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HEADACHE & FACIAL PAIN SECTION

Review Article

Effectiveness of Therapeutic Patient Education for Adults with Migraine. A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective. Our aim was to systematically review and meta-analyze the effectiveness of therapeutic patient education for migraine.

Methods. A literature search of multiple electronic databases (MEDLINE, EMBASE, PEDro, CINAHL, and PsychINFO) was conducted to identify randomized control trials (RCTs) published in the English and Spanish languages up to and including May 2013. Two reviewers independently selected the studies, conducted the quality assessment (Delphi list), and extracted the results. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses method was used throughout the systematic review and meta-analysis. Standardized mean difference (SMD) and 95% confidence intervals (CIs) were calculated for relevant outcome measures (headache frequency, headache disability, self-efficacy, depressive symptoms, and quality of life) and pooled in a meta-analysis using the random effects model.

Results. Fourteen RCTs were included in the systematic review. Only nine studies were included in the meta-analysis. The median quality score was 6.14 ± 1.29 (range: 5–9). There was strong-moderate evidence for intermediate-term effectiveness of therapeutic patient education on headache frequency (five studies: N = 940, SMD = –0.24, 95% CI of –0.48 to –0.01, *P* = 0.03), headache disability (four studies: N = 799, SMD = –1.02, 95% CI of –1.95 to –0.08, *P* = 0.03), and quality of life (three studies: N = 674, SMD = 0.36, 95% CI of 0.05–0.67, *P* = 0.02). There was no evidence for either short-term or intermediate-term effectiveness of therapeutic patient education on self-efficacy or depressive symptoms.

Conclusion. This systematic review revealed strong-moderate evidence for intermediate-term effectiveness of therapeutic patient education for migraine. Further high-quality RCTs are required for conclusive determination of its effectiveness.

Key Words. Behavioral Treatment; Therapeutic Education; Migraine; Meta-Analysis; Systematic Review; Headache Disability; Headache Frequency

Introduction

According to the third headache classification by the International Headache Society (IHS) [1], migraine is a common disabling primary headache disorder with high prevalence and significant socioeconomic and personal impacts. In the Global Burden of Disease Survey 2010,

chronic migraine was ranked as the third most prevalent disorder and the seventh highest specific cause of disability worldwide [1].

Migraine is a neurological disabling disease that affects all aspects of the individual's life and is considered a complex condition based on the interaction of biological, psychological, and environmental factors [2–4]. Some authors suggest that it is a biobehavioral disorder [2,4] that results from a cortical hypersensitivity and an associated social learning process [4]. Behavioral habits and medication intake due to migraine attacks are important factors to keep in mind.

According to Carlson, the biobehavioral approach for the management of chronic craniofacial pain recognizes the importance of psychosocial factors, such as past history of pain, ongoing emotional states, health beliefs, and coping skills, that interact with the physiological disturbances in determining the pain experience for the patients [5]. The biobehavioral approach has five key components that can been used by clinicians: education, skills acquisition, skills consolidation, generalization, and maintenance [6].

A combination of pharmacological and nonpharmacological approaches have been consider a better way to manage migraines and other chronic pain patients [7]. Stanos et al. concluded that the best treatment for chronic migraine was a multidisciplinary treatment including biobehavioral and pharmacological approaches [8].

Biobehavioral treatments (BBTs) for chronic pain patients includes therapeutic patient education (TPE) and self-care, cognitive behavioral interventions, and biobehavioral training (biofeedback, relaxation training, and stress management) [3,5,9]. BBT helps the patient change the way they think about their condition, as well as make changes in maladaptive pain behaviors to healthy behaviors. The treatments are designed to help patients to manage their symptoms and their lives [10].

Educational interventions focused on biobehavioral approaches are used to reduce pain and improve quality of life in migraine sufferers. These approaches try to find the best way to treat chronic pain patients because chronic migraine patients have a complicated pharmacological therapy management [11]. Therefore, the current study focuses its BBT on TPE.

The World Health Organization defined TPE as an education directed by health care providers trained in the education of patients in order to provide the patients' knowledge about the treatment of their disease condition, as well as to obtain the skills to avoid complications while acquiring balance in their lives to improve or maintain their quality of life [12–14]. TPE is designed to train patients in self-managing skills, in adapting the treatment to their specific chronic disease, and in coping abilities and processes [13].

TPE provides contact between the care providers and patients [12] to allow patients to become autonomous in the long term by offering the psycho-pedagogic means that are essential to motivate patients to treat themselves [13].

According to Golay et al., motivation, which is a state of activation in order to improve quality of life, includes an increment of compliance providing knowledge by "trial and error," as well as cognitive conflict or expression. It means that change comes from the within the patient, who becomes the author of his or her own learning process [13].

Daviet et al. [12], who studied TPE for stroke survivors, reported that TPE improves stroke survivor's understanding about their chronic disease and also improves mood and satisfaction levels, which changes their lifestyle after the education approach [13].

TPE has been extensively studied in the management of anxiety, stress, and pain for chronic lower back pain [15]. It is thought that in chronic diseases, TPE should be adapted to the needs of patients and caregivers [12].

BBTs were identified as "grade A" evidence in the American Consortium of Evidence Based Headache Guidelines [16]. It has been proposed that BBT based on educational approaches be used to manage migraines [17]. However, only a systematic review exists [18], but there are no meta-analysis published in the last years.

The purpose of this systematic review and meta-analysis was to conduct a current review of randomized controlled trials (RCTs) concerning the effectiveness of TPE on pain, disability, and psychological outcome among patients with migraine.

Methods

The systematic review was performed using a predefined protocol and subdivided into phases based on rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19].

Inclusion Criteria of the Studies

The selection criteria used in this review were based on methodological and clinical aspects such as the type of study, study population, interventions, and outcome measures.

Type of Studies

We selected RCTs to compare with a control group or other interventions that were methodologically correct. Only studies published in English and Spanish were included.

Patients

The patients of the trials selected had to be over 18 years, diagnosed with migraine or chronic migraine according to the IHS classification.

Therapeutic Intervention

RCTs that were included were based on a TPE approach, with major interventions based on the patients' learning and coping strategies.

Measures of Success

The measures that check the results and effects of the treatment had to assess at least two or more of the related variables: pain intensity, frequency of headache, disability, quality of life, depression symptoms, and self-efficacy. Furthermore, these had to be registered in the short term (<3 months), intermediate term (between 3 months and 12 months), or long term (>12 months).

