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Efficacy of greater occipital nerve block treatment for migraine and potential impact of patient positioning during procedure: Results of randomised controlled trial.

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ABSTRACT

Purpose: Assess the efficacy, and potential impact of patient positioning for 10 minutes immediately post-procedure, of greater occipital nerve (GON) block for treatment of migraine.
Methods: Prospective multicentre non-blinded randomised controlled trial, randomisation and treatment of 60 neurology clinic patients with poorly controlled migraine. Outcomes measured with Headache Impact Test-6 (HIT-6), modified MIgraine Disability Assessment Scale (M-MIDAS), and RELIEF scores.
Results: Patient positioning did not lead to significant difference in RELIEF score (34% vs 11%, p-value 0.10, Chi-squared test) at day 90. When considered in a multiple regression analysis, the sitting position outperformed supine position significantly (p-value 0.04). However, no significant difference in HIT-6 score between the supine (n = 27) and sitting position groups (n = 33) was detected at baseline (p-value 0.76), day 30 (p-value 0.69) or day 90 (p-value 0.54, Mann-Whitney U-test). The HIT-6 score significantly improved post-GON block, from median 67 (baseline pre-GON) to 59 (day 30) and 62 (day 90) for the supine group and a score of 66, 61–62 for the sitting group (all p-value $\leq$ 0.001, intra-group comparison using Wilcoxon test); M-MIDAS achieved similar outcomes. Overall, a significant minimal clinically important improvement was obtained with GON block, and the GON injections were deemed very tolerable by patients (median score of 2 on 10 cm pain scale).
Conclusion: Regardless of patient positioning, GON block is an effective and near-painless procedure for migraine symptom control. Unlike earlier published observational study data, this trial concludes that a sitting patient position immediately post-GON is preferred.

1. Introduction

Primary headache disorders, including migraine, have a high prevalence. In terms of years of life lost to disability, headache disorders ranks amongst the highest worldwide causes of disability. [1,2] When considered separately, worldwide migraine has a one-year prevalence of over 10%, with a higher prevalence in developed countries. [3].

Until the recent emergence of biological antibody therapy [4], oral pharmacological treatment of migraine has been the mainstay of patient management, both in terms of prophylaxis and treatment of headache episodes. However, a subset of patients are treatment-resistant to such prophylaxis and thus offered nerve block treatments. Interventional procedures such as peripheral nerve blocks (PNBs) and trigger point injections (TPIs) have long been used in the treatment of various headache disorders although a common target is the greater occipital nerve (GON). [5] The specific conditions treated with GON block vary and include both primary (e.g. migraine, cluster headache) and secondary (e.g., cervicogenic) headache disorders. [6] To date there is not a

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widely accepted agreement amongst neurologists concerning the optimal GON block methodology. Despite favourable outcomes reported by many practitioners, there is still a relative lack of scientific evidence and data. [7,8].

There is currently no standard approach to managing a migraine patient immediately after a GON block procedure, and this detail is typically not reported on in study reports; patients can recover either sitting upright or lying down. Initial pilot data, obtained by the authors of this present paper, on GON block patients revealed that there may be a difference in GON block efficacy depending on the patient's position straight after the procedure (supine or sitting). [9] Data from a trial in dentistry showed that a patient's position during/after nerve block may influence the efficacy of an anaesthetic agent. [10] However, outcome data from a prospective interventional study is lacking for the effect of patient positioning post-GON block for migraine.

This prospective, multicentre randomised controlled trial (RCT) aimed to determine if patient positioning immediately following GON block (supine versus sitting up) affects the efficacy of the treatment in terms of achieving longer-term headache relief up to 90 days post-procedure, primarily measured with the RELIEF score. As part of the trial, secondary objectives were to assess the feasibility of collating patient reported outcome data using a digital headache diary App called

