Techniques to increase lumbar puncture success in newborn babies: the NeoCLEAR RCT

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Scientific summary

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Scientific summary

Background

The neonatal period carries the highest risk of bacterial meningitis (≈ 1 per 4000–5000 births), which is associated with significant mortality (≈ 10%) and morbidity (20–50%). Meningitis is diagnosed by analysis of cerebrospinal fluid (CSF), obtained via lumbar puncture (LP). LPs are frequently performed in newborns because of the non-specific clinical features of neonatal meningitis. However, LP success rates in newborns are much lower (50–60%) than in older children (78–87%). Unsuccessful LPs include those with heavily blood-stained CSF or LPs that fail to obtain CSF at all. Treatment for suspected or confirmed neonatal meningitis involves intravenous antibiotics, typically for 14–21 days. Unsuccessful LPs lead to repeated attempts, whereas LPs with equivocal or uninterpretable CSF results often prompt cautious treatment with extended courses of antibiotics. Prolonged antibiotic use is associated with a range of complications, including induced antimicrobial resistance. Consequently, interventions to improve neonatal LP success rates should allow more accurate diagnosis of meningitis, which will help reduce unnecessary courses of antibiotic therapy and extended hospitalisation, and will save healthcare resources.

There have been few modifications to the original LP technique. Thus far, the sitting position, as employed for older patients, and 'early stylet removal' (ESR) have been suggested. ESR promises advantages because, in neonates, a 'loss of resistance' on entering the CSF is often indistinguishable and a needle advanced too far can cause venous puncture and a blood-stained tap, impairing CSF interpretation.

We conducted the Neonatal Champagne Lumbar punctures Every time – An RCT (NeoCLEAR) trial to determine the optimal LP technique in neonates in terms of the effect of infant position (sitting vs. lying) and timing of stylet removal [ESR vs. late stylet removal (LSR)] on success [i.e. a CSF red blood cell (RBC) count of < 10,000/mm^3] of first LP.

Methods

Trial design and oversight

The NeoCLEAR trial was a 2 × 2 factorial open-label multicentre randomised controlled trial (RCT), with an internal pilot. The study protocol was published previously. The NeoCLEAR trial was co-ordinated by the National Perinatal Epidemiology Unit – Clinical Trials Unit. The University of Oxford (Oxford, UK) sponsored the trial. Trial oversight was conducted by the Trial Steering Committee and an independent Data Monitoring Committee. The funder [i.e. the National Institute for Health and Care Research (NIHR)] did not have a role in study design, conduct, data collection, analysis or interpretation. Ethics approval was obtained.

Trial population

Eligible infants were inpatients in UK neonatal units and maternity wards who required a LP at a corrected gestational age (CGA) of 27^{+0} to 44^{+0} weeks and with a working weight of ≥ 1000 g. Infants were excluded if they had already had a LP for the same indication, if they were unable to be held in sitting position or if sitting was deemed unsafe.

Trial procedures

Infants whose parents had provided consent were randomised 1 : 1 : 1 : 1 by a one-based system to the following four groups: (1) lying position and LSR, (2) lying position and ESR, (3) sitting position and LSR or (4) sitting position and ESR. Block randomisation was stratified according to site and CGA (four categories: 27^{+0} to 31^{+6} weeks, 32^{+0} to 36^{+6} weeks, 37^{+0} to 40^{+6} weeks and ≥ 41 weeks).

Staff were trained in all four techniques. Any second LP required followed the same allocated technique. The need for any further LPs and the techniques used were determined by the clinical team. Blinding of practitioners was impossible, but the primary outcome was based on laboratory tests performed blinded to allocation.

Outcomes

Participants were followed up until discharge. The primary outcome was the proportion of infants with a successful first LP, defined as a CSF RBC count of < 10,000/mm^3. Secondary outcomes included short-term clinical measures (e.g. number of procedures/attempts per infant, proportions with different CSF-based diagnoses, time taken per procedure, infant movement), resources (e.g. duration of antibiotics, length of stay) and safety (e.g. complications, adverse event reporting).

