Cover page

Short title: Nurse intervention Trial

Full title: Nurse Intervention Trial: The Evaluation of Usefulness of a Headache Nurse

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1.1 Introduction

Patients with headaches assessed in specialized healthcare who are prescribed medication would benefit from follow-up visits to evaluate if the prescribed treatment has been used and if it is effective. In practice, limited outpatient capacity with long waiting lists and delayed follow-up visits will limit the benefits of such planned follow-up. By utilizing nurses with expertise in headaches, the quality of follow-up care in specialized healthcare can be improved. Such task delegation between different healthcare professions has already been established in many clinical departments However; the potential benefit has not been documented in clinical randomized studies, as is the case, for example, with epilepsy nurses (1).

For headaches, the majority of previous studies have focused on the benefits of headache nurses in primary healthcare (2-5). Few previous studies have assessed the benefits of headache nurses in specialized healthcare. A retrospective study conducted in the Netherlands showed that more patients with medication-overuse headache successfully discontinue pain medication in the group receiving close follow-up from headache nurses compared to the group without such follow-up (6). However, randomized studies for headache nurses are lacking. Quality depends on accurate diagnosis, personalized treatment, effective alternatives, patient information, and measurable treatment outcomes documented with headache diaries. Most neurological departments in Norway lack dedicated headache nurses. A randomized prospective study could provide evidence for the inclusion of headache nurses in more departments.

A high quality of follow-up for headache patients in specialized healthcare depends, among other things, on accurate diagnosis, individualized treatment with effective and safe alternatives, providing good information to patients, and measurable endpoints of initiated treatment documented through the maintenance of a headache diary (7-9). The majority of the 18 different neurological departments in Norway currently do not have a dedicated headache nurse. Better justification for including headache nurses in more departments may result if a randomized prospective study demonstrates improved treatment of headache patients with the involvement of headache nurses.

This randomized prospective study will focus on headache patients initiating preventive treatment, where the treating physician identifies a need for follow-up visits in specialized healthcare. The study will clarify whether the implementation (compliance) and overall satisfaction of the patient are better with follow-up by a headache nurse compared to standard follow-up.

2.1. Utility

This study will clarify the effectiveness of two different follow-up strategies for headache patients and thus contribute to increased quality of treatment in specialized healthcare. We aim to document whether the implementation of initiated treatment and overall satisfaction

for headache patients improves with the follow-up by a headache nurse compared to standard follow-up. An optimized follow-up strategy will also be beneficial for individual headache patients being assessed in specialized healthcare. The results of the study will have implications for how specialized healthcare should be best organized for headache patients initiating preventive treatment.

3.1. Problem Statement and Objectives

The main objective is to compare the implementation and satisfaction of initiated treatment for patients with a primary headache diagnosis who receive follow-up from a headache nurse in the initial phase after starting new treatment, compared to standard follow-up where both groups are offered a check-up in specialized healthcare after approximately 3 months. Among the sub-goals in the study is the time to achieve at least a 30% response to treatment relative to the group to which the patients are randomized.

4.1 Methods

This is an open randomized controlled follow-up study to assess the utility of a headache nurse. Eligible for inclusion in the study are headache patients who have been assessed by a neurologist in specialized healthcare and who, during the consultation, have received a definitive primary headache diagnosis and a need for preventive treatment. After completing the initial consultation, eligible patients will receive oral and written information and an invitation to participate.

Potential patients suitable for this study must have undergone a regular consultation with a neurologist before. This consultation includes neurological and somatic examinations, diagnosis of the type of headache based on medical history, review of a completed headache diary, and any additional conducted examinations. The consultation will also involve an assessment of the possible initiation of preventive treatment. A selection of these patients will be prescribed electronic prescriptions for at least one previously untried type of preventive medication. During the consultation, patients will receive oral and written information about the dosage and expected possible side effects of the preventive medication. Those eligible for beta-blocker initiation will undergo an electrocardiogram (EKG) after the consultation. After completing the consultation, eligible patients will receive written and oral information about the study.