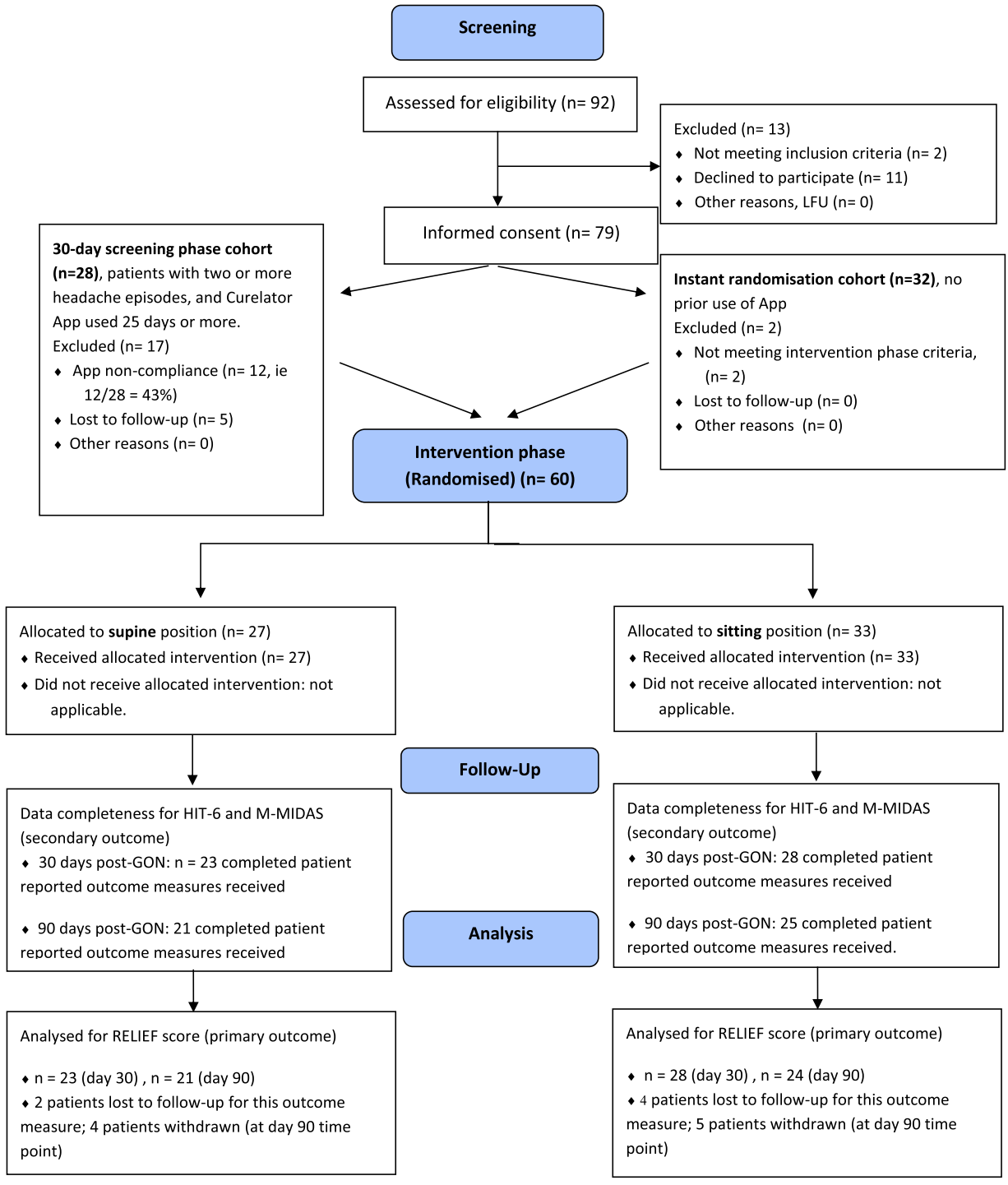

Fig. 1. CONSORT flowchart for PARAGON trial, migraine patient sub-cohort.

N1-Headache™ (Curelator Inc.), and measuring the painfulness of the GON block procedure itself.

2. Methods

2.1. Study design

The PARAGON (PAtient Reported outcomes After Greater Occipital Nerve block) trial is a multi-centre, prospective non-blinded randomised controlled trial assessing patient reported outcomes following Greater Occipital Nerve (GON) block for primary headache disorders. This present paper covers the results for the migraine patient cohort. Full research governance approval was obtained from the National Research Ethics Service (18/SC/0334), Health Research Authority (248606) and the NHS Trusts; the study was also registered on the International Standardised Clinical Trial Number registry (ISRCTN10430251).