Statistics and analysis

The NeoCLEAR trial was designed with 90% power to detect a 10% absolute difference in the primary outcome (estimated comparator group event rate 59%), with a 5% two-sided significance level. Four hundred and eighty-three infants were required for each arm of each comparison (i.e. sitting vs. lying position and ESR vs. LSR). Allowing for 5% attrition, the recruitment target was 1020 infants.

Outcomes were analysed by modified intention to treat (excluding participants who were withdrawn before collection of trial data or who did not undergo LP). For infant positioning, we compared groups (1) lying/LSR plus (2) lying/ESR with groups (3) sitting/LSR plus, (4) sitting/ESR. To assess the timing of stylet removal, we compared groups (1) plus (3) with groups (2) plus (4). We estimated risk ratios (RRs) for the primary outcome and all other dichotomous outcomes, the mean difference for normally distributed continuous outcomes and the median difference (Med D) for skewed continuous variables. The 95% confidence intervals (CIs) were calculated for all effect estimates. Groups were compared using regression analysis, adjusting for the stratification factors used at randomisation (i.e. centre and CGA) and allocation to the other intervention. The latter adjustment was advised after the final statistical analysis plan was signed off and is a noted deviation. Adjusted risk ratios (aRRs) were estimated using log-binomial regression, or using a Poisson regression model with a robust variance estimator in the event of non-convergence. Linear regression was used for normally distributed outcomes and quantile regression for skewed continuous outcomes.

To mitigate multiple testing, inference was restricted to prespecified tested outcomes. A descriptive multiarm analysis was also performed for the primary outcome, other tested outcomes and baseline characteristics (i.e. for each of the four randomised groups). Effect modification between position (i.e. sitting/lying) and the timing of stylet removal (i.e. ESR/LSR) was investigated for the primary outcome using the statistical test for interaction. Prespecified subgroup analyses were conducted for working weight, day of life and CGA at trial entry. Two-sided p-values of ≤ 0.05 were considered to indicate statistical significance.

Results

From August 2018 to August 2020, 1082 participants from 21 centres in the UK were randomised in a 2 × 2 factorial design, resulting in two principal comparisons: (1) sitting position (n = 546) compared with lying position (n = 536) and (2) ESR (n = 549) compared with LSR (n = 533).

A total of 1079 infants had a 'first' LP, and 166 (15.4%) infants had a second LP (each of these LP 'procedures' involved one or more 'attempts'). Nine infants were withdrawn during the trial, but in the case of only one of these participants was consent withdrawn before data collection for the primary outcome. Three infants did not receive a LP, and in the case of a further two infants the consent form was missing. Overall, six infants were excluded, leaving 1076 infants for the final (modified intention-to-treat) analysis: (1) sitting position (n = 543) compared with lying position (n = 533) and (2) ESR (n = 545) compared with LSR (n = 531). All infants were followed up until discharge.

Baseline characteristics were similar for the two groups in both comparisons, as recorded at trial entry and at time of first LP. The majority of infants were born at term, were < 3 days old and were not receiving respiratory support. Raised C-reactive protein was the most common indication for LP.

First comparison: sitting position compared with lying position

The primary outcome – a successful first LP – was achieved in 346 of 543 (63.7%) infants in the sitting arm and 307 of 533 (57.6%) infants in the lying arm [aRR 1.10 (95% CI 1.01 to 1.21); $p = 0.03$; adjusted absolute risk difference 6.1% (95% CI 0.7% to 11.4%), adjusted number needed to treat (NNT) 16 (95% CI 9 to 134)].

Infants allocated to the sitting position were less likely than infants allocated to the lying position to exhibit moderate or severe struggling at the time of needle insertion [169/541 (31.2%) vs. 202/527 (38.4%), aRR 0.82 (95% CI 0.71 to 0.94); p = 0.006]. Other secondary outcomes did not reach statistical significance, but predominantly favoured the sitting position.

