Title: Influence of patient positioning on reported clinical outcomes after greater occipital nerve block for treatment of headache: results from prospective single-centre, non-randomised, proof-of-concept study.

Running title: GON block and patient positioning.

Authors: Jitka Vanderpol[#] FRCP, Leon Jonker PhD**.**

Author details

Dr Jitka Vanderpol, Consultant Neurologist, Neurology Department, Cumbria Partnership NHS Foundation Trust, Penrith, CA11 8HX, UK, jitka.vanderpol@cumbria.nhs.uk

Dr Leon Jonker, Science & Innovation Manager, R&D Department, Cumbria Partnership NHS Foundation Trust, Carlisle, CA1 3SX, UK, leon.jonker@cumbria.nhs.uk

 # Corresponding author:

Dr Jitka Vanderpol, Consultant Neurologist, Neurology Department, Cumbria Partnership NHS Foundation Trust, Penrith, CA11 8HX, UK, *Phone number:* +44 (0) 1768 245500, *Email:* jitka.vanderpol@cumbria.nhs.uk

Declarations of interest: None**.**

Sources of funding: No funding was received for this study

Ethics approval and consent to participate: Research ethics approval was not indicated since the core GON-block procedure did not differ in any of the patients; this was confirmed by use of the Health Research Authority decision tool. Furthermore, no additional clinical or non-

clinical procedures or clinic visits were introduced. Patients consented to undergo the GON-block procedure in line with local guidelines.

Author contributions

JV submitting author, designed the evaluative study, was involved in statistical interpretation of the data, revised the manuscript critically for the intellectual content and has given final approval of the version to be published. JV managed and treated the patients in her capacity of consultant neurologist. LJ contributed to collation of outcomes measures, led on statistical analysis of the data, drafted the manuscript, and provided academic support. Both authors read and approved the final manuscript.

Highlights

- Lying a patient down after GON block extends the achieved headache-free period
- This positional effect is achieved in a variety of headache disorders.
- The positional effect is not dependent on patient or clinical variables.

Abstract

Objective. Greater occipital nerve (GON) block is a treatment option applied for a variety of primary headache disorders. Although a patient's body position is known to have an impact on the effect of local anaesthetics, this has not before been investigated for patients undergoing GON block. Therefore, the clinical effectiveness of either a sitting or supine position was assessed.

Patients and Methods. This evaluative prospective study took place in a single neurology department in the UK. Baseline and follow-up data were collated during standard clinic consultations for 95 consecutive patients who underwent GON block and follow-up consultations for treatment-refractory headache disorder. The GON block procedure was identical for all patients in terms of constitution of the applied medication and volume injected (lidocaine hydrochloride 20 mg and methylprednisolone acetate 80 mg in 2 ml vial). Directly afterwards, patients opted to either sit up (n = 34) or lie down (n = 61) for ten minutes.

Results.

Twenty-seven patients (44%) reported substantial benefit and 17 (28%) complete benefit (pain freedom) for a median duration of 70 days and 84 days in the 'supine' group, compared with 10 (29%) substantial and 6 (18%) complete benefit (pain freedom) for a median duration of 25 days (substantial) and 119 days (complete) in the 'sitting' group. Overall, a supine position results in a longer overall post-GON block headache-free period (p-value 0.007) and median relief score (p-value 0.017) compared to a sitting up position, as determined by Mann-Whitney U-test. Backward multiple linear regression analysis showed that the chronicity of the patient's

condition is negatively associated (beta -0.24, p-value 0.024) and the post-GON block patient position is positively associated (beta 0.25, p-value 0.018) with the achieved headache-free period. Apart from variation in baseline headache characteristics, the 'sitting' and 'supine' cohorts did not significantly differ in terms of other clinical parameters and patient demographics.

Conclusions. Placing a patient in a supine position following a GON block procedure for headache may significantly improve the resulting clinical effectiveness of this treatment. Further research, through a prospective, multi-centre, randomised, controlled trial, is indicated to determine if the initial positive observations in this present pragmatic evaluation can be confirmed.

1. Introduction

Primary headache disorders including migraine, occipital neuralgia, and cluster headache have a high prevalence. In terms of years of life lost to disability, headache disorders rank third among worldwide causes of disability [1]. When considered separately, worldwide migraine has a one-year prevalence of over 10%, with a higher prevalence in developed countries [2].

