Greater occipital nerve modulation and clinical aspects of cluster headache

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CHAPTER 12

Prediction of efficacy of occipital nerve stimulation in medically intractable chronic cluster headache

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Abbreviations: ONS (occipital nerve stimulation); MICCH (medically intractable chronic cluster headache); SF-36 (MOS 36-Item Short-Form Health Survey); MWAFB (mean weekly attack frequency at baseline); RARFB (relative attack reduction from baseline)

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ABSTRACT

Background and objective

Occipital nerve stimulation (ONS) has become an established therapy for medically intractable chronic cluster headache (MICCH), but not all patients respond satisfactorily. A recent report suggested a number of predictors of treatment success. However, this study was small, not adequately controlled, did not use a formal prediction model, efficacy was poorly defined and follow-up was only of short duration. Here, we retrospectively sought (i) reproduction of these success predictors and (ii) identification of possible other predictors in our previously published double-blind randomized controlled ICON trial and long-term follow-up of the efficacy of ONS in MICCH.

Methods

Data from the ICON-trial and long-term follow-up were used to create two predictive models in which two response measures were used: (1) relative difference in attack frequency from baseline at 2 and 5 years after implantation, and (2) perceived effect at 2 and 5 years after implantation. Linear and binary logistic regression analyses were performed to (i) verify the previously detected predictors, and (ii) identify possible other predictors.

Results

We could not reproduce predictors of efficacy previously identified by others. Relative reduction in attack frequency at 24 weeks (B = 0.446, 95% CI 0.130 – 0.763, p = 0.007) and the time to ONS implantation (B = 0.040, 95% CI 0.012 – 0.069, p = 0.007) appeared to be the only significant predictors of objective efficacy at 2 years, and relative attack reduction after 2 years the only significant predictor of objective efficacy at 5 years (B=0.501, 95% CI 0.186 – 0.815, p = 0.003). The odds of experiencing subjective satisfaction with ONS after 2 years increased with a later debut of CCH (95% CI 1.002–1.117, p=0.043) and greater relative reduction in attack frequency at 24 weeks (95% CI 1.003–1.035, p=0.017).

Conclusion

In a controlled setting, we failed to reproduce the predictors of treatment success of ONS for MICCH previously identified by others in an uncontrolled setting. Rapid onset of efficacy after initiation of ONS appeared to be the only predictor of long-term efficacy. Since a large proportion of patients with MICCH improve with ONS, we recommend offering ONS to these severely affected and often desperate patients.

INTRODUCTION

In many countries occipital nerve stimulation (ONS) has become an approved and reimbursed therapy for medically intractable chronic cluster headache (MICCH). Several studies and systematic reviews have documented the efficacy, safety and tolerability. [1-4] Most patients experience subjective (78% are satisfied or very satisfied) and objective (57% show ≥ 50% reduction in attack frequency from baseline) improvement. [1, 2] Yet a significant number of patients do not improve sufficiently.

Reliable predictors of treatment success would help physicians improve indication for ONS in MICCH. A recent report suggested that early onset of CH and CCH, smoking and seasonal or circadian fluctuations are such predictors. [5] However, this study was small and not adequately controlled, did not use a formal prediction model, efficacy was poorly defined or dichotomized and follow-up was only of short duration. [1, 2]

Here we wanted to see if we could (i) reproduce these success predictors and (ii) identify other predictors using formal prediction models and strictly defined outcome in our double-blind randomized controlled ICON study [1] and long-term follow-up [2] of the efficacy of ONS in MICCH at 24 weeks and 2 and 5 years after initiation.

METHODS

Study design and participants

We used the data from the double blind randomized controlled multinational ICON-trial [1] and the 2-8 year prospective open label follow-up of 88 participants of that trial [2] on the efficacy and safety of ONS in MICCH as defined by the European Headache Federation [6]. Other in- and exclusion criteria are described in the respective reports. [1, 2]

Briefly, participants in the ICON trial were implanted after a 12-week baseline period and evaluated double-blind at 24 weeks, after which they were all followed for another 24 weeks for optimal open-label treatment. After completion of the ICON study, Dutch study participants (N=88) participated in a prospective long-term follow-up for up to 9.5 years after implantation, completing two Web-based questionnaires every six months, to assess attack frequency and perceived effect. Quality of life was measured with the MOS 36-Item Short-Form Health Survey (SF-36). [2]

Outcomes

We created two predictive models in which two response measures were used:

1. Relative difference in attack frequency from baseline at 2 and 5 years after implantation
2. Perceived effect at 2 and 5 years after implantation

The following variables were tested as predictors: age at onset of CCH, time to ONS implantation, gender, smoking, mean weekly attack frequency at baseline (MWAFB) and number of ictal autonomic symptoms at baseline, and relative attack reduction from baseline (RARFB) at 4 and 24 weeks and 2 years after implantation.

Statistics

A linear regression analysis was performed with RARFB at 2 and 5 years after implantation as dependent variables, and age at onset of CCH and smoking as independent variables.

Other linear regression analyses were performed with RARFB at 2 and 5 years after implantation as dependent variables, and age at onset of CCH, time since onset of CCH, smoking, gender, MWAFB and number of ictal autonomic symptoms at baseline, and the relative reduction in attack frequency from baseline at 4 and 24 weeks after implantation (and for the model with RRAFB at 5 years, the RARFB at 2 years), as independent variables.

The same linear regression analysis was performed with the percentage increase in SF36 scores from baseline at 2 and 5 years as dependent variable. If a regression model showed that it could significantly predict the dependent variable, the effect of its individual independent variables was calculated.