Based on microscopy of CSF extracted from the first and second LPs (and any culture/polymerase chain reaction results), infants who were sitting were more likely to be 'negative' for meningitis than infants who were lying [396/537 (73.7%) vs. 359/521 (68.9%)], and a result of 'uninterpretable CSF' (i.e. no sample obtained or CSF not possible to analyse, usually due to a **heavily blood contaminated or clotted sample**) was more likely to be recorded for infants who were lying than for infants who were sitting [139/521 (26.7%) vs. 114/537 (21.2%)].

Median duration of antibiotic treatment and length of stay were not significantly different in the sitting and lying arms {median 5 [interquartile range (IQR) 4–6] days in each arm, for both duration of antibiotic treatment and length of stay}.

Four (0.3%) of 1241 first or second LPs, 1 in ESR and 1 in LSR arms, respectively, were abandoned because of cardiovascular deterioration. Lowest oxygen saturation (SpO_2) during the first LP averaged 93% (IQR 89–96%) in the sitting arm and 90% (IQR 85–94%) in the lying arm (adjusted Med D 3.0%, 95% CI 2.1% to 3.9%; $p < 0.001$). Three of 1075 (0.3%) infants required increased respiratory support within 1 hour of their first LP (sitting arm, $n = 1$; lying arm, $n = 2$; not significantly different). The proportion of infants whose lowest SpO_2 fell below 80% during the first LP (analysed post hoc) was 6.6% (35 of 532) in the sitting arm and 14.2% (72 of 508) in the lying LP arm, and this pattern was consistent in preterm and term-born babies.

In 47 of 543 (8.7%) first LPs in infants allocated to the sitting position, at least one attempt involved switching to the lying position [compared with 4/533 (0.8%) infants allocated to the lying allocation, who were switched to sitting]. Of the 47 LPs where there was at least one attempt in which the allocated technique was not adhered to, the decision to change position was mostly made on the second (22/247) or third (24/257) attempt. The decision to change position was usually made by a clinical (45/47). Similarly, for the second LP, the sitting allocation was less often followed [for at least one attempt in 16/76 (22.5%) of infants allocated to sitting vs. 6/90 (7.0%) of infants allocated to lying]. There were no obvious differences in baseline infant characteristics between LPs that were carried out in the allocated position and those that were not.

In prespecified subgroup analyses, the effect of position on the proportion of infants with a successful first LP was consistent across working weight and CGA at trial entry, but a difference in effect was observed between infants enrolled within 3 days of life ($n = 836$, RR 1.14, 95% CI 1.04 to 1.25) and those enrolled after 3 days ($n = 140$, RR 0.9, 95% CI 0.78 to 1.05; $p = 0.001$).

Second comparison: early stylet removal compared with late stylet removal

The primary outcome was achieved in 338 of 545 (62.0%) infants following ESR and in 315 of 531 (59.3%) infants following LSR. There was no significant difference between the groups (aRR 1.04, 95% CI 0.94 to 1.15; $p = 0.45$). There were also no obvious differences between the groups in any of the secondary outcomes.

Either the first or the second LP (4/1242, 0.3%) was abandoned in four infants receiving LP (two in each arm) because of cardiovascular deterioration. Three of 1076 (0.3%) infants required increased respiratory support within 1 hour of their first LP (ESR, *n* =1; LSR, *n* =2; not significantly different). There were no differences in lowest SpO_2, lowest heart rate (HR) or highest HR between the two arms.

The allocated technique was not adhered to in 35 of 1076 (3.3%) first LPs, with similar numbers in each arm (untested outcome). In 13 of 78 infants allocated to ESR, the second LP involved at least one attempt without ESR, compared with 6 of 79 allocated to LSR; however, denominators were small and this was an untested outcome.

The effect of timing of stylet removal on the proportion of infants with successful first LP was consistent across working weight at trial entry, CGA at randomisation and day of life at trial entry.