Those who do not wish to participate will be referred back to their general practitioner for further follow-up, with the possibility of a new referral to specialized healthcare if needed. Those who provide consent to participate will, during subsequent registration with the secretaries at the neurological outpatient clinic immediately after the consultation, be randomized to one of two follow-up options (A or B) for further monitoring in the coming months until the scheduled follow-up, set at approximately 3 months, or later if there is a shortage of available appointments.

Group A will be followed up by a headache nurse through telephone consultations at least two occasions shortly after the initiation of preventive medicine. Participants in this group

will be invited to a planned final follow-up appointment after approximately 3 months with a neurologist, or later if there is a shortage of available appointments.

Group B will have patient-managed follow-up with a planned final follow-up appointment after approximately 3 months with a neurologist. Participants will pick up the prescribed medication and contact their general practitioner or the neurological outpatient clinic by phone if they need advice from a neurologist.

Randomization and storage of research data will be done electronically by eFORSK, where all involved study personnel will have a personal login to eFORSK. Training will be provided before the study commences. The complete questionnaire, consent, and participant list with ID numbers and CV for study personnel will be kept by the project leader in a locked cabinet.

All included patients will be instructed to keep a continuous digital headache diary tailored for this study, which will be downloaded on their mobile phones via a dedicated application called "Brain Twin."

At the start of the study, the physician conducting the consultation will fill out a concise form with headache diagnosis and general health, which will be reflected in the eFORSK. During follow-up consultations for groups A and B, any side effects and the effectiveness of the initiated treatment will be assessed through a review of the headache diary. For those using Valproate, blood tests will be taken after initiation.

Inclusion criteria

- Women and men aged 18 and older with one of the following headache diagnoses based on the International Classification of Headache Disorders, third edition (ICDH3): G44.1 Chronic tension-type headache and/or G43 Episodic and chronic migraine, G44.0 episodic and chronic cluster headache, G44.8; Hemicrania Continua
- Overuse of attack medication consistent with the diagnosis of medication overuse headache does not exclude inclusion.
- Indication for preventive medication where there is at least one alternative with the need for follow-up assessment of effectiveness.

Exclusion criteria

- Uncertain headache diagnosis.
- Need for further investigation after the initial consultation.
- Lack of understanding of information provided in Norwegian, both verbally and in writing.
- Inability to keep a digital headache diary.
- Need for further investigation or treatment of other comorbid conditions requiring follow-up in specialized healthcare.
- Treatment with Onabotulinumtoxin A or Calcitonin-gene-related Peptide (CGRP) inhibitors given with tree months intervals

Endpoints

Primary endpoint: "Compliance": The number of participants who have carried out the trial as prescribed, defined as a minimum duration of two (2) months of the trial.

Secondary endpoints:
1. Number of days from inclusion to at least a 30% reduction in moderate to severe headache frequency compared to the frequency in the last month before the initial consultation.
2. "Compliance" with headache diary: The number of participants with a completed headache diary.
3. Number of responders measured by headache days (≥50% reduction in headache days compared to the corresponding registration before the first consultation).
4. General satisfaction (1-4 scale from the fourth version of the Trøndelag Health study (HUNT4).
5. Number of professional inquiries recorded about included study patients from either headache nurse or general practitioner directed to the responsible neurologist.

Power calculation and analyses

Experiences from four previously conducted treatment studies on migraines with a duration of 30-48 weeks (10) showed a dropout rate of 10% of participants. During 3-5 months of follow-up, an expected dropout of a maximum of 15% is anticipated. In this two-armed parallel study, it is therefore preferable to include 200 patients in each arm (total of 400 patients) (alpha 0.05, 80% power) if one wants to detect a difference in compliance of 15% between follow-up by a headache nurse and standard follow-up (e.g., compliance of 45% versus 30%).

The null hypothesis is that there is no difference in compliance between the groups regardless of the type of follow-up (non-inferiority). By choosing a significance level of 0.05 and 80% power, with a non-inferiority margin of 15%, 162 participants will be required in each group. By including 200 patients in each arm, the study will have sufficient statistical power to potentially conclude whether there is no difference in compliance between the groups.

The primary endpoint will be analyzed using the chi-square test. The difference between the groups will be defined as statistically significant with a p-value <0.05.

4.2. Organisation and collaboration

This study is a collaborative project between the Neurology Clinic at St. Olav's Hospital and the Norwegian Centre for Headache Research (NorHead), Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU).