The trial design is outlined in Fig. 1; as part of the trial patients with other headache disorders were enroled but only participants with migraine are reported on here. The initial trial participation stage could differ for patients. Initially, the following approach was taken: at least 30 days prior to the planned GON block date, patients were enroled into the screening phase of the trial following a written informed consent process. During this period, study subjects would commence using the N1-Headache™ diary App to prospectively record any headache episodes. [11,12] At the GON block clinic appointment date, compliance with use of the N1-Headache™ App was checked. If participants had experienced fewer than two headache episodes over the baseline 30 day data collection period, or if they had used the App for fewer than 24 out of the 30 day (i.e. 80%) baseline diary period, they were excluded from the intervention phase of the trial (see also Fig. 1). A subsequent second batch of patients were enroled into the trial without the requirement of a 30 day screening phase. All migraine patients who were eligible for the intervention phase were randomised for positioning post-GON block and were asked to complete the N1-Headache App for 90 days after their GON block appointment. A 1:1 randomisation schedule, using list generated from freeware randomiser.org and concealed using consecutively numbered envelopes, was applied for the patient recovery position intervention (of supine versus sitting). Block randomisation of six each was used to allow recruitment sites to have sets of randomisation envelopes; this was all performed by the data manager who was not involved in patient recruitment or follow-up. The trial intervention was as follows: directly following conclusion of the GON block procedure the patient was either (a) Lying down horizontally in a supine position for 10 minutes with head rested on pillow at approximately 30 degree angle, or (b) Sitting upright for 10 minutes. The GON block procedure itself has been described in detail before. [9] Serious adverse events were pre-defined in the protocol and the study was managed in accordance with good clinical practice.

2.2. Study subjects

Patients enroled in the trial between October 2018 and January 2020, and was ended when sufficient patients had been enroled; they were attending a Neurology Department for GON block in one of three NHS Trusts in England, due to migraine symptoms refractory to first line treatments. Patients were diagnosed by the treating neurologist in accordance to International Headache Society 2nd Edition guidelines ([a] five or more attacks in lifetime, [b] headache attacks lasting 4–72 hours, [c] at least two features from unilateral location, pulsating/throbbing quality, moderate-severe intensity, aggravation by/causing avoidance of routine physical activity, and [d] at least one feature from nausea, vomiting, photophobia, phonophobia]). [13] Further inclusion criteria for the screening phase of the trial were patients with mental capacity and command of English language, aged 18 years or older who were deemed eligible for the GON block procedure by the treating neurology team, typically patients who have exhausted oral medication and lifestyle change options. Patients were excluded if they were participating in another interventional research study involving an investigational product related to their headache disorder, had a concurrent medical condition that in the opinion of the investigator may have compromised patient safety or study objectives, had received greater occipital nerve blocks in the prior 3 months, or were still headache-free following an intervention.

2.3. Outcome measures

Validated Patient-Related Outcome Measures (PROMs) were utilised to measure the severity of patients' headache disorders at different time points and to assess the effectiveness GON block in combination with the adjunct trial intervention of patient positioning after GON block. Study subjects were asked to complete a set of paper questionnaires at baseline, 30 days prior to GON block, at the GON block appointment, and at 30 and 90 days after GON block. The Headache Impact Test [14] (HIT-6) and modified Migraine Disability Assessment Scale [15] (MIDAS) was recorded at all three time points. At the GON block / randomisation appointment, study subjects were asked 10 minutes after their GON block how painful they thought the injections had been (using a 10-cm visual analogue scale). At 30 and 90 days after GON block, the headache RELIEF score was recorded to determine the degree of pain relief efficacy achieved. [9] The intention was to use participant-inputted data from the N1-Headache diary App to assess headache-free days, number of headache episodes, and headache-related medication use.