Search Strategy

The search of scientific articles was performed using MEDLINE (1950 to May 2013), EMBASE (1988 to May 2013), PEDro (1999 to May 2013), CINAHL (1982 to May 2013), and PsychINFO (1806 to May 2013), with May 15, 2013, being the final date of the search. The terms used for the search were derived from the combination of the following words: "patient education," "patient information," "behavioral therapy," "behavioral treatment," "cognitive treatment," "information booklet," "educational booklet," "educational intervention," "advice," "coping strategies," "web-based intervention," "web-based education," "headache intensity," "quality of life," "headache frequency," "randomized controlled trial," and "migraine." The search strategy was adapted for each database as necessary. Two independent reviewers conducted the search using the same method, and any differences that emerged in this phase were resolved by consensus.

Selection Criteria and Data Extraction

The first analysis of the data was performed by two independent reviewers who assessed the RCTs' relevance regarding the studies' questions and objectives. This first analysis was performed based on information from the title, abstract, and keywords of each study. If there was no consensus, or the abstracts did not contain sufficient information, the full text was reviewed.

In the second phase of the analysis, using the full text, we proceeded to test whether the studies met all of the inclusion criteria. Differences between reviewers were resolved by a process of discussion/consensus moderated by a third reviewer [20]. Data described in the results were extracted by means of a structured protocol that ensured the most relevant information from each study was obtained [21].

Methodological Quality Assessment

The assessment of the methodological quality of the studies was performed using the Delphi list [22]. This instrument was developed through a consensus of experts who established 10 items: 1) randomization performed; 2) random allocation concealed; 3) study groups similar at baseline; 4) inclusion and exclusion criteria specified; 5) outcome assessor blinded; 6) care provider blinded; 7) patient blinded; 8) estimates and measures of variability presented for primary outcomes; 9) intention-to-treat analysis; and 10) index of withdrawals and dropouts described.

Methodological criteria were scored as: yes (one point), no (zero points), or don't know (zero points). The maximum possible score was 10, with a range of 0–10. Studies were considered to be of high quality when they met six or more items [23]. The Delphi list showed good concurrent validity with the Jadad scale (Spearman $r = 0.63–0.71$) and inter-rater reliability between 0.54 and 0.85 [24].

Two independent reviewers examined the quality of all of the studies selected using the same methods, and disagreements between reviewers were resolved by consensus including a third reviewer. The inter-rater reliability was determined using the Kappa coefficient, where >0.7 indicated a high level of agreement between assessors, between 0.5 and 0.7 indicated a moderate level of agreement, and <0.5 indicated a low level of agreement [25].

Classification of Evidence Levels

The qualitative analysis used was based on the classification of the results in evidence levels [23]. Evidence was categorized into five levels depending on the methodological quality as follows: 1) strong evidence: consistent among multiple high-quality RCTs; 2) moderate evidence: consistent findings among multiple low-quality RCTs, and/or clinical controlled trials (CCTs), and/or one high-quality RCT; 3) limited evidence: one low-quality RCT and/or CCT; 4) conflicting evidence: inconsistent findings among multiple trials (RCTs and/or CCTs); and 5) no evidence: no RCTs or CCTs.

Data Synthesis and Analysis

Statistical analysis was conducted using Meta-analysis with Interactive Explanations (MIX, version 1.7, BiostatXL, Mountain View, CA, USA) [26]. The meta-analysis was performed in accordance with the PRISMA guidelines [19].

The same inclusion criteria were used for the systematic review, as well as for the meta-analysis, and included three more criteria: 1) in the results, there was detailed information regarding the comparative statistical data of the exposure factors, therapeutic interventions, and treatment responses; 2) the TPE treatment was compared with a control group or another treatment; and 3) data of the analyzed variables were represented in at least two studies.

To provide a comparison between outcomes reported by the studies, the standardized mean difference (SMD) over time and corresponding 95% confidence interval (CI) were calculated for continuous variables and, if possible, short-term, intermediate-term, and long-term follow-up time points. The statistical significance of the pooled SMD was examined by a *Z*-test.

The effect estimates SMDs were interpreted as described by Hopkins et al. [27]. SMD of 4.0 was represented an extremely large clinical effect, 2.0–4.0 represented a very large effect, 1.2–2.0 represented a large effect, 0.6–1.2 represented a moderate effect, 0.2–0.6 represented a small effect, and 0.0–0.2 represented a trivial effect.

To compare the data, the following statistical tests were performed: the DerSimonian-Laird Q-test to measure the level of heterogeneity, and publication bias was also examined with Egger's regression tests [28]. When the Q-test was significant ($P < 0.05$), this indicated that heterogeneity existed among the studies, and the random effects model was conducted in the meta-analysis.

Results

Study Selection

As shown in Figure 1, a total of 89 studies were identified. Of these, 57 were dismissed because after reviewing the abstracts, it was concluded that these papers did not meet the inclusion criteria. Eighteen studies were withdrawn because six of them were not RCTs, two of them did not mention the population age, two not TPE treatment, five trials did not include patients diagnosed for specific migraine, and three studies included multiple pathologies. Fourteen studies [29–42], all of them RCTs, met the inclusion criteria and were included in the systematic review. Only nine [29,30,34–39,42] of the 14 studies were chosen for further analysis by including them in the meta-analysis.

Methodological Quality Analysis

The trials were evaluated with the Delphi list scale revealed a median score of 6.14 ± 1.29 (range: 5–9). According to the analyses of two reviews, eight [29,30,33,35–39] of the studies' methodologies were acceptable in terms of

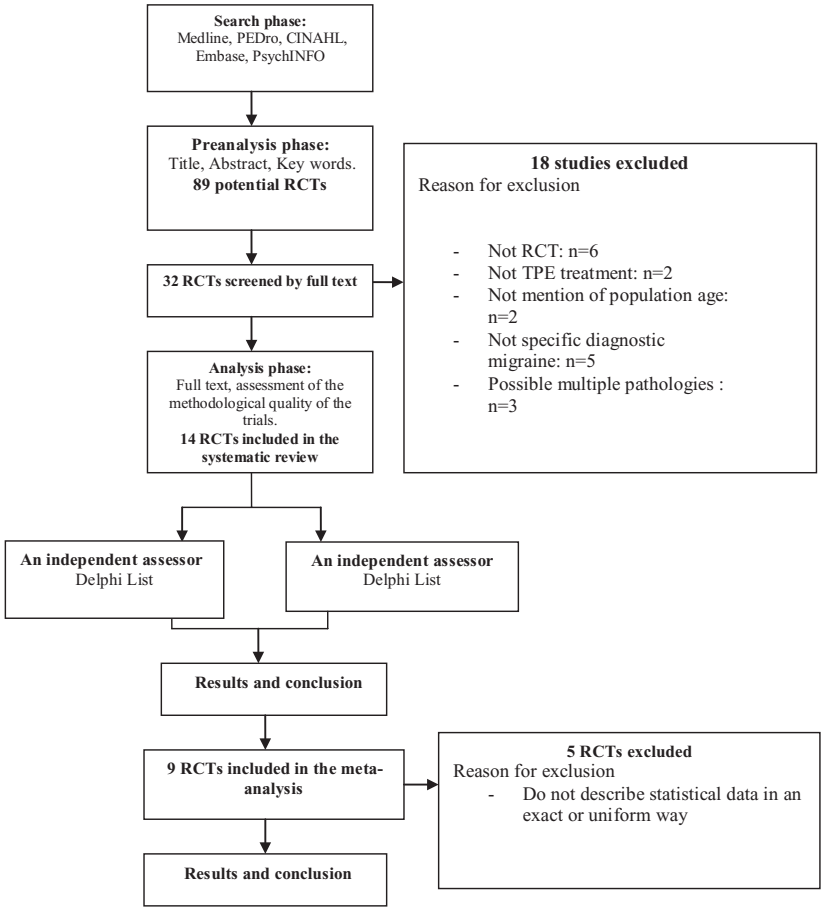

Figure 1 Flowchart of the selection of the clinical trials.

quality, but the other six [31,32,34,40–42] were considered poor quality. Table 1 shows the results of the evaluation according to the Delphi list scale.

