption
  - blinding the data before analysis.

LIMITATIONS

- Anxiety questionnaires were omitted, although anxiety is a known predictor of postoperative pain.
    - This should not affect the results because of the random allocation.
    - The most anxious patients might be more inclined to refuse participation.
- Unstable trimalleolar fractures could no longer be included.

CONCLUSION

- This RCT 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.
- Patients having PNB anaesthesia were more likely to choose the same modality again.

CONCLUSION

- Subgroup analyses revealed lower pain scores and lower morphine consumption for older patients across peripheral nerve block groups.
- The study was not powered for this comparison and the difference in PIOC effect size probability did not reach statistical significance.
- The benefit of PNB may be greater for older patients, which should be explored in future studies.

CRITICAL APPRAISAL

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

CRITICAL APPRAISAL

2. Was the assignment of patients to treatments randomised?	Yes ✓	Can't tell	No
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?	✓		
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

CRITICAL APPRAISAL

6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	Yes	Can't tell	No ✓
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

CRITICAL APPRAISAL

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	**No**
10. How precise were the results? Were the results presented with confidence intervals?	**Yes**

CRITICAL APPRAISAL

	Yes	Can't tell	No
11. Do these results apply to my patient? • Is my patient so different from those in the trial that the results don't apply? • How great would the benefit of therapy be for my particular patient?	✓	✓	
12. Are my patient's values and preferences satisfied by the intervention offered? • Do I have a clear assessment of my patient's values and preferences? • Are they met by this regimen and its potential consequences?		✓ ✓	