2.4. Data analysis

An initial observational study examining patient positioning and GON block had previously been conducted; the sample size calculations were based on these results. [9] The Chi-squared test was used and 80% power and 5% significance was assumed. Non-responders (headache worse, no relief, slight relief) and responders (substantial relief, complete relief) at day 90, as measured with RELIEF score, were to be compared. A priori power calculation using GPower 3.1 software, indicated that a minimum total of 42 migraine patients would need to be enroled to allow a supine versus sitting position comparison and detect an effect size of 0.5; this is equivalent to a 25% difference in response rate between the two patient position groups at day 90 post-GON, as measured with RELIEF score. A participant drop-out rate of 30% at screening phase was factored in. Analysis was performed on a per-protocol basis. However, for the patient-reported outcome measures HIT-6 and modified MIDAS multiple imputation (default five imputations) was applied for missing values and inferential statistics was performed on pooled data. Data recorded via the N1-Headache App and paper case report forms were first collated in Microsoft Excel, followed by analyses performed using SPSS v20. For inferential statistics, Chi-squared test applied for binary data, Mann-Whitney U-test for inter-group ordinal data, Wilcoxon test for intra-group ordinal data, and binary logistic regression for multivariable correlation analysis; a p-value of < 0.05 was considered statistically significant.

3. Results

A total of 92 patients were considered for the study, with 79 enroled and 60 randomised, see Fig. 1. As outlined in the Methods section, an initial cohort commenced the N1-Headache™ App at least thirty days prior to having the GON block procedure. The rationale was to obtain baseline statistics for the participants regarding the severity and frequency of their headaches, which could then be compared using data again recorded using N1-Headache™ App data recorded after the GON block procedure. However, during the initial screening phase after patient enrolment, 12 out of 28 participants (43%) did not use the N1-Headache™ App sufficiently to enable reliable interpretation of the data (see Fig. 1). The challenge is that if the diary is not completed for a given

day, one cannot determine if the patient indeed did or did not have a headache. Bearing in mind that the App was then to be used by patients for a further 90 days, increasing the likelihood of a further increase in attrition rates, the 30-day screening phase was aborted. A further 32 patients were consented where the setup did not require a screening phase using the N1-Headache™ App. Further non-compliance regarding completion of the N1-Headache™ App meant that we could not determine the headache-free days achieved by GON block in relation to either patient positions at recovery post-GON. The App is also designed to monitor patients' medication use; again, due to non-adherence with daily data entry we could not determine if medication use changed before vs after GON block. The results that follow were all obtained using paper-based PROMs.

The treatment arms were well matched between the 'supine' and 'sitting' position both in terms of patient characteristics (age, sex) and headache characteristics (type of disorder, usual headache severity and history of GON block received), as summarised in Table 1. The Likert scale-based RELIEF score, used as the primary PROM for this trial, was applied for both treatment arms. Table 2 shows that 23% of supine position participants and 32% sitting position participants reported substantial or complete relief at day 30, but this was not a statistically significant difference (p-value 0.41, Chi-squared test). At day 90, however, the figures were 11% and 34%, respectively for supine and sitting cohorts for substantial or complete relief, and this was a significant difference (p-value 0.10, Chi-squared test). The relative effect size of efficacy of sitting over supine was 0.25 (Cramer's V) at the day-90 time point, which is less than the pre-defined required effect size of 0.5 for this trial. Fig. 2 summarises the RELIEF data by the five different outcomes that participants could select; subsequent Mann-Whitney U-test comparing that data distribution for supine vs sitting positioning resulted in non-significant p-values of 0.62 for day 30 and 0.50 for day 90. The supine and sitting position result in a similar percentage of patients who experience an worsening effect or no effect of GON block (Table 2). A multivariable binary logistic regression analysis was conducted to determine if variables interact to influence the response to GON block at day 90, as measured by the RELIEF score (binary non-responder versus responder categorisation as per Table 2). Table 3 shows that in an initial model there are no variables that are significantly associated with improved GON block efficacy. However, after elimination of variables with the weakest associations, only two variables remain, namely migraine chronicity and patient position immediately post-GON block; only the latter is significantly associated with a substantial/complete response at day-90 after GON block. Due to the challenges with obtaining data from all participants, only 41 out of the initial 60 randomised participants could be included for this regression analysis, resulting in wide 95% confidence intervals for some of the variables.