The two reviewers had discrepancy in the evaluation of two RCTs. The discrepancy for those two studies concerned their scores for items 2 and 6. A consensus was reached after the third reviewer intervened. The inter-rater reliability of the methodological quality assessment was high ($\kappa = 0.93$, 95% CI 0.90–0.95).

Most of the studies lacked assessor, care provider, and blinding of the patients.

Study Characteristics

The characteristics (sample size, intervention, follow-up period, and main results) of the data were extracted and are presented in Table 2.

Characteristics of TPE in Patients with Migraine

Two studies (14.28%) [32,39] used Internet in their behavioral treatments, employing a multimodal behavioral treatment via Internet [39] or a web BBT. They also included diet educational approach [32]. Three studies (21.42%) [29,30,37] educated the patients in a biobehavioral approach based on relaxation.

The medication intake TPE approach was used in two studies (14.28%) [38,41] that were based on the medication safety described by Bromberg et al. [38] avoiding medication overuse as described by Holroyd et al. [41].

Only one of the included trials (7.14%) used sleep modification and TPE in its biobehavioral approach [31]. Six trials [33–36,40,42] gave the patients an educational approach based on reading guides (14.28%) [34,42] or lectures, and classes by a professional (28.57%) [33,35,36,40]. The varieties of TPE used in the studies are explained in Table 2.

Characteristics of Therapies Used in the Control Groups

Seven RCTs [29,30,35,36,38,40,41] used an usual pharmacological care treatment in the control group applying two of them the current treatment in the waitlist control [29,30]. Two of the studies [34,37] divided the control treatment into two groups, one of them was based on a placebo plus an optimized acute therapy (OAT), and the other was based on medication plus OAT. One trial [31] used therapy based on placebo plus medication as the control group. Muscular relaxation therapy was used as the control in two RCTs [32,39]. One trial subdivided the treatment and placebo groups into patient education or no patient education [33]. Only one trial designed its control group as a minimal contact education therapy [42].

Systematic Review Results

Five RCTs (35.7%) evaluated the effects of a TPE and obtained statistically significant results in disability and quality of life by the MIDAS questionnaire [29,30,35,36,40]. Two of them showed positive results at 6 months [35,40]. The headache self-efficacy questionnaire assess self-efficacy about headache outcome in patients and were evaluated in four trials [29,30,34,38] (28.57%). Only one of the studies showed statistically significant results of the self-efficacy at 6 months [38].

Table 1 Methodological quality of the studies included in the systematic review (Delphi list scores)

Trial	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Total
Rothrock et al. [40]	1	1	1	0	0	0	0	1	0	1	5
Matchar et al. [35]	1	1	1	1	0	0	0	1	0	1	6*
Fritsche et al. [42]	1	0	1	1	0	0	0	1	0	1	5
Cady et al. [33]	1	1	1	1	1	0	1	1	1	1	9*
Hedborg et al. [39]	1	1	1	1	0	0	0	1	1	1	7*
Merelle et al. [29]	1	1	0	1	1	1	0	1	1	1	8*
Merelle et al. [30]	1	0	1	1	0	0	0	1	1	1	6*
Bromberg et al. [38]	1	1	1	1	0	0	0	0	1	1	6*
Lemstra et al. [36]	1	1	1	1	1	0	0	1	1	1	7*
Seng et al. [34]	1	0	0	0	0	1	1	1	0	1	5
Holroyd et al. [37]	1	1	1	1	0	1	1	0	0	1	7*
Calhoun et al. [31]	1	1	1	1	0	0	0	0	0	1	5
Holroyd et al. [41]	1	0	1	1	0	1	0	0	0	1	5
Hedborg et al. [32]	1	0	1	1	0	0	0	1	0	1	5

Items: (1) Was a method of randomization performed?; (2) Was the treatment allocation performed?; (3) Were the groups similar at baseline?; (4) Were the elegibility criteria specified?; (5) Was the outcome assessor blinded?; (6) Was the care provided blinded?; (7) Was the patient blinded?; (8) Were point estimates and measures of variability presented for the primary outcome measures?, (9) Did the analysis include an intention-to-treat analysis?, (10) Is the withdrawal/dropout rate described?
*Studies that have an acceptable quality.

Table 2 Characteristics of the included studies (N = 14)

Studies	Patients	Format of education	TPE	Control Intervention (CI)	Outcome measures	Follow-up	Main results
Matchar et al. [35]	N = 614	1. Informative class (headache types/triggers/ treatment options) 2. Diagnosis and treatment by a professional 3. Proactive follow-up by a care manager	TPE	Usual care (by primary care provider)	MIDAS H Frequency SF-36 PHQ-9	6 months 12 months	At 6 months TPE treatment showed improvements in disability and quality of life by MIDAS ($P = 0.008$) At 3 months patients in TPE group showed a reduction of headache frequency At 6 months EI group showed reduction in depressive symptoms.
Fritscher et al. [42]	N = 150	Guided reading containing information about physiological and psychological aspects of migraine	Biblio group	Behavioral minimal contact therapy	H Frequency Overuse drugs Headache disability Depression	1 month 3 months 12months	Headache days, migraine days; EI = CI Improvements at short and long term in depression and disability
Hedborg et al. [39]	N = 83	Multimodal behavioral treatment (for behavioral modification) via Internet	GA. Hand massage + MBT GB. Extended baseline + MBT	Placebo treatment	MADRS PQ23 Changes in migraine frequency	5 months 8 months 11 months	GA, GB > 50% reduction in migraine frequency
Merelle et al. [29]	N = 129	Identification and modification of triggers (affective, cognitive, and behavioral) psychological self-regulation skills/ relaxation	TPE	Waitlist control	H. frequency SF-36 (m, p) HSE HLS MIDAS	Preintervention Postintervention	EI Patients with high headache attack frequency showed better improvements ($P = 0.03$)
Merelle et al. [30]	N = 127	Identification and modification of triggers (affective, cognitive, and behavioral) psychological self-regulation skills/relaxation	TPE	Waitlist control	H frequency SF-36 (m, p) HSE HLS MIDAS	6 months	H frequency decreased in EI at 6 months Quality of life improve overtime