Oral pharmacological treatment of primary headache disorders is the mainstay of patient management, both in terms of prophylaxis and treatment of headache episodes. However, interventional procedures such as peripheral nerve blocks (PNBs) and trigger point injections (TPIs) have long been used in the treatment of various headache disorders. Nerve blocks by means of Botulinum toxin type A or anaesthetic agents such as lidocaine or bupivacaine are established treatment modalities [3,4,5]. Although various nerves – such as lesser occipital, auriculotemporal, supratrochlear and supraorbital nerves, sphenopalatine ganglion, cervical spinal roots, and facet joints of the upper cervical spine - a common target is the greater occipital nerve (GON). There is not a widely accepted agreement among headache specialists with regards to the optimal methodology, such as used injecting technique, type and doses of the local anaesthetics and the role of corticosteroids [6]. The specific conditions treated also vary and include both primary (e.g. migraine, cluster headache) and secondary (e.g. cervicogenic) headache disorders [7].

Sitting up following a GON block procedure is currently considered the standard way of managing a patient, however studies do not actually specify this within their methodology. This

study evaluates whether the patient's positioning following GON block affects the efficacy of the treatment in terms of achieving a headache-free period and overall degree of headache relief.

2. Materials & Methods

2.1 Patients & setting

Consecutive patients referred to and under the care of single secondary care NHS neurological Headache clinic in the UK, who had headache symptoms refractory to first line treatments, were considered for this evaluation. The patients presented between June 2016 and June 2017 for GON block treatment, and were diagnosed in accordance to International Headache Society 2nd Edition guidelines [8]. The categorisation of different conditions as part of this evaluation was 'chronic migraine', 'episodic migraine' (including hemiplegic), 'cluster headache', 'occipital neuralgia', and 'other conditions' (including trigeminal autonomic cephalalgia, hemicranias continua, cervicogenic headache, occipital neuralgia). Since this concerns an initial evaluation, no defined inclusion or exclusion criteria such as age restrictions or focus on specific condition(s) were applied, other than allergy to the used local anaesthetic in one case, previously identified by dentist.

2.2 Clinical intervention

This concerns a prospective evaluation of positioning of a patient following GON block, and how this may influence the effectiveness of the nerve blockage. Therefore, the GON block application itself was identical for all patients. Patients were injected unilateral or bilateral (depending on headache distribution) injection containing combined local anaesthetic with steroid (lidocaine hydrochloride 20 mg with methylprednisolone acetate 80 mg provided in 2 ml vial), injected at a third of a distance from the external occipital protuberance on an imaginative line between

external occipital protuberance and mastoid process. Whilst the GON block was applied, the patient was in a sitting position on a chair or bed - the latter in case patient was known to be prone to fainting. The only difference in practice occurred directly following completion of the GON block procedure. Patients were offered the choice between: a) sitting up vertically and b) lying down horizontally with head 30 degrees raised, both for 10 minutes directly after completion of the GON block injection procedure. At this stage, the treating clinician did not disclose whether either of the two is favourable. Patients were given a headache diary (Hull Headache Diary [9]) to complete. Follow-up of patients was according to the local clinical practice.

2.3 Outcome measures and statistical analyses

To evaluate any difference in effectiveness depending on patient position following GON block, existing patient-reported outcome measures, already applied in standard clinical practice, were used. These include migraine-free period following GON block (in weeks) and subjectively perceived level of the symptoms relief (RELIEF scale): 'negative effect', 'no effect/benefit', 'slight benefit', 'substantial benefit' (i.e. equivalent to reduction in pain and symptoms severity from severe to, mild to moderate, or from moderate to, mild), or 'complete relief' (i.e. equivalent to freedom from headache/pain and associated symptoms). Due to the incorporation of this evaluation into standard clinical practice, there was a variance in when patients reported back for a follow-up clinic appointment. All patients were asked to complete a headache diary and if not available then verbal recollection was accepted. Any patients who lacked mental capacity to comply with this were excluded.

A power calculation to determine the required sample size was not conducted as this evaluation is the first published report on changing patient position and therefore no effect size could be

referred to. Data was first collated in Microsoft Excel and all analyses were performed using SPSS v20. For all inferential tests, a p-value of < 0.05 was considered statistically significant.

