A Propensity Score Matching Study on the Effect of OnabotulinumtoxinA Alone versus Short-Term Psychodynamic Psychotherapy Plus Drug-of-Choice as Preventive Therapy in Chronic Migraine: Effects and Predictive Factors

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Medication overuse headache · OnabotulinumtoxinA · Nonpharmacological migraine treatment · Disability

Abstract
Objective: The objective of this study was to test the superiority of multidisciplinary approach, that is, Short-Term Psychodynamic Psychotherapy (STPP) plus drug of choice, versus monotherapy, that is, OnabotulinumtoxinA (OnaBoNT-A). Method: We consecutively recorded data from chronic migraine (CM) patients, with or without medication overuse headache (MOH), who underwent STPP or OnaBoNT-A, with a 3-month follow-up schedule. Headache days and analgesics intake were monitored as primary outcome measures. Propensity score matching (PSM) was used to eliminate discrepancies between groups. Discriminant function analysis (DFA) was used to pinpoint predictive factors associated with the clinical response. Results: 96 patients with CM (64% with MOH) were treated with STPP and 54 (59% with MOH) with OnaBoNT-A. At baseline, OnaBoNT-A patients had more failed preventive therapies, more years of illness and chronicity, and were older; STPP patients were more depressed and had a higher HIT-6. Both STPP and OnaBoNT-A patients showed a significant reduction of headache days (STPP: −14 vs. OnaBoNT-A: −14.3) and analgesics intake (STPP: −12.3 vs. OnaBoNT-A: −13.5 pills/month), respectively. MOH diminished more in STPP, adherence was higher in OnaBoNT-A. Results were confirmed after PSM balancing of the groups for those variables that resulted as different (but age). Conclusion: OnaBoNT-A monotherapy produced similar results to psychotherapy plus medication, after correcting for baseline differences.

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Introduction

Chronic migraine (CM) patients, with or without medication overuse headache (MOH), represent the larger share of migraine patients referring to specialized headache clinics [1, 2]. These CM patients are difficult to treat, and only one out of five comply with preventive treatment and less than half clinically improve [3].

CM is difficult to manage because it is a complex “ensemble” of disorders rather than a single entity. Many somatic (e.g., asthma, obesity) and psychiatric (e.g., anxiety, depression, bipolar disorder) comorbidities concur to draw, together with chronic headache, a personalized pattern of disability in these patients [4].

Besides making the burden of CM heavier, these comorbidities can also reduce the chance of therapeutic success in other ways. Comorbidities may, indeed, contraindicate the use of certain preventive migraine medications due to their side effects (e.g., β-blockers in depressed patients) or drug-drug interaction with medications used for the treatment of comorbidity itself [5]. Therefore, the choice of the best therapeutic option for these patients is difficult, and patients could benefit from a global approach [6], which should comprehend also nonpharmacological, rehabilitative, or pharmacological noninteracting [7–9] interventions.

An interesting nonpharmacological option is psychotherapeutic support. Our group previously demonstrated that the short-term psychodynamic psychotherapy (STPP), a form of psychotherapy widely used in the treatment of several psychiatric diseases [10–12], reduced headache days and decreased the chance of relapse into medication overuse, when added to pharmacological therapy in MOH patients [13].

To avoid drug-drug interactions also the treatment with OnabotulinumtoxinA (OnaBoNT-A) is particularly important. OnaBoNT-A has specifically been approved as preventive therapy of CM in adults, after the results obtained by two large multicenter RCTs [14, 15]. Interestingly, the treatment with OnaBoNT-A also improved depression and anxiety in CM patients with a greater benefit in those patients that showed an improvement of pain symptoms [16]. Due to the possible overlapping effects provided by OnaBoNT-A or a multidisciplinary approach, in the present study we tested the hypothesis that a multidisciplinary (drug-of-choice primed by STTP) approach can be superior to only OnaBoNT-A.

Method

Patients’ Recruitment and Baseline Evaluation

We consecutively recruited all adult patients (age >18 years) affected by CM with and without MOH (ICHD-III 1.3 and 8.2) who were considered to start STPP or OnaBoNT-A as preventive treatment in the Headache Center at the Department of Human Neurosciences, Sapienza – University of Rome. We excluded patients without a clear headache diagnosis or the coexistence of two different headaches (except MOH), and with other severe neurological or psychiatric diseases. We also excluded patients with contraindications to perform OnaBoNT-A (e.g., neuromuscular junction disease, allergy to OnaBoNT-A, use of anticoagulant therapy, and so on). We considered as screening failure the interruption of the treatment after the first administration of OnaBoNT-A or the noncompletion of the first phase of STPP (Brief Psychodynamic Interview meetings, see below). After that point, patients, who quit the study, were considered as dropouts in the analysis. All patients underwent neurological examination and, when appropriate, instrumental investigations (e.g., neuroimaging, electroencephalogram).