Bromberg et al. [38]	N = 185	Migraine-specific knowledge/migraine self-management skills/emotional coping/communication skills/medication safety	TPE	Control group	HSE HSLCIn MIDAS Depression	3 months 6 months	EI greater than CI in; H self- efficacy, social support, relaxation, pain catastrophizing, depression symptoms and stress at 6 months
Lemstra et al. [36]	N = 80	Exercise therapy lectures/dietary lecture/massage therapy	TPE	Control group	H frequency Beck Pain disability	3 months	EI better than CI in H frequency, Beck and Pain disability
Seng et al. [34]	N = 176	Migraine management workbook/audiotape lessons/guided home practice of behavioral migraine management skills	OAT + PLACEBO + BMM OAT + β blocker + BMM	OAT + PLACEBO OAT + β blocker	HSE HSLC (in, ex) Quality of life	5 months 16 months	EI large increases than CI in HSE and HSCLin and large decreases in HSCLex
Holroyd et al. [37]	N = 232	Pathophysiology, migraine management skills, muscle relaxation, migraine triggers and prodromal signs, techniques into patient daily routine, stress management, and thermal biofeedback	OAT + PLACEBO + BMM OAT + β blocker + BMM	OAT + PLACEBO OAT + β blocker	H frequency MSQL	10 months 16 months	Combined β blocker and behavioral migraine management improve outcomes in headache frequency at 16 months.
Calhoun et al. [31]	N = 43	Behavioral sleep modifications (8 hours in bed, eliminate television, reading and music in bed, visualization technique, move supper and limit fluids, discontinue naps	BSM group	Placebo group	Headache Index H frequency	Preintervention Postintervention	EI reported statistically significant reduction in headache frequency ($P = 0.01$) than CI
Rothrock et al. [40]	N = 100	Standardized course of didactic instruction regarding biogenesis and management	Headache school	No school	H frequency H severity MIDAS	1 month 3 months 6 months	At 6 months the school group showed reduction in quality of life and disability; MIDAS ($P < 0.05$)

Table 2 Continued

Studies	Patients	Format of education	TPE	Control Intervention (CI)	Outcome measures	Follow-up	Main results
Cady et al. [33]	N = 207	Patient's open-ended question about awareness of migraine symptoms/health care providing give a list of frequent migraine associated symptoms/health care provider summarize the information learned by the patient in parts 1 and 2	Rizatriptan with M TPE Rizatriptan without M TPE	Placebo with M TPE Placebo without M TPE	Hours free of pain	2 hours 24 hours	Headache frequency: A greater proportion in the rizatriptan + TPE group reported pain freedom at 2 hours compared with those in the rizatriptan + no TPE group
Hedborg et al. [32]	N = 76	Web based, stress physiology/physical activity/diet/thought patterns/handling of emotions/attitudes	GA. Hand massage + MB GB. Extended baseline + MBT	Placebo treatment	MADRS PQ23 Changes in migraine frequency	5 months 8 months 11 months	At the end of the MTB, total drug consumption decreased by 22% ($P = 0.029$), corresponding to 27% fewer with migraine headache improving at 8 months the mental quality of life.
Holroyd et al. [41]	N = 34	Identify and monitor signs of headache onset/develop methods for keeping ergotamine readily available/adopt an experimental attitude toward decisions about abortive medication/avoid overuse of medication	SAT + BEI	SAT	Headache activity/medication use/psychological symptoms	Preintervention Postintervention	Patients in BEI group attempted to abort a greater percentage of their migraine attacks (70% vs 40%) and showed larger reduction in headache activity (e.g., 40% vs 26% reduction in the second month of treatment)

TPE = therapeutic patient education; H = headache; Pbo = placebo; w/out M TPE = with migraine therapeutic patient education, without migraine therapeutic patient education; GA = group A; GB = group B; G.C = group C; MBT = Internet-based multimodal behavior treatment; MADRS-S = Montgomery–Åsberg Depression Rating Scale; PQ23 = Quality of life questionnaire; HSLC = Headache Specific Locus of Control Scale; HMSE = Headache Management Self-Efficacy Scale; MSQOL = Quality of life Questionnaire; CPCI-42 = Chronic Pain Coping Inventory -42; HSES = Headache Management Self-efficacy Scale; PSC = Pain Catastrophizing Scale; DASS-21 = Depression Anxiety Stress Scales; PGIC = Patient Global Impression of Change; OAT = optimized acute treatment; BMM = behavioral migraine management; BSM = behavioral sleep modification; SAT = standard abortive therapy; BEI = brief educational intervention.

Eight RCTs evaluated headache frequency (57.14%) [29–31,33,35–37,42] by measuring it at 2 hours after medication (Rizatriptan) intake in one trial [33], at 3 and 6 months in two trials, respectively [35,36], and at 16 months after the treatment in one trial [37]. They all showed reductions of the headache frequency.

Depressive symptoms were evaluated in five studies (35.71%) [35,36,38,39,42] by different questionnaires: the Hospital Anxiety and Depression Questionnaire [42], Depression Anxiety Stress Scale [38], the patient health questionnaire short-form [35], the Montgomery–Åsberg Depression Rating Scale [39], and the Beck Depression Inventory [36]. All trials showed statistically significant post intervention outcomes, showing a reduction in depressive symptoms in two studies at 6 months [35,38].

Quality of life could be measured with the SF-12 questionnaire that is divided into two parts: physical quality and mental quality, which were assessed in eight studies (57.14%). The physical quality of life showed statistically significant results in four trials [29,30,34,35] with the SF-36 questionnaire that was used in three of them [29,30,35] showing positive effects at 6 months, whereas the migraine specific quality of life questionnaire was used in one of them at 16 months [37]. The mental quality of life was measured with the SF-36 questionnaire in three studies and the Home Situation and Mood Questionnaire in one [39] and showed increased scores in these four RCTs [29,30,35,39]. One RCT showed significant outcomes at 6 months [35] and another showed significant outcomes at 8 months in another [39]. The main results of each study are shown in Table 2.

Meta-Analysis Results

Meta-Analysis of Psychological Outcome Measures

Six RCTs evaluated the effects on depressive symptoms of TPE when compared with control groups. Meta-analysis of these studies showed no difference in the reduction of depressive symptoms in the short term (three studies [36,38,42]: N = 350, SMD = –1.48, 95% CI –3.34 to 0.36, $Z = 1.57$, $P = 0.11$; heterogeneity: *Q-value* = 107.2, $P < 0.001$; Figure 2). There was no evidence of publication bias ($P = 0.36$). There were also no changes in the intermediate term (four studies [35,38,39,42]: N = 692, SMD = –0.91, 95% CI –2 to 0.16, $Z = 1.66$, $P = 0.09$; heterogeneity: *Q-value* = 93.3, $P < 0.001$; Figure 2). There was no evidence of publication bias ($P = 0.33$).