3. Results

A total of 103 patients underwent the GON block procedure and chose one of the post-procedure positions. Six patients did not attend their follow-up clinic visit, one patient lost capacity due to mental health problems and one patient died, and therefore no outcome measures could be obtained from them. This left 95 patients to analyse, with 34 patients opting for the sitting position and 61 for the supine position. Table 1 summarises the two resultant cohorts in terms of patient demographics and distribution of different clinical diagnoses. Figure 1 visualises the distribution of different conditions amongst the two cohorts, 'sitting' and 'supine'. The patients' baseline clinical characteristics in terms of headache severity, episode duration and frequency are summarised in Table 2.

[insert Table 1, Figure 1 & Table 2 here]

The median gap between GON block procedure and follow-up clinic visit took place after a median 113 days (minimum 28 - maximum 354) for the 'sitting' group and 139 days (31 – 476) for the 'supine' group (p-value 0.072, Mann-Whitney U-test). A significant difference in both headache-free period and RELIEF scale score was observed between the two groups. In a sitting position, the mean and median headache-free period was 33 and 7 days respectively (minimum

0 – maximum 182) whereas for the supine position it was 67 and 56 days (0 – 280; p-value 0.007, Mann-Whitney U-test). A comparison of responders shows that 27 (44%) reported substantial and 17 (28%) complete benefit (pain freedom) for a median duration of 70 days and 84 days respectively in the supine group. In the sitting group, there were 10 (29%) substantial and 6 (18%) complete benefit (pain freedom) responders, for whom the headache-free periods were a median duration of 25 days (substantial) and 119 days (complete) in the group of patients sitting after the procedure.

The median reported outcome for the RELIEF scale score was 'slight effect' for sitting and 'substantial effect' for supine (p-value 0.017, Mann-Whitney U-test). Figure 2 summarizes the distribution of patients over the different RELIEF scale categories, whereas Figure 3 explores whether certain RELIEF scores differ in terms of headache-free period achieved between the two intervention arms. Spearman correlation analysis shows that overall and within each arm there is a significant association between an improved RELIEF score and an increased headache-free period (rho 0.76, p-value <0.001 for combined cohort; rho 0.77, p-value < 0.001 for sitting; rho 0.70, p-value <0.001 for supine).

[insert Figure 2, Figure 3 here]

Since the two main patient-reported outcome measures - RELIEF scale score and headache-free period - correlate very closely, the latter was used as a dependent to determine if any variables other than patient position post-GON block may be associated with this outcome measure in a positive or negative fashion. Table 3 demonstrates that increased chronicity of the patient's headache disorder is significantly associated with a shorter headache-free period, and conversely a supine position is significantly associated with a longer headache-free period.

Overall there were few adverse reactions associated with the GON block procedure, and there was no significant difference in incidence between the two groups (p-value 0.45, Chi-squared test). In patients who sat up following GON block, there were three patients with one symptom, whereas in those who lied down afterwards there were eight patients with a single and two patients with two different symptoms. Symptoms were tenderness and/or slight swelling of injection sites, itchiness and mild hair loss at injection site.

[insert Table 3 here]

4. Discussion

This study aimed to investigate whether a patient's body positioning immediately after a GON block procedure may influence patient-reported outcome measures within a standard patient management setting. As a result patients with a variety of different headache disorders were treated and followed up for varying lengths of time, and patients were at liberty to decide which position to opt for post-GON block. A significantly improved outcome is seen in patients who lay down in a supine position, as opposed to the patients continued to sit down once the GON-block procedure was completed. The patients who report a substantial effect score on the RELIEF scale appear to benefit relatively most from a supine position, both in terms of actually achieving said benefit and the associated improved headache-free period. Once a patient experiences a complete benefit, there is no longer a significant difference in the headache-free period. Regression analysis suggests that only chronicity of the headache disorder can negatively influence this, for the variables that were included in our analysis. In our cohorts, the chronicity of the condition did not differ significantly between the two intervention groups (see Table 1),

and this therefore did not impact on the association seen between a supine position and improved headache symptoms.