At baseline, we recorded demographic and headache characteristics (see Table 1) as well as migraine history (both years since migraine onset and years since the migraine chronicity). As primary outcomes to study the overall effect of the treatment, we recorded the number of monthly headache days and the monthly use of analgesics for treating the attacks. Validated scales for disability (HFT-6 and MIDAS) and psychiatric comorbidities (Hamilton Rating Scale for Depression and Anxiety) were recorded at baseline and during follow-up visits and represented secondary outcome measures. Pragmatic criteria used in our headache clinic were used for prediction (online suppl. Table 1S; for all online suppl. material, see www.karger.com/doi/10.1159/000525152). The study was approved by our Ethics Committee and conducted according to the Declaration of Helsinki. All patients participating in the study gave written informed consent for the use of their clinical data.

Study Design

STPP was proposed as the initial approach to first-visiting patients according to their profile. Patients were instructed about STPP (see below for details), and about the fact that, in case of failure of STPP, a personalized pharmacological preventive therapy would have been added. On the other hand, OnaBoNT-A was proposed to patients fulfilling the Italian Agency for Drugs criteria for the use of OnaBoNT-A (i.e., failure of at least two preventive treatments). All patients were instructed to fill the monthly headache diary and record the number of acute headache medications used. Clinical evaluation of patients was performed every 3 months, recording monthly headache days and number of acute headache medications used each month, according to our standard and the PREEMPT protocol.

OnaBoNT-A was administered following the PREEMPT protocol in 31 sites of head-neck district, 5 UI for each site with a total of 155 UI [14, 15]. OnaBoNT-A was administered every 12 weeks for 5 sessions. No other preventive therapy was added during these 5 administrations. The starting dose was always 155 UI and, when appropriate, the dosage of OnaBoNT-A was increased from the second visit according to the “follow the pain” protocol (195 UI).
Patients underwent two-phase psychotherapy [17, 18]. The first phase, the Brief Psychodynamic Interview (BPI), is mostly diagnostic and it is developed during the first four meetings. The object of BPI is to identify the inner conflict of the patient and is conducted using associative anamnesis and initial interpretation techniques. Therapeutic STPP is delivered during the second phase of eight meetings (over 60 days). STPP is inspired by the Freudian technique (psychoanalyst’s neutral attitude, free associations), but it also relies on contextual modifications occurring in the face-to-face psychoanalytic setting (transference and countertransference). In its main core, STPP directly aims at a central psychological problem to help patients recognize it and, possibly, solve it. During the BPI, if the patient resists the attempt to identify the inner conflict or, instead, reaches its complete comprehension, the psychotherapy is interrupted. At the first follow-up visit (90 days), all patients who didn’t reach a CR started a standard preventive pharmacological therapy, while CR patients continued clinical follow-up. From the second follow-up visit (180 days), therapies were increased or substituted if needed; otherwise, they were stopped if patients reached CR according to the treating physician’s choice.

Statistical Analysis

Parametric and nonparametric tests were used according to normality of data. Continuous baseline data were analyzed with ANOVA with post hoc comparison between groups. Categorical baseline data were analyzed with the χ² test with Yates’ correction. We used repeated measures ANOVA for evaluating the time-depending dynamics of groups. Considering dropouts, within and in-between group results were controlled by post hoc comparison with Bonferroni correction. To compare the size of the response between groups, the propensity score matching (PSM) was used for a second analysis. PSM is a statistical analysis that mimics randomization, since it reestablishes balance between groups according to the propensity of individuals to be treated in a certain way. PSM pairs observations (matches) from groups and trimmed notmatched cases, that is, patients with an absolute standard bias >0.20. PSM was implemented by a logistic regression approach [19]. Baseline variables with a significant difference between groups were chosen as parameters on which to perform the matching rather than using an aprioristic approach.

Discriminant function analysis (DFA) to identify factors associated with early (90 days) and late (360 days) response (for these results, see online suppl. Materials). DFA estimates the linear combination of covariates separating individuals according to an outcome of interest [20–22].

Results

Real-World Comparison between OnaBoNT-A and STPP Plus Pharmacological Therapy

We consecutively recruited 152 CM patients who underwent STPP or OnaBoNT-A treatment. Two patients resulted as screening failures; therefore, 150 patients were considered for the analysis. Fifty-four patients were treated with OnaBoNT-A (59% with also MOH) and 96 with STPP (64% with also MOH) (see Table 1).