TPE was significantly more effective when compared with the control group in improving the quality of life in the intermediate term (three studies [30,35,37]: N = 674, SMD = 0.36, 95% CI 0.05–0.67, $Z = 2.28$, $P = 0.02$; heterogeneity: *Q-value* = 6.26, $P = 0.04$; Figure 3). There were no differences in the short term (two studies [29,30]: N = 245, SMD = 0.06, 95% CI –0.19 to 0.31, $Z = 0.47$, $P = 0.63$; heterogeneity: *Q-value* = 0.01, $P = 0.9$; Figure 3). There was no evidence of publication bias ($P = 0.33$).

Four RCTs that included self-efficacy variables were analyzed in the meta-analysis and showed no difference in the short term (three studies [29,30,38]: N = 390, SMD = 1.62, 95% CI –0.17 to 3.43, $Z = 1.76$,

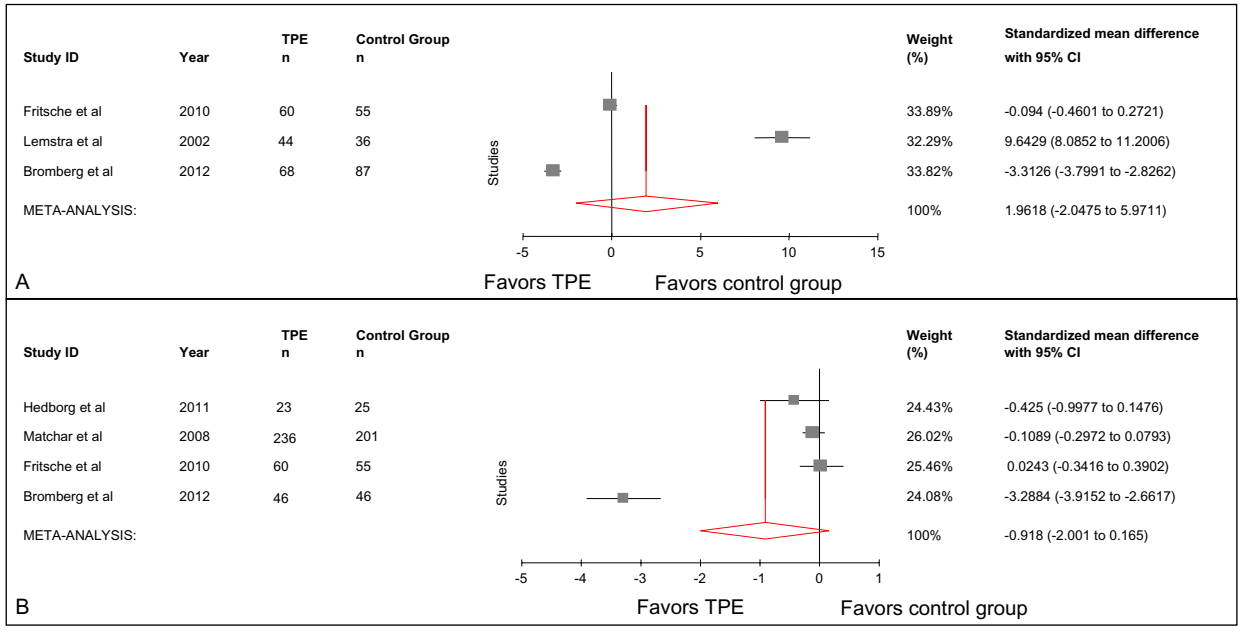

Figure 2 Forest plots of therapeutic patient education (TPE) vs control group effect on depressive symptoms. (A) short term; (B) intermediate term.

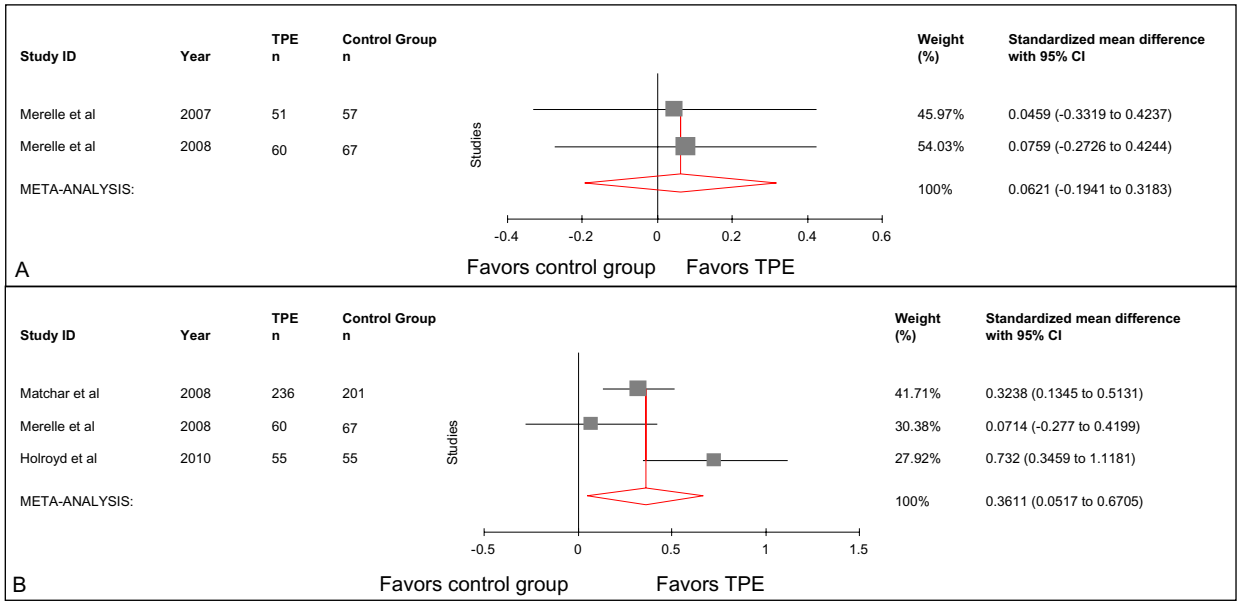

Figure 3 Forest plots of therapeutic patient education (TPE) vs control group effect on quality of life. (A) short term; (B) intermediate term.

