Clinical pain research

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Cryoneurolysis for cervicogenic headache – a double blinded randomized controlled study

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Abstract

Background and aims: Cervicogenic headache (CEH) is a debilitating condition and analgesics have limited effect. Percutaneous cryoneurolysis is thus still in use although the clinical evidence is lacking. We present a randomized, controlled study to assess the clinical efficacy of cryoneurolysis compared with a corticosteroid combined with a local anaesthetic.

Methods: In a university-based outpatient pain clinic we performed a randomized, double blinded, comparative study with an 18-week follow-up. After positive diagnostic test blocks 52 eligible patients were randomly allocated in a ratio of 3:2, 31 participants to occipital cryoneurolysis and 21 participants to injections of 1 mL methylprednisolone 40 mg/mL (Depo-Medrol®) combined with 1 mL bupivacaine 5 mg/mL.

Results: We observed a significant pain reduction of more than 50% in both treatment groups, slightly improved neck function and reduced number of opioid consumers. After 6–7-weeks, however, pain intensity increased gradually, but did not reach baseline within 18 weeks. Although cryoneurolysis provided a more prolonged effect, the group differences did not reach statistical significance. Health related quality of life and psychological distress improved minimally. A large number reported minor and transient side effects, but we found no significant group differences. After 18 weeks, 29% rated the headache as much improved, and 12 (24%) somewhat improved, but a large proportion (78%) reported need for further intervention/treatment.

Conclusions: Cryoneurolysis provided substantial, but temporary pain relief, and the effect was not significantly different from injections of a corticosteroid combined with a local anaesthetic. Participants were selected by a single test block, and the neurolytic procedure was guided by anatomical landmarks and nerve stimulation. A stricter patient selection and an ultrasound-guided technique might have improved the results. Cryoneurolysis provides temporary pain relief not significantly superior to corticosteroid injection, and the results question the value of occipital cryoneurolysis for a chronic pain condition like CEH.

Implications: Occipital cryoneurolysis may be considered when non-invasive treatments appear insufficient, but only for patients who have responded substantially to test blocks. A risk of local scar and neuroma formation by repeated cryoneurolysis, leading to neuropathic pain has been discussed by other researchers.

Keywords: cryoneurolysis; cryoablation; cryoanalgesia; treatment; occipital; cervicogenic headache.

1 Introduction

Cervicogenic headache (CEH) is a debilitating condition and is frequently associated with long term sick leave [1]. The prevalence rates in previous European studies vary from 15 to 18% [2, 3], and in patients with a defined whiplash-associated disorder Australian researchers diagnosed CEH in 53% of the patients [4]. In contrast to these rates, two small Norwegian population studies have presented prevalence rates of 0.17% and 4.1%, respectively [5, 6].

CEH is a controversial diagnosis [7], but is categorised as a secondary headache (ICHD-II 2004) related to injury, inflammation or degenerative changes in the cervical spine [8, 9]. It is typically characterized by unilateral headache, with frequent attacks of moderate to severe intensity spreading from the neck up to occiput and sometimes even to the frontotemporal area [10]. The patients

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may report blurred vision, dizziness, and hypersensitivity to light and sound and the symptoms may thus mimic migraine. However, it has rarely the throbbing and pulsating character [8–11].

Analgesics have limited effect [12], and there is no standard algorithm on how to treat refractory cases of CEH [13]. As the index area of pain is innervated by well-defined branches of the nerve roots C2 and C3, like the greater occipital nerve (GON), lesser occipital nerves (LONs) including the greater auricular nerve (GAN), local anaesthetic nerve blocks have been used clinically to diagnose CEH [14].

Some pain centres apply occipital cryoneurolysis to prolong the analgesic effect [15–17]. This represents a nerve destructive technique where freezing is applied to block nerve conduction. Freezing the nerve leads to crystal formation with rupture of cell membranes, protein denaturation, and cellular dehydration [16], but obliteration and damage to the vasa nervorum and autoimmune responses have also been suggested as potential mechanisms [15, 18, 19]. The endoneurium and basal lamina of the Schwann cells, however, remain intact and the nerve has therefore a potential to regenerate [20–22].

The evidence on cryoneurolysis is mostly based on non-randomized studies or case series [17, 23]. So far, there is only one randomized, controlled trial available on patients with knee osteoarthritis [24] and none support occipital cryoneurolysis for CEH. To improve the clinical evidence on long-term effect for patients with CEH, we performed a randomized, controlled study which compared occipital cryoneurolysis with injections of a corticosteroid combined with a local anaesthetic. Our hypothesis was that occipital cryoneurolysis provides longer pain reduction than a corticosteroid injection.

2 Materials and methods

2.1 Design

The study had a prospective, randomized, double blinded, comparative design with an 18-week follow-up. Patients were randomly allocated in a ratio of 3:2 to either occipital cryoneurolysis or injections of a corticosteroid combined with a local anaesthetic.