So how does one explain these observations – what is the mode of action? The distribution and action of local anaesthetics is dependent on numerous variables. As summarised by Greene in his review (1985), patient characteristics, type of anaesthetic and its concentration, and type of injection all influence the eventual outcome [10]. Published research into body position and drug effect related to headaches is non-existent and one has to venture into other specialist areas for potential clues as to why lidocaine and prednisolone may be more effective when a patient is moved horizontally after the injections, is it possibly the physical spread of the molecule around the injection site, passive diffusion and migration or haematogenous transport? In anaesthetics, the prone position – similar to supine at least in terms of the patient being horizontal as opposed to vertical - brings about safety issues such as a decrease in cardiac index [11]. Though the direct cardiovascular risks mentioned here are not relevant to positioning post-GON block, they may give some indication of how an anaesthetic may possibly reside in the cephalic region for longer when compared to the sitting position. The spread of anaesthetics after injection into cerebrospinal fluid (CSF), for example, is dependent on three main factors: displacement of CSF, interplay density of CSF and anaesthetic agent, and gravity – the latter being partly influenced by the patient's position [12]. To illustrate the effect of body position: Buhre et al (2000) investigated the physiological changes in anaesthetised patients when changed from supine to sitting position [13]. They observed decreases in intrathoracic blood volume, cardiac index and stroke volume index. The opposite movement and the subsequent impact on a patient's physiology were not investigated. Nerve block, however, is not identical to injection into CSF, where the Brownian motion plays major role.

In the treatment of spasticity, migration of Botulinum toxin has been studied; whilst efficacy depends on accurate selection and identification of intended targets, it also may be determined by physical spread of the molecule from the injection site, passive diffusion, and migration to distal sites via axonal or haematogenous transport [14]. In dentistry, nerve block anaesthesia is widely applied, and recently a variation in patient position was assessed to evaluate the degree of anaesthesia achieved in either sitting or supine position. Crowley demonstrated that inferior alveolar nerve block using 2% lidocaine with 1:100,000 adrenaline was achieved sooner and for a longer period if the participant was in a supine position when compared to sitting up – the difference was statistically significant [15]. In his study, 110 healthy participants volunteered for both positions to allow matched analysis. Unlike in this present GON-block study, the anaesthetic was delivered with the same patient in one of the two positions by means of a cross-over study design with a two week gap between treatments. During the anaesthetic injection and the duration of the 55-minute long evaluation period, the patient continued to stay in said position.

Caution is indicated concerning the interpretation of the results presented here. Although the evaluation is prospective in nature, patients were not allocated to the post-procedure position (sitting vs supine) in a randomised fashion; they were given a choice, which in itself introduces a risk of bias. On the other hand, consecutive patients were included in the evaluation. The study was conducted in a single centre, rather than at multiple sites, which is not ideal since GON block depends heavily on an experienced and well trained clinician for a safe procedure. On the other hand, variability is likely reduced when one clinician treats all patients as happened in this study. The patient population was not controlled in any way, which resulted in multiple conditions

being included in the evaluation; although regression analysis indicated that this may not necessarily be a significant factor in terms of efficacy of GON block and patient position. The sample size does not lend itself to analysis of sub-groups of patients with a specific condition (e.g. cluster headache). Nonetheless, the significant positive effect of a supine position on headache-free time and reduction in severity of headaches post-GON block warrants further investigation. This could be by means of a prospective randomised trial with a set follow-up period and possibly the use of e.g. a phone application to aid participants to record their headache episodes. The 'intervention' is cost neutral compared to current practice where patients are already allowed to recover from GON block injections, currently in a sitting position. If indeed a supine position increases the chance of an elongated headache-free period and a reduction in headache severity, then this very straightforward change in clinical practice may actually have economic benefits.

5. Conclusions

Placing a patient in a supine position following a GON block procedure for headache may significantly improve the resulting clinical effectiveness of this treatment. Further research, through a prospective, randomised, controlled trial, is indicated to determine if the initial positive observations in this present pragmatic evaluation can be confirmed.

Acknowledgements: Mrs Charlotte Halliday, research practitioner, Cumbria Partnership NHS Foundation Trust, for administrative support.