$P = 0.07$; heterogeneity: $Q\text{-}value = 113.3$, $P < 0.001$; Figure 4) or in the intermediate term (three studies [30,34,38]: N = 307, SMD = 2.44, 95% CI –0.03 to 4.92, $Z = 1.93$, $P = 0.05$, heterogeneity: $Q\text{-}value = 135.8$, $P < 0.001$; Figure 4). There was no evidence of publication bias for the meta-analysis in short-term outcomes ($P = 0.14$), but there was for the intermediate-term analysis ($P = 0.03$).

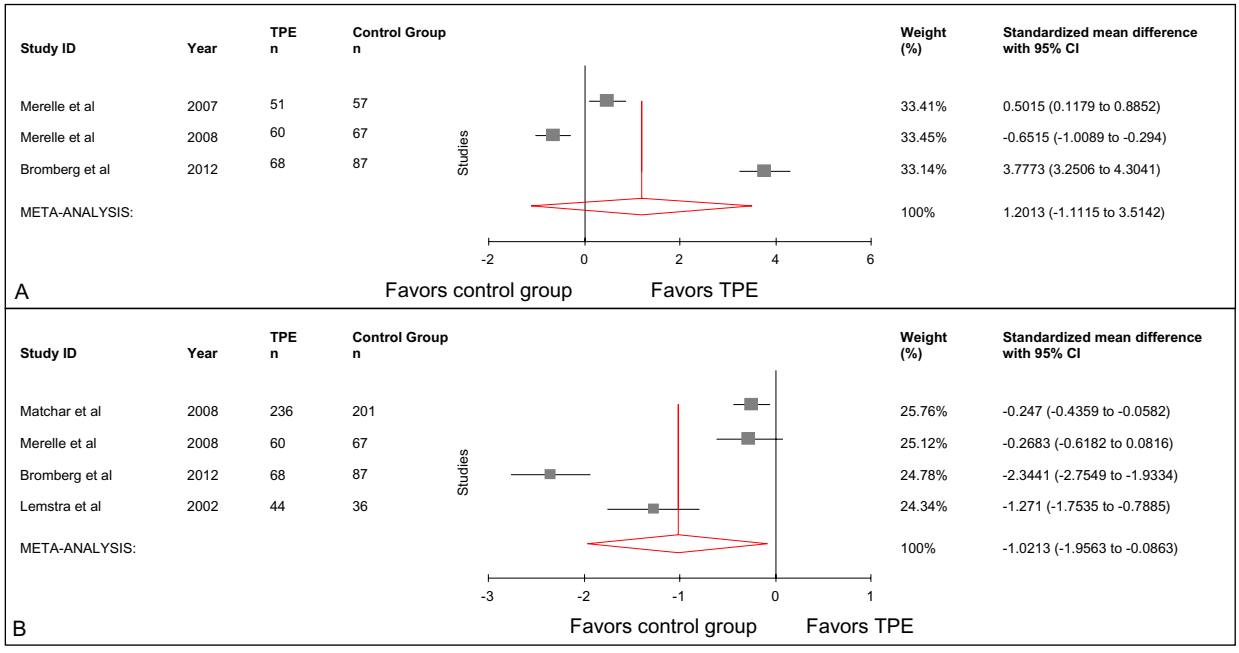

Figure 4 Forest plots of therapeutic patient education (TPE) vs control group effect on self-efficacy. (A) short term; (B) intermediate term.

Meta-Analysis of Pain Outcome Measures

TPE was significantly more effective when compared with the control group at improving headache disability in the intermediate term (four studies [30,35,36,38]: N = 799, SMD = –1.02, 95% CI –1.95 to –0.08, Z = 2.14, P = 0.03; heterogeneity: Q-*value* = 93.1, P < 0.0001; Figure 5), but there were no differences in the short term (five studies [29,30,36,38,42]: N = 585, SMD = –0.26, 95% CI –0.64 to 0.11, Z = 1.38, P = 0.16; heterogeneity: Q-*value* = 20.9, P = 0.0003; Figure 5). There was no evidence of publication bias for either of the two meta-analyses (short term, P = 0.88; intermediate term, P = 0.27).

A total of seven RCTs evaluated the effects of TPE when compared with the control group on headache frequency. The meta-analysis for these studies showed difference in the reduction of headache frequency in the intermediate term (five studies [30,35,37,38,42]: N = 940, SMD = –0.24, 95% CI –0.48 to –0.01, Z = 2.05, P = 0.03; heterogeneity: Q-*value* = 11.43, P < 0.02; Figure 6). There was no evidence of publication bias (P = 0.97). There were also no changes in the short term (four studies [29,30,36,42]: N = 430, SMD = –0.39, 95% CI –0.78 to 0.002, Z = 1.94, P = 0.05; heterogeneity: Q-*value* = 12.48, P = 0.005; Figure 6) and long term (two studies [37,42]: N = 115, SMD = 0.03, 95% CI –0.22 to 0.29, Z = 0.26, P = 0.78, heterogeneity; Q-*value* = 0.62, P = 0.43; Figure 6). There was evidence of publication bias for the meta-analysis in the short term (P = 0.02).

Discussion

This meta-analysis revealed that TPE provided improvements in disability and quality of life and decreased the frequency of migraines in the intermediate term. Finally, 14 studies were included, and the majority of them showed positive effects when treating migraine patients with TPE and other behavioral treatments. This intervention has been used to treat other chronic pain conditions, such as whiplash-associated disorders or lower back pain [43,44]. TPE is focused on improving coping strategies to reduce stress, increase relaxation, and internal locus of control [45].

Recently, another systematic review in German by Fritsche et al. summarized various forms of BBT for migraine [18]. There were some differences with our review. For example, the inclusion and exclusion criteria, such as the kind of therapy included (biofeedback training and progressive muscle relaxation), or population sample characteristics (children). In fact, these features differentiate our study from other systematic reviews or meta-analyses published. Most of these studies focus on children and adolescents, and study different types of recurrent pain, including headaches [46–49]. Trautmann et al. recommended that future studies should identify the function of