2.2 Setting

The study was carried out at a University-Hospital Pain Clinic, approved by The Regional committee for Medical and Health Research Ethics (10.09.2002, reference number 344-02150), and did not receive any external funding.

2.3 Recruitment and selection

We recruited CEH patients by advertising in a local newspaper. Inclusion criteria included unilateral CEH, diagnosed according to the Sjaastad criteria [14], with a maximum headache intensity of ≥40 (0–100 scale), not responding to conservative treatment, and with an age between 18 and 65 years. Exclusion criteria included bleeding diathesis, allergy to a local anaesthetic agent, local skin infection, progressive or serious cardiovascular disease, diabetes mellitus, pregnancy, cognitive deficiency, previous cryoneurolysis or occipital injection with a local anaesthetic agent last 4 weeks (8 weeks if corticosteroid), and language barriers.

A total of 172 persons responded to the advertisement between October 2002 and April 2003, and of these 86 individuals were screened with a self-report questionnaire. Sixty-seven persons were invited for further examination by an experienced physiotherapist (SMA) and subjected to diagnostic test blocks carried out by an experienced interventionist (HH).

2.4 Diagnostic nerve blocks

The diagnostic blocks of the GON and LONs and in some cases the GAN were conducted under aseptic conditions after infiltration of lidocaine 10 mg/mL with adrenaline 5 μg/mL into the subcutaneous tissue. The insertion of a 14 G introducer needle was guided by anatomical (muscular and bony) landmarks [25] and high-frequency stimulation (100 Hz) with the SL 2000 Lloyd Neurostat Cryosurgical System (Integra Neurosciences, previous Spembly Medical, Newbury Road, Andover, Hampshire, SP10 4DR, England) including an 18 G cryoprobe (Lloyd cryosurgical probe, Series 44 44-1H3 S/N Art code 146800M2). Stimulus duration remained at 10 ms while the voltage decreased from two volts down to a level between 0.5 and 0.2 V. To obtain an optimal position close to the target nerve, paraesthesia should still be perceived in the area of maximal pain before 1.5–2 mL of bupivacaine 5 mg/mL was injected.

Pain intensity and side effects were registered 30 min, 2 h and 24 h after the test block. Those who satisfied inclusion criteria (listed above) and reported a clinically significant response (preferably >50% pain reduction) after 30 min and 2 h, were found eligible for inclusion. They

received detailed information including potential side effects and complications before informed consent was obtained.

2.5 Randomisation and blinding

The participants were randomly allocated by computer-generated sequence generation carried out by one of the researchers (JHR), not involved in the intervention. The allocation was kept concealed in an envelope until the day of intervention. As participants were lying in a prone position with extensive covering, and the skin infiltrated by a local anaesthetic agent, they were not able to observe nor register what kind of treatment that was given. Participants and assessor (SMA), the latter not present at treatment, were kept blinded throughout the follow-up.

2.6 The cryoneurolysis procedure

The intervention was performed percutaneously. Under aseptic conditions cutaneous and subcutaneous tissue was infiltrated with lidocaine 10 mg/mL with adrenaline 5 μg/mL. The needle insertion (14 G introducer needle) was guided by anatomical (muscular and bony) landmarks [25] and high-frequency nerve stimulation (100 Hz), as described for the diagnostic test block.

The cryoneurolysis was performed by the SL 2000 Lloyd Neurostat Cryosurgical System and the 18 G cryoprobe inserted through the introducer needle. The cryoprobe is an adaptation of Amoils' gas-expansion prototype and with 8–10 L/min N_2O gas, circulating within a closed tubal system of the cryoprobes, the tip temperature drops rapidly down to −60 °C (Adiabatic principle/Joule-Thompson effect). This low temperature is necessary to freeze, disrupt the cell membrane, and induce cell death [15]. Each freezing session lasted for 90 s and was repeated 2–3 times with intervals of 1.5–3 min to increase the lesion size (ice-ball) [16, 26]. To avoid nerve avulsion, we defrosted the probe for 30 s before it was withdrawn.

2.7 The control procedure

The intervention was similarly performed under aseptic conditions. After infiltration with lidocaine 10 mg/mL with adrenaline 5 μg/mL into the subcutaneous tissue the needle insertion was guided by anatomical (muscular and bony) landmarks [25] and nerve stimulation (as described for the diagnostic test block). Then 1 mL methylprednisolone 40 mg/mL (Depo-Medrol®) combined with 1 mL bupivacaine 5 mg/mL was injected.

2.8 Data collection

The outcome measures follow the IMMPACT recommendations [27]. *Primary outcome* was "worst pain intensity" quantified by a 0–100 scale and based on daily records during the first 6 weeks transformed to weekly replicates, and weekly records from week 7–18.

Secondary outcomes included numbers of successful treatment (30% and 50% pain reduction), procedural pain, side effects and complications, and changes in psychological distress, health related quality of life, self-reported change in neck function and range of active cervical movement (ROM) like flexion, extension, left and right lateral flexion, right and left rotation, and the patients' global impression of change, specific impression of change of pain (headache), consumption of analgesics, occupational status, how they experienced the treatment, need for further treatment, desire for a repeated intervention or another treatment.