6. References

1. Steiner TJ, Birbeck GL, Jensen RH, Katsarava Z, Stovner LJ, Martelletti P (2015). Headache disorders are third cause of disability worldwide. *J. Headache and Pain*, 16**,** 58
2. Robbins MS, Lipton RB (2010). The epidemiology of primary headache disorders. In *Seminars in neurology* , 30, 107-119.
3. Terzi T, Karakurum B, Üçler S, İnan LE, Tulunay C (2002). Greater occipital nerve blockade in migraine, tension-type headache and cervicogenic headache, *J. Headache Pain* 3, 137–141.
4. Levin M (2010). Nerve blocks in the treatment of headache. *Neurotherapeutics*, 7, 197-203.
5. Escher CM, Paracka L, Dressler D, Kollewe K (2017). Botulinum toxin in the management of chronic migraine: clinical evidence and experience. *Therapeutic advances in neurological disorders*, 10, 127-135.
6. Tobin J, Flitman S (2009). Occipital nerve blocks: when and what to inject?. *Headache: The Journal of Head and Face Pain*, 49, 1521-1533.
7. Ashkenazi A, Blumenfeld A, Napchan U, Narouze S, Grosberg B, Nett R, et al (2010). Peripheral nerve blocks and trigger point injections in headache management–a systematic review and suggestions for future research. *Headache: The Journal of Head and Face Pain*, 50, 943-952.
8. Olesen J, Steiner TJ (2004). The International classification of headache disorders, 2nd edn (ICDH-II).
9. Hull Headache Diary, http://www.bash.org.uk/about/headache-diary/ (last accessed 10 March 2018)

10. Greene NM (1985). Distribution of local anesthetic solutions within the subarachnoid space. *Anesthesia & Analgesia*, 64, 715-730.
11. Edgcombe H, Carter K, Yarrow S (2008). Anaesthesia in the prone position. *British journal of anaesthesia*, 100, 165-183.
12. Hocking G, Wildsmith JAW (2004). Intrathecal drug spread. *British Journal of Anaesthesia*, 93, 568-578.
13. Buhre, W, Weyland, A, Buhre, K, Kazmaier, S, Mursch, K, Schmidt M, et al. (2000). Effects of the sitting position on the distribution of blood volume in patients undergoing neurosurgical procedures. *British journal of anaesthesia*, *84*(3), 354-357.
14. Ramirez-Castaneda J, Jankovic J, Comella C, Dashtipour K, Fernandez H, Mari Z (2013). Diffusion, Spread, and Migration of Botulinum Toxin. *Movement disorders* 28, 1775-1783.
15. Crowley, CE. Anesthetic efficacy of an upright versus a supine position for inferior alveolar nerve block. MSc Dissertation. The Ohio State University , 2016 https://etd.ohiolink.edu/!etd.send_file?accession=osu1470051706&disposition=inline (last accessed 8 March 2018).

Table 1, Patient characteristics for each post-GON block group

variable	Sitting (n=34)	Supine (n=61)	p-value
Sex, male / female (n/%)	11/23	17/44	0.65#
Patient age, mean years (95% CI)	45 (39-50)	46 (42-50)	0.82*
Age patient diagnosed, mean years (95% CI)	29 (22-35)	28 (22-33)	0.49*
Chronicity of patient's condition, mean years (95% CI)	17 (12-23)	20 (16-24)	0.29*
GON previously administered, yes / no (n/%)	6 (18%) / 28 (82%)	20 (33%) / 41 (67%)	0.11#
Type of condition (n, %)	Chronic migraine (15, 44%); Migraine other (7, 21%); Occipital neuralgia (4, 12%); Cluster headache (1, 3%); Other (7, 21%)	Chronic migraine (28, 46%); Migraine other (10, 16%); Occipital neuralgia (10, 16%); Cluster headache (4, 7%); Other (9, 15%)	0.82#

#Pearson Chi-squared test. *Mann-Whitney U-test

Table 2, Patients' baseline clinical characteristics for each post-GON block group

	Sitting (n=34)	Supine (n=61)	p-value*
Baseline severity score			0.027
Mild-moderate, n (%)	2 (6%)	0 (0%)	
Moderate, n (%)	6 (18%)	5 (8%)	
Moderate-severe, n (%)	19 (56%)	34 (56%)	
Severe, n (%)	7 (21%)	22 (36%)	
Baseline duration score			0.017
Up to an hour, n (%)	1 (3%)	10 (16%)	
Hour up to 4 days, n (%)	16 (47%)	33 (54%)	
More than 4 days to constant, n (%)	17 (50%)	18 (30%)	
Baseline frequency score			0.90
Up to 4 a month, n (%)	3 (9%)	9 (15%)	
Once weekly to 4 per week, n (%)	5 (15%)	7 (12%)	
Most days, n (%)	12 (35%)	15 (25%)	
Daily or constant, n (%)	14 (41%)	28 (48%)	

*Mann-Whitney U-test

Table 3, backward multiple linear regression analysis: headache-free period (days) as dependent

Variable	Beta	p-value
Sex	-0.089	0.43
Patient age (yrs)	-0.020	0.86
Chronicity of condition	-0.21	0.12
History of GON block	0.069	0.54
Main diagnosis	-0.043	0.74
Baseline headache severity	0.033	0.77
Baseline headache duration	-0.054	0.65
Baseline headache frequency	0.11	0.34
Patient position post-GON	0.23	0.041*
Most significant variables		
Chronicity of condition	-0.24	0.024*
Patient in supine position post-GON	0.25	0.018*

*statistically significant correlation (p-value < 0.05)

Figure 1, Distribution of patients' headache diagnosis for each post-GON block group.