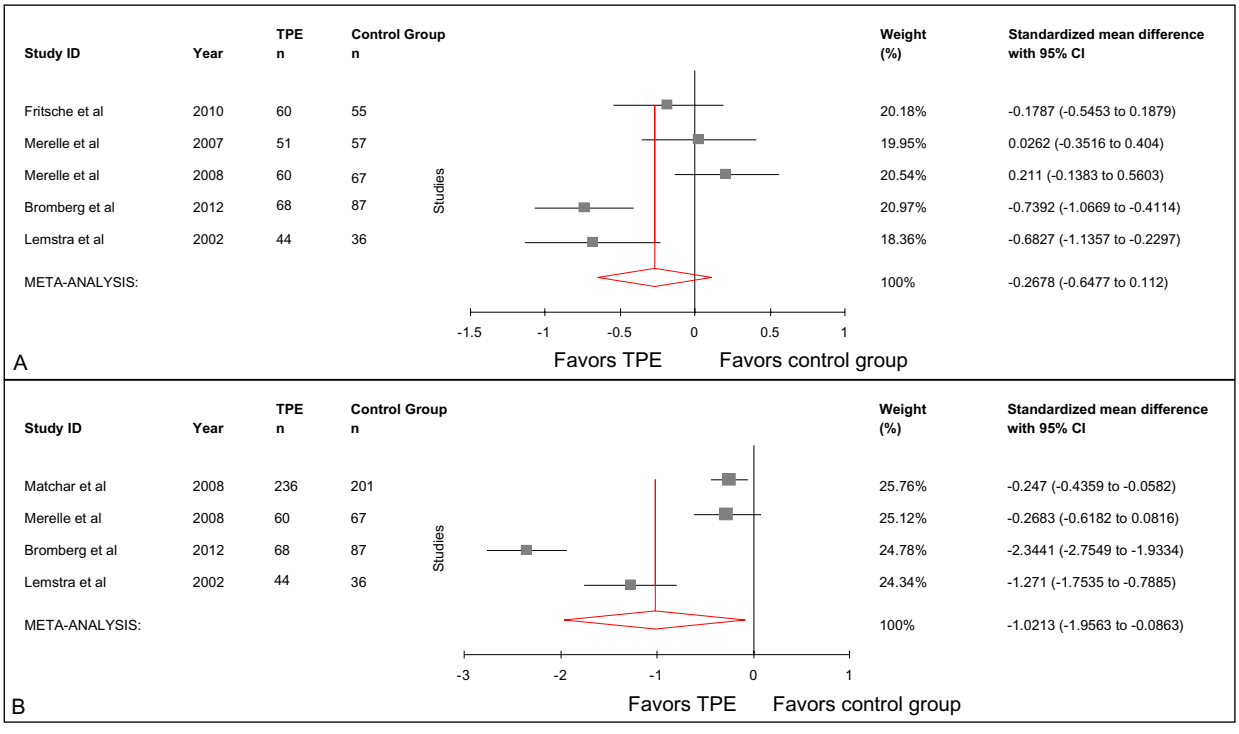

Figure 5 Forest plots of therapeutic patient education (TPE) vs control group effect on headache disability. (A) short term; (B) intermediate term.

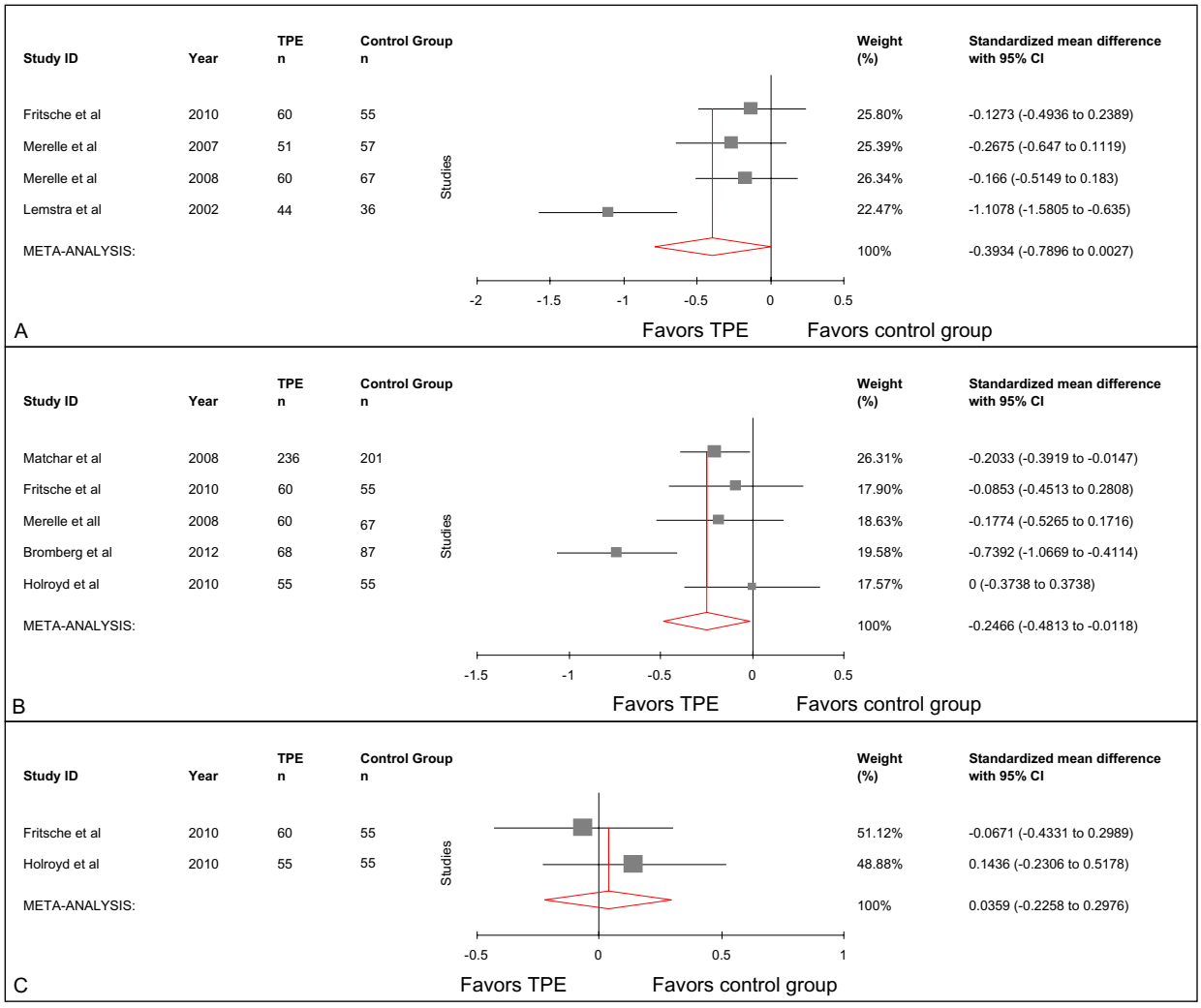

Figure 6 Forest plots of therapeutic patient education (TPE) vs control group effect on headache frequency. (A) short term; (B) intermediate term; and (C) long term.

some mediators of self-efficacy and determine the effects of behavioral treatment on the quality of life [47].

Most of the published reports on migraines investigate the frequency of headaches, MIDAS, locus of control, self-efficacy, quality of life, and depressive symptoms. Five aspects regarding variables of the main analysis of the present study are discussed below.