Before treatment the participant filled in a questionnaire including demographics (gender, age, height and weight and occupational status) and clinical information about comorbidity and headache (onset and duration, temporal pain profile, location, worst and least pain intensity during the last week and last month), other symptoms like sensitivity to light and sound, blurred vision, dizziness, lack of concentration and memory, psychological distress by Hopkins Symptom Check List 25 (HSCL 25) and Health-related Quality of Life by RAND 36 (Version 1) including eight domains such as vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. A physical examination assessed active range of cervical ROM with a goniometer and counted number of palpable trigger points in the neck and occipital region.

After treatment the participants recorded worst and least pain intensity on a 0–100 scale in a diary, daily during the first 6 weeks and weekly during the next 12 weeks. At the 1, 6 and 18-week follow-ups they were asked to report on side effects or complications, their own experience of neck movement, their impression of change in neck movement (5-point scale, with 1 = much better, 5 = much worse), health-related quality of life and psychological distress, migraine, and consumption of analgesics. An independent and blinded assessor (SMA) investigated active cervical ROM. In cases of missing values, the subjects were politely

asked to give an answer. At the final meeting (week 18) they were also asked to report on their global impression of change (5-point scale; 1 = much better, 5 = much worse), their impression of change of the headache (5-point scale, 1 = much worse, 5 = much better), occupational status, how they experienced the treatment, whether they were in need of further treatment, wanted another treatment or to repeat the intervention, their experience of the intervention (rated by a 4-point scale; 1 = very uncomfortable and 4 = not uncomfortable at all), and rated the result of the intervention compared to previous treatments at the pain clinic (graded by a 3-point scale; 1 = worse, 2 = same, 3 = better).

2.9 Statistics

For the statistical analyses we used the SPSS statistical package, version 25 and Excel (Microsoft Office 2016). To compare categorical variables between two groups, we used the Chi Square (χ^2) test or Fisher exact test when any of the cells had expected values less than 5. To perform paired categorical comparisons, we used NcNemar test.

Baseline comparisons for continuous variables were carried out by General Linear Model Repeated Measures as the residuals were found normally distributed on the Q-Q plot. A subanalysis was performed of those who obtained >50% pain reduction to the test block, to assess the success rates of the two treatments (i.e. numbers who reached 30% or 50% pain reduction after treatment). Group comparisons with continuous variables were carried out by the GLM Univariate ANCOVA to adjust for different baseline levels or by the Independent sample Student *t*-test as the data were found normally distributed on the Q-Q plot. The data analysis of the secondary outcome variables presented is considered exploratory. Consequently, multiple tests were done without multiplicity correction [28]. The selected sample size of the study is supported by previous and more recent randomized, controlled intervention studies of the occipital nerves and medial branches [29–32].

3 Results

A total of 52 patients were included in the study, 27 (52%) were males and 25 (48%) females. Those subjected to cryoneurolysis were younger ($p = 0.001$) with mean age of 45.8 (10.5) years vs. 55.8 (8.3) years in the injection group. Thirty-one participants received cryoneurolysis while 21 injections on the occipital nerves with a corticosteroid in combination with a local anaesthetic. One participant in the injection group dropped out at the last follow-up (Fig. 1).

3.1 Headache characteristics

Average duration of the headache was 13 (SD 10) years. Half of the participants (*n*: 26) reported a history of whiplash and 10 participants another injury to the head or neck. About one fourth (*n*: 12) had no history of injury. A high proportion (42%) reported concomitant migraine.

All participants suffered from unilateral occipital headache, and for the large majority (80–90%) the pain radiated to the frontal, temporal, or orbital areas of the head (Table 1). At inclusion the participants reported high pain intensity scores during the last week [mean 63 (SD 23) in the injection group and 68 (SD 20) in the cryoneurolysis group], and a clinically significant response to the test block, for 70% of the sample more than 50% pain reduction after 30 min and 2 h. Neither group differences of baseline characteristics nor responses to test blocks reached statistical significance (See Table 1).

3.2 Pain assessment

For the primary outcome measure, pain intensity, we observed substantial and statistically significant pain reductions in both treatment groups from pain intensity scores at 63 (injection group) and 68 (cryoneurolysis group), respectively down to a score approximating 30, which is equivalent to a 50% reduction in the injection group and 55% after cryoneurolysis. From week 6 and 7 after the intervention, pain increased gradually and levelled off at 50 in the injection group and 40–45 in the cryoneurolysis group and did not reached baseline within 18 weeks (Fig. 2).