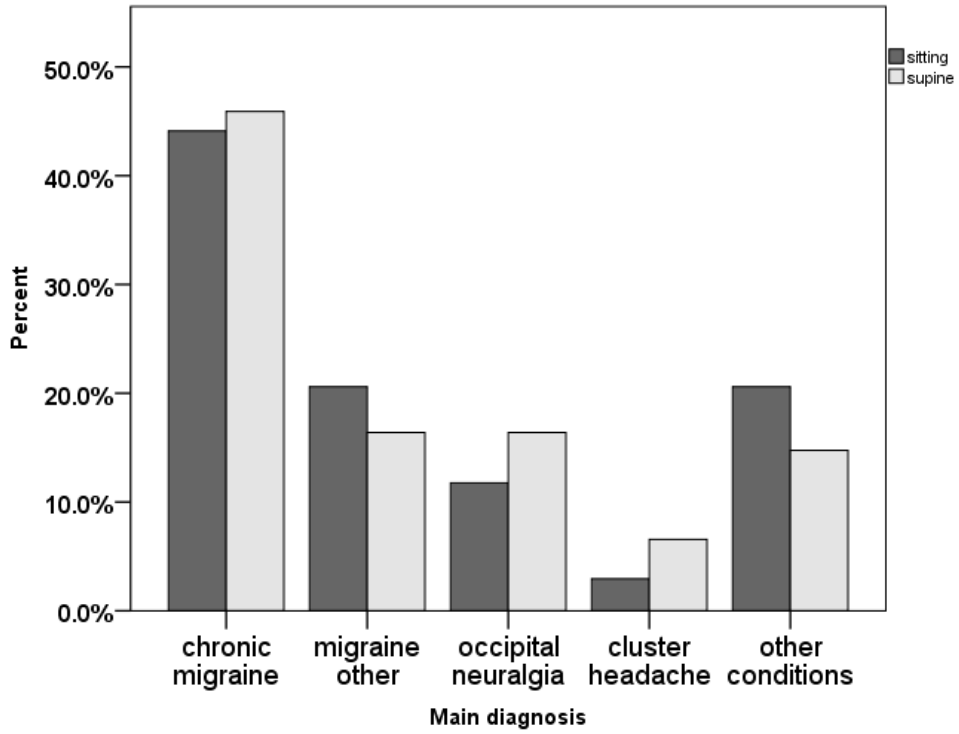


Figure 2, Patients' RELIEF scale score distribution for each post-GON block group