The efficacy of the GON block procedure and potential for patient positioning immediately after the procedure was also appraised using the HIT-6 score and modified MIDAS score. Table 4 outlines the results

Table 1
Patient characteristics for respective post-GON block groups at baseline.

variable	Randomised to supine position (n= 27)	Randomised to sitting position (n= 33)
Sex, n (%)	2 male (7%) / 25 female (93%)	4 male (12%) / 29 female (88%)
Patient age, mean years (95% confidence interval)	35 (31–40)	40 (35–45)
Chronicity of migraine condition, median years (interquartile range)[#]	7 (15)	17 (17)
Average headache severity at baseline, n (%)[#]	Mild 1 (4%) Moderate 9 (35%) Severe 16 (61%)	Mild 1 (3%) Moderate 18 (55%) Severe 14 (42%)

n = 26 for supine position group.

Table 2
Migraine RELIEF score post-GON procedure.

Follow-up time point	RELIEF outcome, binary	Non-responders[a]	Responders[b]	p-value (Chi-squared)
Day 30	Supine (n = 23)	77%	23%	0.41
	Sitting (n = 28)	68%	32%	
Day 90	Supine (n = 21)	89%	11%	0.10
	Sitting (n = 24)	66%	34%	

[a] Migraine worsened, no relief, or slight relief;
[b] Substantial relief or complete relief

obtained with this validated measurement. Although no significant difference in score was seen between the two treatment arms at either baseline, day 30 or day 90, a significant improvement in HIT-6 score was achieved at day 30 and day 90 for each treatment arm when compared to baseline pre-GON block. The results for the overall participant cohort are also shown in Table 4. As part of the trial, the degree of injection-related pain experienced by patients 10 minutes post-GON block was measured using a visual analogue scale (range 0 – 10 cm). The median patient pain level in the supine position group was 2.0 (inter-quartile range [IQR] 1.5, n = 25) whereas for the sitting position group it was again a median of 2.0 (IQR 2.0, n = 32), which was a non-significant difference (p-value 0.33, Man-Whitney U-test). No adverse events in relation to the trial intervention, patient positioning for 10 minutes after GON block procedure, were observed.

4. Discussion

This study aimed to assess the impact of patient positioning immediately post-GON block on the efficacy of said clinical procedure. A meta-analysis involving randomised controlled trials of migraine patients has shown that pain, headache-free days, and oral analgesic medication consumption are all improved upon GON block when compared to control patients. [16] In terms of response rates to GON block, an earlier study by Tobin and Flitman identified 21 articles researching benefit of GON block and found that the duration of reported benefit was between 1 and 4 weeks in most studies. The reported benefit did not exceed median of 32 days after a single treatment in any of the studies. [8] Any further improvements made to the GON block procedure would be welcome and may benefit patients. A retrospective audit on a cohort of headache disorder patients, both migraine and other headache disorders, suggested a putative role of patient position once the GON block procedure is complete. [9] Therefore this prospective randomised controlled trial was devised to investigate this further.

In terms of the efficacy of GON block, the earlier findings of a difference in efficacy of GON block depending on patient positioning post-procedure [9] could not be replicated. In fact, a trend to an effect into the opposite direction – sitting position being superior to supine position - was observed. The primary outcome, RELIEF score categorised as non-response (migraine worsened, no relief, slight relief) and response (substantial or complete relief) is not significantly better in the patients in supine or sitting position for 10 minutes after GON block, as shown in Table 2, Table 4, and Fig. 2. However, when other variables are considered simultaneously then patient positioning (ie a sitting) does outperform a supine position. Although the results in terms of GON block efficacy and patient positioning found here are the exact opposite of those found in an original non-randomised evaluation, the potential negative impact of chronicity of the migraine condition on GON block efficacy was also found in the initial evaluation we conducted. [9] When other patient reported PROMs are considered, HIT-6 and M-MIDAS, again no statistically significant difference is observed between the two groups. Taken together, the sitting position may be the preferred option for clinicians to apply when performing GON block in other to optimise the likelihood of achieving substantial to complete relief for their migraine patients, but the benefits are likely to be small. The chance of a