Group comparisons at 1, 6, and 18 weeks (Table 2) and the average levels of week 1–6 and week 7–18 showed no significant differences. For weekly group comparisons, adjusted for different baseline pain levels (Univariat ANCOVA), the cryoneurolysis group reported statistically significantly lower pain levels at week 7 ($p = 0.02$) and week 17 ($p = 0.04$) but not for the other weeks (Fig. 2). Neither did the proportions of successful treatments within each group (i.e. those who achieved 30% and 50% reduced pain intensity) differ significantly at the three follow-ups (Table 3). A subanalysis, including only the participants who obtained >50% pain reduction after test

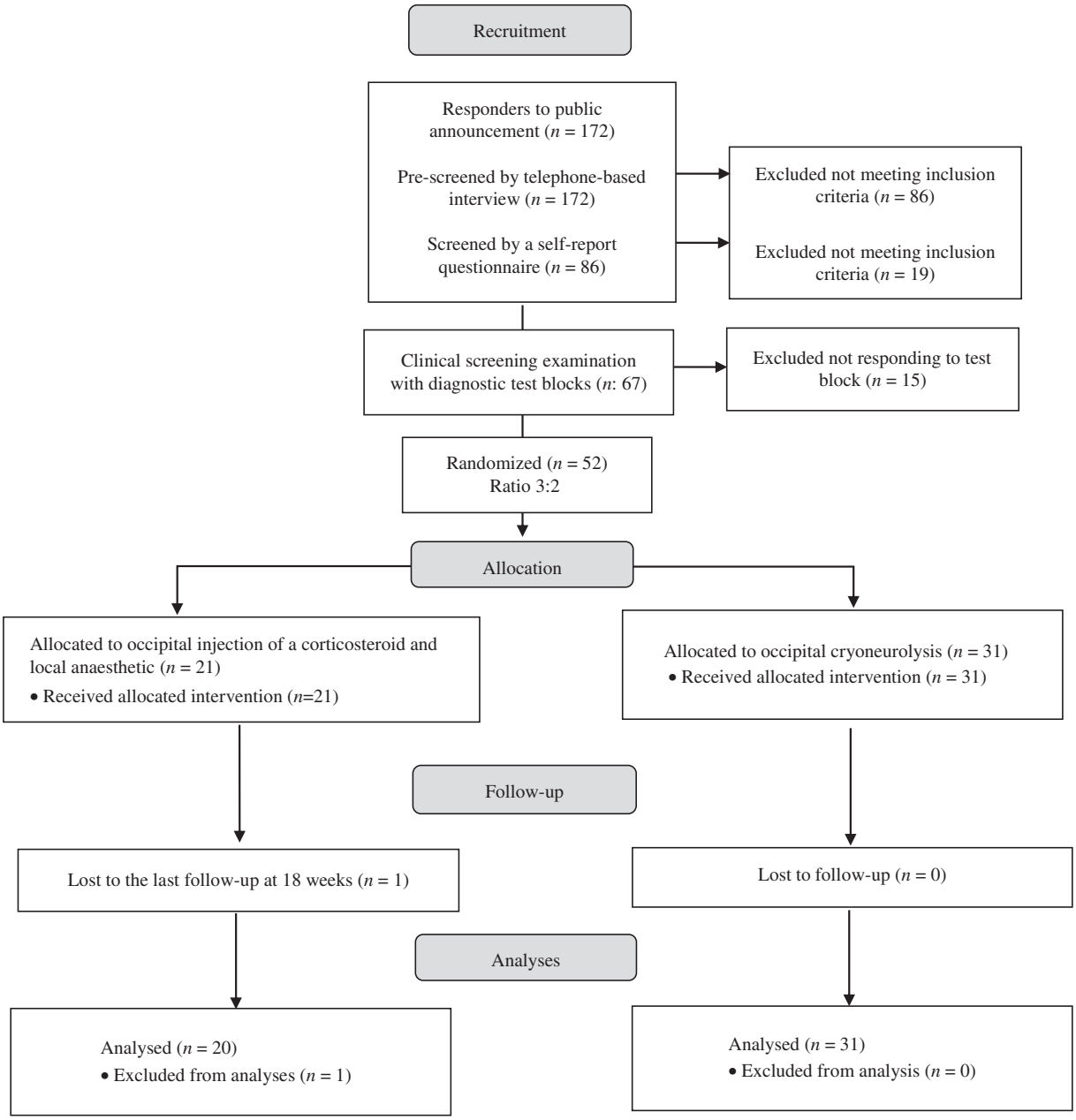

Fig. 1: Flow chart.

block, did not improve the numbers who reached 30% or 50% pain reduction after treatment.

After 18 weeks 15 of the whole sample (29%) rated the headache as much improved, 12 (24%) somewhat improved while 24 (47%) as unchanged, but none reported worse headache. We found no significant difference between the groups (group-specific data are shown in Table 4). Even so, large proportions reported need for further intervention (70% in the injection group vs. 83% in the cryoneurolysis group) and desire to another treatment (70% in the injection group vs. 77% in the cryoneurolysis group).