A binary logistic regression model was used to predict the perceived effect (response or no response as stated by the participant) of ONS at 2 and 5 years after implantation. Sex and smoking were used as categorical predictors, age at onset of CCH, time since onset of CCH, MWAFB and number of ictal autonomic symptoms at baseline were used as continuous predictors.

Finally, a bivariate correlation between age at onset of CCH and time to ONS implantation was analysed.

In case of missing data due to device removal for lack of effect, the last observation was carried forward, and the perceived effect was scored as ‘no effect’. The relative increase in attack frequency was limited to 100% to prevent outliers (2 cases after two years and one after five years).

RESULTS

Participants

Table 1 shows the baseline data from all 88 participants. Data from 61 (79%) participants were used for the 2-year analysis and from 42 (48%) participants for the 5 year analysis. A detailed description regarding follow-up, loss to follow-up and drop-out has been published in the previous reports. [1, 2]

Table 1 – Baseline characteristics

	Total	2Y cohort	5Y cohort
Participants, N	88	61	42
Sex (n, % male)	58 (66%)	41 (67%)	27 (64%)
Smoking (n, %)	65 (74%)	47 (77%)	32 (76%&
Autonomic symptoms (n, median [IQR})	5 [3 – 6]	5 [4 – 7]	5 [4 – 6]
Age at CCH debut (mean ± SD)	39± 14	39 ± 13	39 ± 13
Years since onset of CCH (mean ± SD)	6 ± 5	6 ± 5	5 ± 4
Mean weekly attack frequency at baseline	20 ± 14	20 ± 13	21 ± 15

Difference in attack frequency from baseline

The model in which smoking and age at onset of CCH were used as independent predictors does not significantly predict relative difference in attack frequency after 2 years (R2 = 0.029, p = 0.417) or 5 years (R2 = 0.034, p = 0.458).

The model in which smoking, age at onset of CCH, time to ONS implantation, sex, MWAFB, number of ictal autonomic symptoms, relative attack reduction at 4 and 24 weeks were used as independent predictors, significantly predicts a decrease in relative attack frequency at 2 years (R2 = 0.347, p = 0.003). Further analysis shows that the relative attack reduction at 24 weeks (B = 0.446, 95% CI 0.130 – 0.763, p = 0.007) and the time to ONS implantation(B = 0.040, 95% CI 0.012 – 0.069, p = 0.007) are predictors of relative attack reduction at 2 years.

The model in which smoking, age at onset of CCH, time to ONS implantation, sex, MWAFB, number of ictal autonomic symptoms, relative attack reduction at 4 and 24 weeks and at 2 years were used as independent predictors, significantly predicts a decrease in relative attack frequency at 5 years (R2 = 0.546, p = 0.001). In this model, only attack reduction at 2 years is a predictor of relative attack reduction at 5 years (B=0.501, 95% CI 0.186 – 0.815, p = 0.003).

No predictors for the SF36 scores (mental health sum-score, physical health sum-score and general health) were observed and no correlation between age at onset of CCH and time to ONS implantation was observed.

Perceived effect

The odds for perceiving a positive effect of ONS at 2 years increase by 6% for each year that CCH started later (95% CI 1.006 – 1.123, p = 0.029) and 2% for every percent attack reduction at 24 weeks (95% CI 1.003 – 1.035, p = 0.017). No predictive factors were observed for perceiving a positive effect at 5 years.

DISCUSSION

Using data from the double-blind randomized controlled ICON study and prospective long-term follow-up, we were unable to reproduce smoking and age of onset of CCH as previously reported predictors of objective and subjective long-term effectiveness of ONS for MICCH. In contrast, response at 24 weeks and 2 years appeared to be strong positive predictors of long-term response to ONS. Furthermore, a longer duration of CCH prior to ONS treatment was a moderate predictor of a positive response at 2-years but not at 5 years. Finally, a later onset age of CCH was associated with greater treatment satisfaction at 2 years but not at 5 years. This is consistent with results from another study [5] and from the ICON follow-up study showing that nearly three-quarters of participants who experienced an attack reduction of ≥ 50% after the first year maintained this response for most of the subsequent 4.2 ± 2.2 years. [2]

Possible reasons for the discrepancy with the previous study [5] are that the study that suggested early onset of CH and CCH, smoking and seasonal or circadian fluctuations as predictors of efficacy [5] was small and not adequately controlled, did not use a formal prediction model, efficacy was poorly defined (and dichotomized) and follow-up was only of short duration. We could not analyze the effect of seasonal or circadian fluctuations because we do not have such data.

Developing a robust, evidence-based prediction model usually requires a large data set that allows the use of a training and a validation cohort. However, because MICCH and ONS implantation are relatively rare, this is not possible. Consistency in interventional procedure is also critical, but despite efforts to standardize ONS surgery, differences in lead placement persists. Finally, anatomical differences in the location of the greater occipital nerve (GON) may result in different distances of leads to the GON between patients, potentially influencing the intended effect and further complicating prediction. [7] Therefore, most studies to date have failed to identify predictors of treatment success. [8, 9]

In conclusion, in a controlled setting we failed to reproduce the predictors of treatment success of ONS for MICCH previously identified by others in an uncontrolled setting. The effect after 2 years after initiation of ONS appeared to be the only predictor of long-term efficacy, making a short-term test stimulation not feasible. Since a large proportion of patients with MICCH improve with ONS, we recommend offering ONS to patients with MICCH and evaluating after 24 weeks whether to continue treatment with ONS.

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APPENDIX 1

ICON study group

Investigators are listed by center

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