In the raw analysis, repeated-measure ANOVA showed a progressive reduction of headache days from 0 to 360 days (F = 27.6, p < 0.0001) with no global difference between groups (F = 2.6; p = 0.11). Time-group interaction was similar for both groups (F = 0.85; p = 0.49) (see Table 2; Fig. 1a). At 90 days, the larger drop in the mean number of headache days per month is observed with both OnaBoNT-A patients (~6.9 headache days/month) and STPP (~9.4 headache days/month) compared to baseline (see Table 2).

The post hoc comparison showed that the two groups only differed at 180 days follow-up with a better improvement in STPP (~8.4 headache days/month) versus OnaBoNT-A (~5.9 headache days/month) (p = 0.04 after cor-

| Table 1. Baseline demographic and clinical features of the OnaBoNT-A and STPP group at baseline |
|---------------------------------|----------|----------|----------------|----------------|----------------|----------------|
| Age (years) | 54.75 (±15.08) | 41.31 (±13.05) | <0.001 | 0.03 |
| School years | 12.16 (±4.53) | 13.23 (±3.69) | 0.121 |
| Headache years | 34.16 (±16.59) | 23.71 (±12.93) | <0.001 | 0.29 |
| Chronicization years | 11.63 (±10.47) | 6.10 (±7.31) | <0.001 | 0.47 |
| HIT-6 | 56.84 (±9.20) | 64.66 (±8.29) | <0.001 | 0.13 |
| MIDAS | 52.03 (±47.79) | 55.33 (±49.80) | 0.695 |
| HAM-D | 9.56 (±7.99) | 16.80 (±9.01) | <0.001 | 0.28 |
| HAM-A | 14.75 (±7.95) | 17.66 (±9.52) | 0.061 |
| HA days | 25.47 (±6.25) | 23.70 (±6.40) | 0.107 |
| N° analgesics | 20.24 (±22.10) | 17.12 (±15.16) | 0.311 |

Significant differences are marked in bold. Data are presented with mean and standard deviation. While age still remains significantly different (p = 0.03), the other parameters were all paired after trimming.
At 360 days, the STPP group reached on average −14 headache days/month, while the OnaBoNT-A group had on average −14.3 days/month. At 360 days, both groups had a significant reduction compared to baseline (after post hoc comparison with Bonferroni correction: \( p < 0.0001 \) for both groups), but the difference was not significant between groups (see Table 2).

The intake of acute headache medications also decreased over time. \( (F = 9.65; p < 0.0001) \) with no significant global difference between groups \( (F = 1.19; p = 0.28) \) nor in the time-group interaction \( (F = 0.19; p = 0.94) \) (see Fig. 1b; Table 2). STPP patients had a larger decrease at 90 and 180 days (see Fig. 1b). Considering the interruption of MOH, we found that the number of MOH patients significantly decreased in the STPP compared to the OnaBoNT-A group at 3 months \( (p < 0.001) \).

In the OnaBoNT-A group, 23 out of 54 completed the 1-year follow-up. From the original sample, 15 (28%) achieved a complete response, 3 (5.6%) had a partial response, and 5 (9.2%) maintained CM. In the STPP group, out of 96 patients, 21 reached the 12-month evaluation. In 17 (18.1%) patients, a complete response was achieved,
Baseline Group Differences and Propensity Score

At baseline, OnaBoNT-A patients were older, with more years of migraine and more years of chronicization than STPP patients. By contrast, STPP patients had a higher score on HIT-6 and HAM-D scales (ANOVA $F = 10.8, p < 0.001$). Complete baseline clinical and demographic details of STPP and OnaBoNT-A groups were described in Table 1. These parameters resulted significantly different after post hoc comparison and were thus used as covariates for PSM (see Table 1). After PSM, 36 matched couples of patients were selected. In this subset of patients, PSM succeeded to pair all covariates except age. Age resulted higher in OnaBoNT-A group being patients on average older by 7.67 years also after the trimming. The global course of the results did not change. After the trimming, the analysis confirmed the results obtained on the original sample, with headache days reduction being significant at 180 days with a greater reduction in the STPP group and acute headache medications consumption being significantly greater in STPP at 90 and 180 days (see Table 2).

DFA and Prediction

For this section, refer to online supplementary materials.

Discussion

The present study yielded results on the comparison between OnaBoNT-A versus STPP plus pharmacological therapy. We opted for a pragmatic-inspired observational design rather than a randomized clinical trial because it is not possible to provide correct randomization in trials involving a psychotherapeutic approach, since the acceptance of the psychotherapy treatment is the nominal requirement for it to succeed.

Our study showed the overall beneficial effect on headache days and painkillers intake in both OnaBoNT-A and the STPP-plus drug-of-choice groups. In the long run, the two treatments work equally well. Patients of the STPP plus drug group had fewer headache days at 3 months and less acute headache medications consumption at 3 and 6 months after PSM correction. The number of MOH patients significantly decreased after 3 months in the STPP group, according to previous data [13].