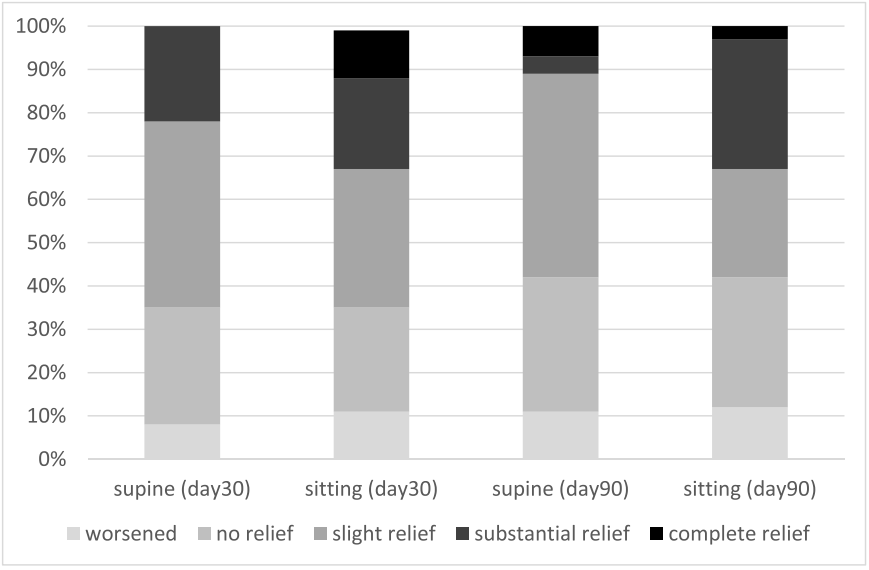

Fig. 2. Migraine RELIEF score distribution at follow-up time points and by different patient position immediately post-GON block.

Table 3
Binary logistic regression to assess association between variables and RELIEF outcome (non-responder vs responder to GON block) at day 90 as dependent.

Variables (measurements taken at baseline; *italic* if reference point)	p-value	Odds Ratio	95% confidence interval for Odds Ratio
Initial model:			
Sex (*male* vs female)	0.56	3.41	0.058–201.73
Patient age	0.49	1.04	0.94–1.15
Chronicity of migraine condition	0.092	0.92	0.83–1.02
Average headache severity	0.85	1.21	0.18–8.21
Prophylactic medication use (*no* vs yes)	0.61	1.78	0.20–15.80
Rescue medication use (*no* vs yes)	0.55	0.36	0.012–10.52
Patient position immediately post-GON (*supine* vs sitting)	0.062	8.98	0.90–89.79
HIT6 total score	0.44	0.90	0.68–1.18
M-MIDAS total score	0.27	1.03	0.98–1.07
Final model after backward likelihood ratio elimination:			
Chronicity of migraine condition	0.13	0.94	0.88–1.02
Patient position post-GON (*supine* vs sitting)	0.040	6.75	1.09–41.93

Participants, n = 41. Nagelkerke R^2 value = 0.31 (initial model) and 0.20 (final model).

detrimental effect to GON efficacy should be limited if a patient would want to lie down for a short period after receiving GON block instead of remaining seated.

When efficacy of GON block itself is considered, for each treatment arm a minimal clinically important difference (MCID) – equating to an improvement in HIT-6 score of at least 2.5 points [17] – was observed three months after the procedure when measured with HIT-6. In a single cohort of migraine patients another research group observed a reduction of HIT-6 by 5.3 points which is similar to the average 5 points improvement (at day 90) seen with the patients in this present study. Others have made a HIT-6 score of <60 the benchmark for treatment response for severe headache disorder cases, for example when looking at efficacy of Botulinum toxin for treatment of migraine [18], and on that basis GON block was effective in the current trial at day 30, but no longer at day 90 when assessing HIT-6 scores. Due to the variability in migraine severity, frequency and nature of headaches amongst different patients and patient populations, indirect comparisons with results from other studies are fraught with pitfalls. A direct comparison in a head-to-head trial can determine the relative performance of GON block versus other treatment modalities.

In addition to assessing the efficacy of GON block, patients were asked how painful they felt the GON block procedure was – this was asked using a visual analogue display survey 10 minutes after completion of the GON procedure when the patient positioning intervention was complete. The median score across all participants was 2 out of 10, described as 'mild annoying pain' on the survey, which suggests GON block is very tolerable. To our knowledge this had not been measured before and for clinicians it is worth having this reference score to hand if patients enquire about how painful GON block may be. Others have

Table 4
HIT6 and MIDAS PROM at baseline and at post GON-block intervals.