3.3 Procedural pain

Thirty minutes after the cryoneurolysis pain intensity averaged 30, and 9 (29%) participants reported a pain level >40. Average pain intensity after corticosteroid injections was significantly lower at 15 ($p = 0.02$) and only three participants (15%) reported a pain level >40. Among those who underwent cryoneurolysis, 11 (35%) participants needed intravenous dosages of an opioid (alfentanil) vs. only two (10%) in the injection group. At the end of the study (18 weeks), 37% rated cryoneurolysis as moderately to very uncomfortable vs. 24% in the corticosteroid

Table 1: Baseline characteristics.

	Whole sample *n*: 52 Mean (SD)	S+LA group *n*: 21 Mean (SD)	Cryo group *n*: 31 Mean (SD)	*p*-Value[a]
Demography				
Age (years)	49.8 (10.8)	55.8 (8.3)	45.8 (10.5)	0.001
Headache duration (years)	15 (10)	18 (11)	13 (9)	0.08
	n (%)	*n* (%)	*n* (%)	
Males	27 (52%)	11 (52%)	16 (52%)	0.96
Females	25 (46%)	10 (48%)	15 (48%)	
Occupational status				
Full time work	16 (32%)	5 (24%)	11(38%)	0.64
Part time work	2 (4%)	1 (5%)	1 (3%)	
Receiving social benefits	28 (56%)	13 (62%)	15 (52%)	
Receiving age pension	4 (8%)	2 (10%)	2 (7%)	
Pain attribution				
Wiplash injury	26 (50%)	11 (52%)	15 (48%)	0.26
Other head or neck injury	10 (19%)	6 (29%)	6 (19%)	0.72
No injury	12 (23%)	5 (24%)	7 (23%)	1.0
Pain location				
Right side (*n*: 51)	29 (57%)	11 (52%)	18 (60%)	0.59
Left side (*n*: 51)	22 (43%)	10 (48%)	12 (40%)	0.59
Pain radiating to:				
Vertex (*n*: 51)	31 (61%)	9 (45%)	22 (71%)	0.09
Orbital area	46 (88)	18 (86%)	28 (90%)	0.61
Temporal area	43 (83%)	15 (71%)	28 (90%)	0.08
Frontal area	41 (79%)	18 (86%)	23 (74%)	0.32
The jaw	25 (48%)	12 (57%)	13 (42%)	0.28
Temporomandibular and ear region	28 (54%)	14 (67%)	14 (42%)	0.13
Shoulder	41 (79%)	15 (71%)	26 (84%)	0.28
Arm	32 (62%)	12 (57%)	20 (65%)	0.59
Number of analgesic consumers				
Participants taking analgesics regularly	22 (42%)	10 (48%)	12 (39%)	0.89
Participants taking analgesics when needed	37 (71%)	18 (86%)	19 (61%)	0.28
Participants taking opioid	27 (52%)	13 (62%)	14 (45%)	0.24
Previous treatments				
Injections with LA and corticosteroid	25 (48%)	10 (48%)	15 (48%)	0.96
Radiofrequency	7 (13%)	1 (5%)	6 (19%)	0.13
Physiotherapy	42 (81%)	17 (81%)	25 (81%)	0.98
Manual therapy	34 (65%)	14 (67%)	20 (65%)	0.87
Acupuncture	35 (67%)	17 (81%)	18 (58%)	0.08
TENS/Electroacupuncture	16 (31%)	8 (38%)	8 (26%)	0.35
Other treatments	13 (25%)	4 (19%)	9 (29%)	0.42
Cervical range of movement				
Flexion	41.8^0 (13.0^0)	39.9^0 (11.6^0)	43.1^0 (13.8^0)	0.4
Extension	45.0^0 (17.2^0)	45.3^0 (13.4^0)	44.7^0 (19.6^0)	0.9
Right rotation	48.6^0 (13.4^0)	48.3^0 (14.7^0)	48.8^0 (12.7^0)	0.9
Left rotation	47.9^0 (13.1^0)	48.9^0 (13.5^0)	47.3^0 (12.9^0)	0.7
Lateral right flexion	31.5^0 (12.0^0)	31.1^0 (13.7^0)	31.7^0 (11.0^0)	0.9
Lateral left flexion	31.3^0 (10.2^0)	29.8^0 (9.9^0)	32.4^0 (10.3^0)	0.4
HSCL 25 sum score	1.8 (0.5)	1.7 (0.4)	1.9 (0.6)	0.2
Health-related quality of life (RAND 36)				
Mental health	68.85 (18.50)	72.38 (14.14)	66.45 (20.83)	0.23
Vitality	37.58 (19.46)	43.67 (16.79)	33.66 (20.30)	0.07
Bodily pain	31.81 (21.37)	36.86 (25.10)	28.39 (18.08)	0.16
General health	56.02 (20.62)	55.89 (21.02)	56.10 (20.74)	0.97
Sosial function	63.52 (26.06)	66.88 (25.09)	61.21 (26.37)	0.41

Table 1 (continued)