Multiarm analysis: comparing four randomised groups (sitting plus early stylet removal, sitting plus late stylet removal, lying plus early stylet removal and lying plus late stylet removal)

No significant interaction between infant position and timing of stylet removal was detected ($p = 0.14$). Multiarm baseline characteristics and analyses did not reveal any new obvious differences (only those previously described for the sitting position compared with the lying position; see *First comparison: sitting position compared with lying position*).

Serious adverse events

Four serious adverse events (SAEs) were reported during the trial. Three SAEs were deemed unrelated to LP. One infant, from the sitting/LSR group, developed a scrotal haematoma 2 days after LP. The infant did not undergo further investigations to identify a cause for this, and so a relationship with the LP could not be ruled out. Therefore, this event was deemed 'possibly related'.

Discussion

The NeoCLEAR trial is, to the best of our knowledge, the first adequately powered RCT examining different LP techniques in newborns. The sitting position was superior to the lying position for achieving a successful first LP, with a NNT of 16. Sitting LP was also better tolerated in terms of infant struggling, SpO_2 and HR. Timing of stylet removal did not influence LP success.

Our results might be explained by the anatomical advantages of sitting position described in neonates: (1) the intervertebral spaces widen when the infants lean forward to adopt a (natural) kyphotic position; (2) the CSF passively sinks to the lowest point of the spinal canal and close to the entry site of the needle; and (3) this position is more comfortable for the baby, as evidenced by the reduced struggling we observed. At the time of the study, the only other paediatric RCT of sitting compared with lying position, by Hanson *et al*., involved 168 infants who were < 90 days of age in a paediatric emergency room setting.[32] In that trial, the success rate did not differ significantly between groups (lateral group 63/82, 77%; sitting group, 61/85, 72%; difference 5.1%, 95% CI −8.2% to 18.3%).

The suggestion that higher LP success rates could be achieved with ESR was based on reports of increased success rates with non-styletted needles. However, non-styletted needles are associated with iatrogenic intraspinal epidermoid tumour formation and, therefore, the technique of ESR was introduced. Subsequent observational studies suggested that ESR was associated with increased success rates in infants. At the time of the study, to the best of our knowledge, the NeoCLEAR trial is the first RCT to have investigated ESR and has demonstrated no significant benefit in it for neonatal LP. Therefore, we cannot advise for or against early or late stylet removal in neonates.

Our safety analysis showed greater physiological stability for sitting LP, in keeping with previous observations. Other secondary outcomes lacked statistical significance, including resource outcomes.

The NeoCLEAR trial has several strengths. To the best of our knowledge, it is the largest RCT, to date, investigating modifications to traditional LP technique, and the only such RCT in newborns. We chose to investigate modifications that came at no additional cost and were easily learned. The results are clear-cut, showing a significantly higher success rate for LPs with more interpretable CSF results when infants were held in a sitting position.

Limitations include the fact that many practitioners were unfamiliar with sitting LP before the NeoCLEAR training sessions, and this may have led to more practitioners switching from the allocated sitting position to the lying position following an initially unsuccessful attempt. It could be speculated that success rates would have been even higher if there had been more experience of sitting position LP among practitioners, and if fewer practitioners had switched position. We did not investigate LPs carried out in infants with a CGA of under 27 weeks or over 44 weeks. Furthermore, most infants were born at or near term and had working weights above 2.5 kg and, therefore, we cannot extrapolate our results to infants born extremely pre or post term or to those of significantly different working weights. In addition, in the subgroup analyses of gestational ages, although the inconsistent effect of sitting position may well be a chance finding and/or due to confounders, the NeoCLEAR trial was underpowered to detect a significant difference for those beyond day 3 of life.

In conclusion, the NeoCLEAR trial demonstrates that sitting position is superior to lying position for neonatal LP success rates (NNT 16), with no significant benefit for ESR. Adopting the sitting position is cost neutral, safe, well tolerated, and easy to learn. The results would be applicable in similar settings worldwide and should promote the sitting technique becoming the standard for neonatal lumbar puncture.

Trial registration

This trial is registered as ISRCTN14040914 and as Integrated Research Application System registration 223737.

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