PROM	HIT6			Modified MIDAS		
Variable	**Randomised to supine position**	**Randomised to sitting position**	**p-value (supine vs sitting)#**	**Randomised to supine position**	**Randomised to sitting position**	**p-value (supine vs sitting)#**
Baseline score, median [IQR][a]	67 [6]	66 [5]	0.76	28 [39]	30 [17]	0.29
Day 30 score, median [IQR][b]	59 [10]	61 [15]	0.69	17 [26]	15 [29]	0.16
Baseline vs day30, p-value*	<0.001	<0.001		<0.001	<0.001	
Day 90 score, median [IQR][c]	62 [11]	62 [6]	0.54	19 [32]	20 [19]	0.065
Baseline vs day90, p-value*	<0.001	<0.001		<0.001	<0.001	

#Mann-Whitney U-test; *Wilcoxon test; asupine n = 27 and sitting n = 33; bsupine n = 23 and sitting n = 28; csupine n = 21 and sitting n = 25.

asked about the relief of headache pre- and immediately post-GON, which is a question of GON block efficacy, not the painfulness of the GON block procedure itself. [19].

A strength of this study is the prospective randomised controlled approach to following up our initial findings on patient positioning and GON block using retrospective data. [9] In addition, patients were recruited from three different regional sites, rather than a single unit. One major general drawback concerning headache-related research is the dependence on patient recall and paper headache diaries which may not match data recorded prospectively. [20] To strengthen the approach of this study, patient related outcome measures (PROMs), through the use of the validated HIT-6, modified MIDAS, and RELIEF questionnaire were used. The intention of this study was for participants to utilise the digital N1-Headache™ App to prospectively and digitally record the incidence of any headaches experienced, as well as their intensity and length. This would then allow the calculation of certain headache outcomes (headache-free period and change in medication use) post-GON block per patient positioning group. Major non-compliance with the N1-Headache™ App meant that this plan – to monitor participants for 30 days prior to having their GON block - had to be aborted in order to achieve the planned number of trial participants to assess GON block efficacy. Only data from paper-based measures such as HIT-6, modified MIDAS, and RELIEF was used for analyses. Another limitation of this study is the lack of blinding of participants and also not using a blinded metrologist; the former is impossible with the intervention that was assessed, whereas the latter was also not practical since outcome measures for migraine are all patient-reported. This trial may be subject to different biases, such as whether the trial sample is representative of the wider migraine patient population [21], and non-responder bias due to participants not responding at follow-up time-points after they had entered the trial phase. The intended use of a digital headache diary App was intended to address potential for recall bias, since the diary was to be completed daily; however, non-compliance with the diary App impeded this approach. [22].

From this study we conclude that GON block, on average, significantly improves pain associated with headache disorders and that this can be sustained relief; this confirms findings from other studies. [6,8,16,17] The GON block procedure is not reported to be particularly painful by patients. How a patient is positioned straight after a GON block procedure – i.e. either supine or sitting upright - does not appear to affect the eventual efficacy of the injected analgesic. Patient and or clinician preference, or constraints of the clinic setup, may therefore guide practice on that front. Future research would benefit from focusing on the relative performance of GON block versus other interventions such as Botulinum toxin injection and the new family of CGRP antagonist biological therapies. Ideally, PROMs should be collected from patients prospectively using digital technology. However, a lack of compliance with daily electronic diary completion may reduce patient-related data quality; a balance may have to be struck for electronic diaries to collate sufficient information whilst not overburdening their end users.

Ethics approval and consent to participate

Approval was issued by the UK National Research Ethics Service (18/SC/0334), Health Research Authority (248606), and relevant NHS organisations prior to the study commencing. Written informed consent was obtained from each patient in line with Declaration of Helsinki. Patients consented to undergo the GON-block procedure in line with local clinical guidelines. The trial was registered on a public database, reference number ISRCTN10430251 (https://doi.org/10.1186/ISRCTN10430251).

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CRediT authorship contribution statement

Leon Jonker: Formal analysis, Funding acquisition, Methodology, Project administration, Writing – original draft. **Gina Kennedy:** Data curation, Investigation, Writing – review & editing. **Jitka Vanderpol:** Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing. **Fayyaz Ahmed:** Data curation, Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors have no competing interests to declare that are relevant to the content of this article.

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