	Whole sample *n*: 52 Mean (SD)	S+LA group *n*: 21 Mean (SD)	Cryo group *n*: 31 Mean (SD)	*p*-Value[a]
Physical function	75.82 (22.84)	74.30 (23.21)	76.85 (22.91)	0.70
Role-physical	30.21 (38.23)	28.95 (41.89)	31.03 (36.39)	0.86
Role-emotional	54.86 (44.29)	61.11 (44.65)	51.11 (44.41)	0.46

Group comparisons of the categorical variables were performed by the χ^2 test and Independent Sample Student *t*-test for continuous data. No post hoc tests were performed. [a]Significant group differences with $p < 0.05$. Cryo = cryoneurolysis; S + LA = corticosteroid combined with local anaesthetic injection; HSCL 25 = Hopkins Symptom Check list 25.

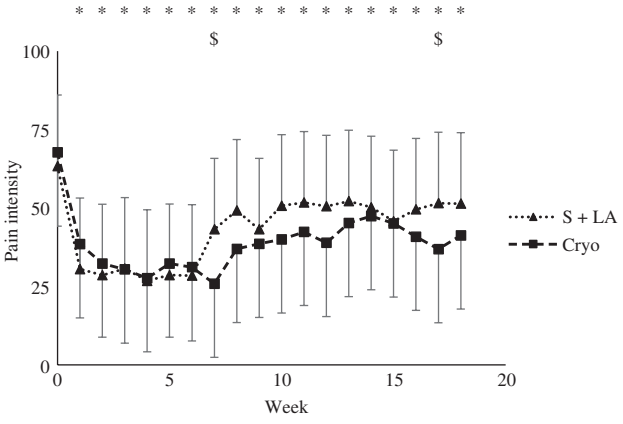

Fig. 2: Values are presented as means with standard deviation. From week 1–6 daily records of pain intensity are averaged and presented as weekly replicates. Statistical within-group comparisons were performed with GLM Repeated measurement (*n*: 46). Due to different baseline levels between-group comparisons (*n*: 51) were performed with Univariate ANCOVA with baseline pain intensity as covariate. Post hoc tests were not performed. *indicates a statistically significant difference from baseline ($p \leq 0.002$) (within-group comparison) while $ indicates a statistically significant difference between the groups ($p < 0.05$). VAS = visual analogue scale; Cryo = cryoneurolysis; S + LA = corticosteroid combined with local anaesthetic injection.

injection group. However, despite these numbers 46 out of 50 (92%) wanted repeated treatment, and we found no difference between the groups.

3.4 Neck function

Baseline range of movement (ROM) of the whole sample was moderately limited (70–75%) compared with normal data on people between 35 and 45 years [33, 34] and improved slightly at the follow-ups, and statistically significant only for right rotation ($p < 0.001$).

At the three follow ups 32%, 29%, and 29% reported an impression of improved neck movement after cryoneurolysis vs. 52%, 39%, 28% after corticosteroid injections (Table 4). The participants who experienced worse neck movement after cryoneurolysis, declined from 10% to 6%. No one reported worse neck movement after corticosteroid injections. We found no significant group difference.

3.5 Occupational status

At baseline a total of 16 participants (35%) worked full time while 28 (61%) received social benefits. After 18 weeks the

Table 2: Maximum headache intensity before and after treatment (*n*: 52).

Issue	Baseline		Week 1		CI	*p*-Value	Week 6		CI	*p*-Value	Week 18		CI	*p*-Value
	Mean	SD	Mean	SD			Mean	SD			Mean	SD		
Whole sample	66	21	35	24		<0.001[a]	30	22		<0.001[a]	45	33		<0.001[a]
S+LA	63	23	31	21	−18.6 to 7.9	0.42[b]	28	20	−13.3 to 11.4	0.88[b]	51	35	−7.2 to 30.2	0.22[b]
Cryo	68	23	38	21			31	20			41	35		

The statistical within group comparisons (differences to baseline) were performed with GLM Repeated Measures, while between-group comparisons were performed with Univariate ANCOVA with baseline pain intensity as covariate due to different baseline levels. [a]*p*-Value is based on within-group comparison. [b]*p*-Value is based on between-group comparisons (*n*: 51). Daily records of pain intensity are averaged to weekly replicates and presented for week 1 and 6. Statistical significance considered when *p*-values < 0.05 and no post hoc tests were performed. SD = standard deviation; CI = 95% confidence interval; Cryo = cryoneurolysis; S + LA = corticosteroid combined with local anaesthetic injection.

Table 3: Group comparisons on number of responders to treatment (*n*: 50).

Issue	Week 1			Week 6			Week 18		
	S+LA	Cryo	*p*-Value	S+LA	Cryo	*p*-Value	S+LA	Cryo	*p*-Value
Pain reduction		*n* (%)			*n* (%)			*n* (%)	
>30%	13 (62)	18 (62)	0.99	12 (57)	22 (76)	0.16	9 (47)	12 (46)	0.94
>50%	12 (57)	14 (48)	0.54	10 (48)	17 (59)	0.44	8 (42)	9 (35)	0.61

Group comparisons of the categorical variables were performed by the χ^2 test for both 30% and 50% reduction of pain intensity. We considered *p*-values < 0.05 as statistically significant as post hoc test for multiple comparisons were not performed. Cryo = cryoneurolysis; S + LA = corticosteroid combined with local anaesthetic injection.