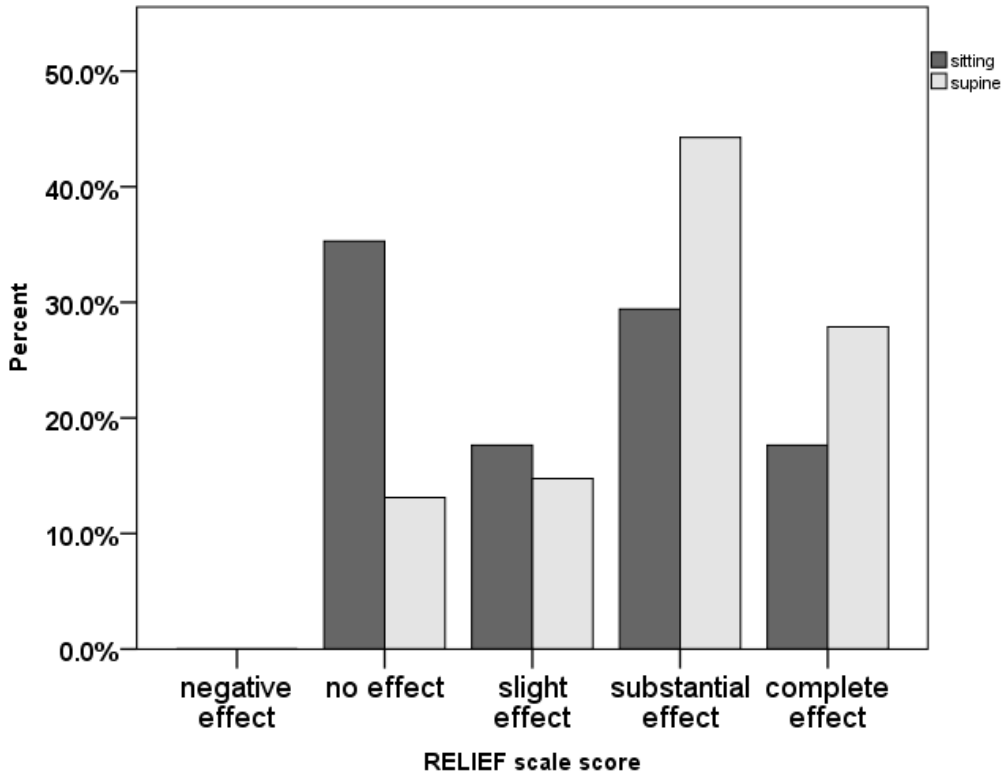
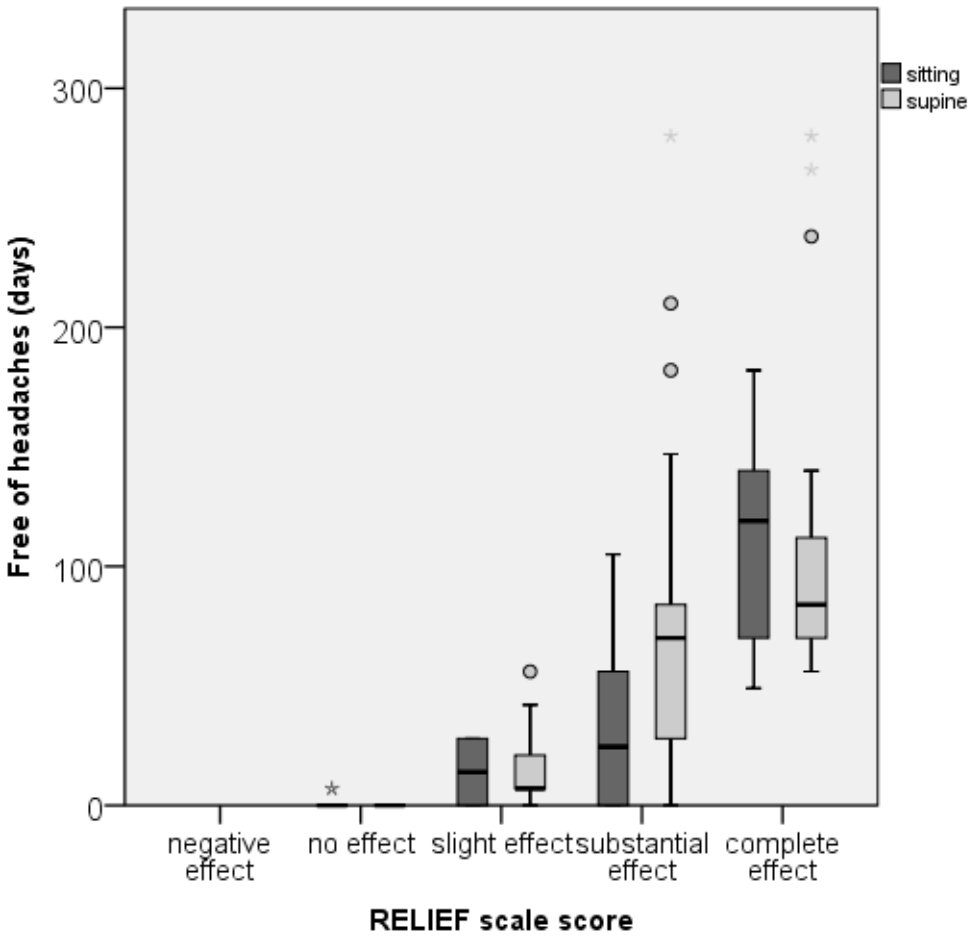


Figure 3, Box and whiskers plot correlating RELIEF score with headache-free period, per GON-block group


sitting
supine
300
200
100
0
Free of headaches (days)
negative effect
no effect
slight effect
substantial effect
complete effect
RELIEF scale score