However, STPP arm was concerned by 78% (STPP) versus 55% (OnaBoNT-A) rate of dropouts. Such a rate of discontinuation is high but in line with recent data from the pharmacological arm of the FORWARD trial [23]. The adherence dropped mostly at the time of the latest follow-up (12 months). This pattern of dropping out could most likely reflect a failure of treatment efficacy with CM and MOH relapse and possibly in part the normal time-related turnover of attending CM patients.

From the literature, we know that only 9% of patients drop and discontinue treatments for clinical improvement [3]. Since in our setting both groups had the larger improvement early after the beginning of the two therapies, we can speculate that a part of dropouts occurred for improvement, although it is likely that the larger part is due to therapy inefficacy. In part, it could also depend on the advice to quit overuse [24] or as a direct consequence of the clinical improvement.

Since at baseline the two groups differed for several demographic and clinical features (see Table 1 for details), we performed a PSM to mimic randomization in the two groups, as suggested in recent real-world studies [25]. In our sample, patients with long history and more lines of failed therapies were addressed to OnaBoNT-A and patients showing depressive symptoms (who later obtained higher scores in the HAM-D) to STPP. This is not surprising since enrolled patients should be those that most likely would receive that treatment in real life. After matching patients with the PSM, results were highly confirmed, strengthening their robustness even if age remained different between groups. Instead of forcing the PSM to reach an improbable better match (results didn’t change after PSM successfully resolved 4 out of 5 bias), further reducing the number of patients, we preferred to repeat the analysis with this matching to have more than 30 subjects per group, a number high enough to compensate for unpredictable variables that could alter the outcome, according to the central limit theory [26].

We also investigated the role of baseline characteristics in determining early and late response, obtaining
significant results for the pooled data and OnaBoNT-A group (see text, online suppl. Tables 2S, 3S; online suppl. Fig. 1S). The number of headache days per month at baseline resulted as the most important predictive factors for early response, and resulted proportional to the chance of response: NR had the higher baseline number of headache days, while PR patients had an intermediate value, and CR patients had the lowest one. It suggested that achieving a better outcome is easier in patients with fewer days of headache, suggesting that adequate treatment should be started before the frequency of headaches becomes daily, that is, more than 25 days/month (see online suppl. Fig. 2S). Moreover, baseline painkillers consumption and the level of school education are the most important factors for the 12 months’ response.

Some shortcomings of this study should be mentioned. One possible limitation in the interpretation of the data is that we decided to add pharmacological preventive therapy in STPP only in a second stage and not from the beginning, due the pragmatic nature of the study. However, a different study design, adopting concomitant use of STPP and preventive medication from the start, could have provided different results than ours. Another limitation regards the effectiveness of STPP as preventive therapy alone since a large share of patients in the STPP group added preventive medications, so the effect in that group could be due largely to pharmacological effects. We can draw some conclusion only for the first part of the study, in which patients were under STPP alone. In this phase, about the 10% of patients were able to revert to EM and remained episodic up to 12 months. We cannot infer clearly on which is the exact STPP role in the long run.

Conclusions

Our study showed that OnaBoNT-A alone was as effective as STPP plus medication over 1 year and provided more adherence and a lower dropout rate, but STPP was instead more effective on interrupting MOH in the short period. OnaBoNT-A responses seems to be better predicted by multivariable models. Migraine is an incredibly disabling condition and the treatment should include pharmacological and nonpharmacological instruments in a most tailored treatment. This study could help in understanding the effects of each therapeutic option in unique disability-resolving frame.

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Statement of Ethics

The study was reviewed and approved by Ethics Committee of “Azienda Ospedaliera Universitaria Policlinico Umberto I and Azienda Ospedaliera Sant’Andrea” (approval number 4839). All patients participating in the study gave written informed consent for the use of their clinical data. The study conducted according to the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no competing interest.

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Author Contributions

Michele Alessiani, Barbara Petolicchio, Alessandro Viganò, and Vittorio Di Piero designed the study; Michele Alessiani, Barbara Petolicchio, Massimiliano Toscano, and Marta Puma collected clinical data; Barbara Petolicchio and Massimiliano Toscano performed BoNT-A injections; Rita De Sanctis and Ciro Franzese performed statistical analysis; Alessandro Viganò supervised statistical analysis; Romina Di Giambattista and Edmond Gillieron supervised STPP; Chiara-Camilla Derchi reviewed the content and helped in organizing and drafting supplementary materials. Alessandro Viganò and Vittorio Di Piero supervised the study; all authors participated in results discussion and interpretation; Michele Alessiani and Alessandro Viganò drafted the manuscript; Barbara Petolicchio, Chiara-Camilla Derchi, Rita De Sanctis, and Vittorio Di Piero revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.
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