Table 4: Patients' impression of change after 18 weeks (*n*: 51).

Issue	Much improved		Moderately improved		Unchanged		Moderately worse		Much worse	
	S+LA	Cryo	S+LA	Cryo	S+LA	Cryo	S+LA	Cryo	S+LA	Cryo
										n (%)
Global status	7 (44)	16 (62)	5 (31)	3 (12)	10 (24)	6 (20)	0 (0)	0 (0)	0 (0)	1 (4)
Headache intensity	5 (25)	10 (32)	5 (25)	7 (23)	10 (50)	14 (45)	0 (0)	0 (0)	0 (0)	0 (0)
Neck movement	3 (14)	4 (13)	3 (14)	5 (16)	14 (67)	20 (65)	0 (0)	1 (3)	0 (0)	1 (3)

Group comparisons of the categorical variables were performed by the χ^2 test. We considered *p*-values < 0.05 as statistically significant as post hoc test for multiple comparisons were not performed. There were no statistically significant differences between the groups. Cryo = cryoneurolysis; S + LA = corticosteroid combined with local anaesthetic injection.

number in full time work had increased to 20 (43%) and on social benefits decreased to 23 (50%). We found no significant change from baseline nor between the groups. Participants on old age pension (*n*: 4) were excluded from the analysis.

3.6 Psychological distress

At baseline, HSCL 25 sum score averaged 1.83 (SD 0.49), indicating increased psychological distress for the whole sample, but we observed no significant change throughout the study nor any group differences even when adjusting for different baseline between the groups.

3.7 Health-related quality of life

For health-related quality of life (RAND 36) we measured large variations between the different domains from high levels on physical function and mental health, to low levels for bodily pain, vitality and physical role. During the follow-up there was minimal improvement from baseline, except for bodily pain at the 6-week follow up ($p = 0.03$), and a significant group difference (lowest level in the injection group) only for mental health at the 18-week follow up ($p = 0.04$).

3.8 Global impression of change and grading of the interventions

At the 18-week follow up 23 (55%) of the participants reported "much improved" and 8 (19%) "moderately improved" global status. One of the participants reported a worse global status. (Group specific data are shown in Table 4.) The participants rated the occipital interventions superior to previous treatments at the pain clinic, but statistical comparisons of these global measures showed no group difference.

3.9 Consumption of analgesics

At baseline 23 of the participants (44%) took analgesics when needed while 11 (21%) reported regular use. At the end of the study these numbers had declined to 16 (31%) and 5 (10%), respectively. We found a corresponding reduction in the number of opioid consumers from 26 (50%) to 22 (42%), but the change from baseline nor the group difference did not reach statistical significance.

3.10 Side effects and complications

We received several reports of transient and minor side effects such as local pain/tenderness, dizziness, and sedation; the day after intervention by 15 participants (29%), and at the three follow-ups by 9 (17%), 4 (8%) and 1 (2%), respectively, but the group differences did not reach statistical significance. One participant became acutely ill immediately after a small injection (3 mL) of methylprednisolone and bupivacaine close to the minor occipital nerve. She developed transient disturbed consciousness, visual problems, unilateral motor deficiency, and chest pain and was immediately transferred to the intensive care unit. Cardiac and neurological examination, however, could not give any explanation, and she recovered within a few hours without any sequelae and was willing to complete the study.

4 Discussion

4.1 Main findings

This is the first published randomized, controlled trial on CEH comparing occipital cryoneurolysis with injections of corticosteroid combined with a local anaesthetic. Our main finding is that both corticosteroid injections and cryoneurolysis provide clinically significant pain reduction (50% and 60%, respectively). After 6 and 7 weeks, the effect gradually subsided and pain intensity reached a level 85% and 60% of baseline, respectively. We also observed a trend towards a lower number of opioid consumers. At the 18-week follow up a large majority (74%) of the participants reported much or moderately improved global status while approximately half of the participants reported less pain/headache (57%) or improved neck movement (57%) (Table 4). This may reflect that global status is also influenced by other factors than the analgetic effect. The effect of increased attention as a study participant (Hawthorne effect) has been shown to have a strong influence on study outcomes [35]. To sum up, there was no overall significant difference between the two treatment groups, and the pain reduction was not associated with any reduction in psychological distress, improvement in overall health related quality of life nor neck function.