Project leader Knut Hagen is a professor of Neurology and has been affiliated with the National Competence Service for Headaches for 15 years, combined with a position as a consultant involved in the assessment and follow-up of headache patients since 2005. He is currently the academic leader for the establishment of a new national quality register for

severe primary headaches, along with a position as a medical advisor at the Clinical Research Unit, Central Norway, St. Olav's Hospital

4.2.1 Other collaborating hospitals

Oslo University hospital and Haukeland University Hospital

4.3. Timeline

The study is approved by the Regional Ethics Committee (REK) in January 25, 2023. The inclusion of the required number of patients and the completion of the follow-up period will likely be finished within 3 years (in the end of 2026).

4.4 Publication plan

Study results will be published in an international journal that allows for open access. Results will also be communicated to healthcare institution leadership, the healthcare system, and the department, as well as in understandable formats for newspapers, digital media, and blogs in collaboration with user representatives.

4.5 Budget

Financial support has been granted by the Joint Research Committee for the period 2023 to 2025. This includes funding for a nurse in a 50% position. The infrastructure of the Norwegian Centre for Headache Research (NorHead) will be used for the involvement of study personal from Oslo University hospital and Haukeland University Hospital.

5. References

1. Grethe Helde, Gunnar Bovim, Geir Bråthen, Eylert Brodtkorb. A structured, nurse-led intervention program improves quality of life in patients with epilepsy: a randomized, controlled trial. Epilepsy Behav 2005 Nov;7(3):451-7.

2. Veenstra P, Kollen BJ, de Jong G, Baarveld B, van den Berg P. Nurses improve migraine management in primary care Cephalalgia 2016 Jul;36(8):772-8.

3. Cady R, Farmer K, Beach ME, Tarrasch J. Nurse-based education: an office-based comparative model for education of migraine patients. Headache 2008 Apr;48(4):564-9.

4. van den Berg JSP, Steiner TJ, Veenstra PJL, Kollen BJ. Migraine Nurses in Primary Care: Costs and Benefits. Headache. 2017 Sep;57(8):1252-1260

5. Pijpers JA, Louter MA, de Bruin ME, van Zwet EW, Zitman FG, Ferrari MD, Terwindt GM. Detoxification in medication-overuse headache, a retrospective controlled follow-up study: Does care by a headache nurse lead to cure? Cephalalgia. 2016 Feb;36(2):122-30.

6. S Greenfield, A L Komaroff, H Anderson. A headache protocol for nurses: effectiveness and efficiency, Arch Intern Med 1976 Oct;136(10):1111-6.

7. Schramm S, Uluduz D, Gouveia RG, Jensen R, Siva A, Uygunoglu U, Gvantsa G, Mania M, Brachinsaky M, Filatova E, Latysheva N, Osipova V, Skorobogatykh K, Straube A, Eren OE, Martelletti P, De Angelis V, Negro A,

Linde M, Hagen K, Radojicic A, Zidverc-Trajkovic, Podgorac A, Paemeleire K, De Pue A, Lampl C, Steiner TJ, Katsarava Z. Headache service quality: Evaluation of quality indicators in 14 specialist-care centres. J Headache Pain 2016 Dec;17(1):111

8. Peters M, Perera S, Loder E, Jenkinson C, Gil Gouveia R, Jensen R, Katsarava Z, Steiner TJ. Quality in the provision of headache care. 1: systematic review of the literature and commentary. J Headache Pain 2012; 13:437–447

9. Michele Peters, Crispin Jenkinson, Suraj Perera, Elizabeth Loder, Rigmor Jensen, Zaza Katsarava, Raquel Gil Gouveia, Susan Broner, Timothy Steiner. Quality in the provision of headache care. 2: defining quality and its indicators. J Headache Pain 2012 Aug;13(6):449-57.

10. Jenssen AB, Stovner LJ, Tronvik E, Sand, Helde G, Gravdahl GB, Hagen K. The analyses of four randomized placebo-controlled trials in migraine preventive treatment. The Journal of Headache and Pain J Headache Pain. 2019 Dec 27;20(1):119. doi: 10.1186/s10194-019-1067-z.