4.2 Optimal cryoprobe position?

The short-lasting effect of cryoneurolysis may reflect that the endoneurium and basal lamina of the Schwann cells may remain intact despite the cryoablation and the nerve can regenerate within a few weeks [20–22]. However, in our study the insertion of cryoprobes was only guided by anatomical (muscular and bony) landmarks and nerve stimulation. The operator could thus not visualize the exact distance to the nerve trunks which is critical as the ice-ball, surrounding the probe tip, has a sharp temperature gradient from the centre to the surface, equivalent to 10 °C/mm [16]. The cryoprobes should therefore not be placed more than 4–5 mm away from the target nerve.

Previous studies have demonstrated considerable interindividual variations in the configuration of the nerve trunks [36–38] and distance between GON and the midline of the intermastoid line [37, 39]. The probe position might thus have been suboptimally placed. The introduction of new image-guided techniques is from this perspective highly interesting. In a small feasibility study [40] participants with unilateral occipital neuralgia were subjected to nerve stimulation and CT guided cryoneurolysis. Five of the six participants reported more than 50% pain reduction at the 3-month follow-up. This is comparable with our findings during the first 8 weeks, but superior to our findings after 12 weeks. CT is, however, a resource intensive procedure with high radiation exposure and ultrasound guidance is probably a more feasible technique for occipital neurolysis. Pingree and coworkers performed a small, non-controlled study on patients with occipital neuralgia or CEH to investigate the effect of ultrasound-guided GON block [41] at the point where the nerve courses superficially to the obliquus capitis inferior muscle. They reported significant pain reduction after 4 weeks. In a more recent publication Stogicza et al. describes an ultrasound guided technique to identify the proximal GON, between C2 spinous and C1 transverse process over the inferior oblique capitis muscle, for neurolysis of the proximal GON [42]. In future studies ultrasound guided techniques should thus be applied, but our approach is still widely used clinically, and we therefore find our results highly relevant.

4.3 Patient selection

The short-lasting effect could also reflect a suboptimal selection of participants. In a small retrospective study (*n*: 38) with occipital neuralgia patients subjected to unilateral or bilateral occipital cryoneurolysis, those with a moderate response to the test block (50–74% pain relief) reported 45% relief after an average of 4 months (which is a slightly inferior to our data), while patients with

>75% relief to the test block had still 71% pain relief after 8 months [43]. The paper does not provide information about which time point(s) the response was assessed, but the findings may indicate that a stricter patient selection might have improved the results. In our study the selection was based on one single test block and usually >50% pain reduction, but the success rates did not improve by excluding 10 participants who reported <50% pain reduction to the test block.

4.4 Side effects and complications

One-third of the participants (31%) rated the cryoneurolysis procedure as moderate to very uncomfortable. Minor side effects were rather common (29%), restricted to the first week, and included symptoms like local tenderness, dizziness, and sedation. We observed one potentially serious complication after an injection of bupivacaine and methylprednisolone. The participant was admitted to the intensive care unit and recovered without any sequelae. The examination gave no clear explanation. However, this case emphasizes the need for complication readiness during such procedures. It should also be noted that this study, with a small sample size and limited follow up, cannot provide evidence regarding the risk of occipital cryoneurolysis, particularly not when repeated over time.

4.5 Strengths and other limitations of the study

An important strength of the present study is the randomized, controlled and blinded design. Both participants and assessor were kept blinded throughout the follow up. The study had also a small drop-out rate and low number of missing values. Furthermore, the primary outcome measure was based on 42 daily pain records during the first 6 weeks and weekly pain records the next 11 weeks, which makes it a robust measure. With one single and well-trained interventionist, performing the treatments, we could reduce the statistical variance which is essential to demonstrate how effective these interventions might be in a clinical setting. The 18 week follow-up was also long enough to define the effect duration of occipital cryoneurolysis.

As shown in Table 1 the sample is representative for patients suffering from CEH [2, 5]. They reported long duration (average 13 years) of intense headache, moderately limited range of neck movement, phychological distress, and impaired health related quality of life. Although a high proportion (42%) suffered from migraine, only a few attacks were reported during the follow up. All these factors, listed above, increase the validity and generalisability of our findings.

A limitation is that we did not assess how effective the blinding procedure was. A "blinding test" has therefore been recommended in later years and self-assessment of pain intensity may be subjected to bias. With a limited sample size of 52 patients the study is also hampered by the risk of type II error.

5 Conclusion

For patients with CEH occipital cryoneurolysis and injections of a corticosteroid combined with a local anaesthetic provide substantial pain reduction but with a limited duration. We found no significant difference between the two treatments. The pain reduction was associated with a trend towards reduced opioid consumption, but no or minimal improvement in health-related quality of life, neck function and psychological distress.

6 Implications

We suggest that occipital cryoneurolysis or steroid injections is restricted to highly selected patients where non-invasive treatment is insufficient and who respond substantially to occipital test blocks. The effect can probably be improved and extended by including an ultrasound-guided technique. Potential adverse effects by repeated occipital cryoneurolysis sessions are not well documented and beyond the scope of this study, but scar and neuroma formation [44], and risk of neuropathic pain [45] have been discussed by other researchers.

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Authors' statements

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