Depressive Symptoms

In the present study, there were no indications that TPE reduced depressive symptoms. However, it is known that there are frequent symptoms in migraine patients in addition to those experienced by those with chronic primary headaches [50]. Unlike in our analysis, in another meta-analysis, TPE was effective for elevated depressive symptoms in other chronic condition (e.g., for cancer patients) [51]. It is possible that the presence or absence of pain may explain the difference between both studies. Moreover, lacking knowledge of the baseline of pretreatment scores for the measures of depressive symptoms leave us thinking whether the problem was the lack of treatment effect or a floor effect where it is difficult to reduce the patient's symptoms significantly. Then, we must take into account that a possible floor effect could be in operation.

There are available several evidence based on psychological treatments to cope with depression, it probably referral high depressed migraine patients to them.

Finally, although there are numerous studies linking migraine with depression [52–54], and TPE seems to be an effective tool for decreasing the symptoms of depression [55], according to our results, TPE does not have much impact. This was unexpected as depression and anxiety are regarded as the most important psychosocial factors in episodic migraines becoming chronic [56], and

we thought that TPE would be effective. However, it is interesting to note that the isolated symptoms of depression that are often comorbid with migraine are different from major depression, where symptoms occur with greater intensity.

Quality of Life

It should be emphasized that in our meta-analysis, it was revealed that TPE improved the quality of life at the intermediate term. Additionally, all articles that analyzed this variable were of high methodological quality. This concept reflecting concern with the modification and enhancement of life attributes, for example, physical, political, moral and social environment; the overall condition of a human life [57]. Similar to the conclusions that we reached, Nash et al. concluded that cognitive-behavioral treatment for chronic headache sufferers could improve quality of life [58]. It should be taken into account that one of the main predictors for the development chronic migraine is the damage to the quality of life [59].

Self-Efficacy

In social cognitive theory, self-efficacy has been considered fundamental for obtaining a change in behavior [60,61] and has been regarded as an important factor mediating the outcome of headaches in behavioral studies [62]. Nevertheless, the effectiveness of TPE to increase self-efficacy in patients with migraine in the short term or intermediate term has not been observed. Other studies that have examined changes in headache self-efficacy using psychological treatment of migraine patients have suggested that headache self-efficacy increases substantially with cognitive behavioral therapy [16,63]. However, these studies had some limitations; studies without control groups cannot determine whether headache self-efficacy changes were due to intervention. The results of psychological variables in Mérelle's studies significantly changed during the short term and maintained the results up to 6 months in the internal locus of control, chance locus of control, and self-efficacy [29,30]. With good quality studies, Mérelle et al. in 2007 and Bromberg et al. in 2012 noted improvements in self-efficacy in migraine patients after receiving TPE [29,38]. We observed a non-significant trend in this outcome variable in the short term and intermediate term ($P = 0.07$ and $P = 0.05$, respectively). These results are also supported by other studies, which show significant improvements in other variables, such as pain acceptance, pain catastrophizing, improved psychological distress, patient global impression of change, and positive pain coping strategies after behavioral interventions [38,42]. Some interesting correlations were obtained by Seng et al., who observed that patients with high baseline chance locus of control scores exhibited a larger increase in self-efficacy scores than participants with low baseline chance scores, and subjects in the TPE group with low baseline internal locus of control exhibited larger increases in self-efficacy scale scores [34]. However, the quality of this study was poor and had many limitations. We give some value to false beliefs and their relationship with self-efficacy improvements, considering that this fact seems to be important for the patient's recovery.

Headache Disability

Intermediate-term improvements were found in headache disability when patients were treated with TPE. Disabilities associated with migraines are strictly related to its severity. Some areas remain functioning, such as communication, mobility, self-care, society activities, or relationships, whereas others are particularly affected [64]. An avoidance-based lifestyle may be extremely stressful, and this stress may produce chronic migraines and disability [65].

In this work, three of the studies examined at intermediate term were high-quality studies and showed the most significant results of TPE in reducing disability in patients with migraines [36,38]. Besides TPE, other interventions, such as physical therapy [66,67] or peripheral nerve stimulation, are also able to reduce disability in those complex treatment patients [68,69]. In this way, some authors suggest that earlier tertiary-level intervention may avoid the complications of migraine that occur in some patients and the increasing costs and utilization of care associated with higher disability [70].

Headache Frequency

Differences in the reduction of headache frequency in the intermediate term have been demonstrated. A good quality study by Bromberg et al. presented the most significant results at the intermediate term [38].

Headache frequency is the main issue for migraine patients and is strongly associated with increasing disability. Therefore, it is known that the combination of TPE and beta-blockers yield greater reduction in the frequency of headaches and days with headaches [37]. It is possible that group interventions, as proposed by Lemstra et al., may be useful for patients as people tend to mirror themselves on the others improving headache frequency, intensity and duration, quality of life, pain related disability, and depressive symptoms [36].

It is clear that improvements in disability, quality of life, and frequency of headaches were occurred in the intermediate term, but not in the short term. It might be too ambitious to aim for a significant decrease in these factors immediately after the TPE due to the participants, as they may still be in the process of learning to adapt their lifestyle. According to the process of learning and memory, necessary time is required to consolidate the information received. The studies of Fuster and Alexander (published from 1971 and later) support the idea of memory consolidating in the intermediate/long term [71,72].

It is worth noting that this is the first meta-analysis that collected information about the clinical effectiveness of TPE for migraine and chronic migraine patients.

Limitations

This study has several limitations. First, our meta-analysis did not have enough data to make long-term statistical evaluations. Second, only eight of 14 studies showed acceptable methodological quality, whereas the other six papers had five points on the Delphi scale. It must be noted that two of the nine articles selected for the meta-analysis obtained low methodological quality scores, which may have distorted the results from the systematic reviews and meta-analyses. Third, the research in PsychINFO database could lead to bias because retrieves unpublished dissertations from North America and excludes the rest of dissertations.

Additionally, there is a lack of information from gray literature, which was not examined, and includes Conference Papers Index, Dissertation Abstracts, or System for Information on Grey Literature in Europe. Fourth, the blinded intervention status was not considered to be possible in some studies, and it is possible that there were variations in the results due to special attention and interest received by different groups (known as Hawthorne effect). Undoubtedly, the use of blinding processes is of great importance in the development of high-quality clinical trials. Indeed, not using this system may result in certain studies not reaching a sufficient level of evaluation quality. However, currently, there is much controversy on this topic between different researchers in the field of psychology. When viewed from a behavioral point of view, some authors say that it is not necessary to blind patients or therapists because they are actively involved in the acquisition of skills and not just passive. Although it looks complicated, it might be interesting that some quality studies focus their goal in the improvement of blinding strategies in those disciplines. Moreover, the fact that patients were volunteers in a few of the studies could lead to bias. However, according to Rains et al., the use of TPE for headache is mostly either infeasible or simply not possible; only rarely is blinding meaningfully achievable in administration of BBT [73]. The fifth limitation arises from the fact that our research was limited to the English and Spanish languages, and there are some recent papers in German that focus on this issue. The sixth limitation relates to the high attrition rates from Internet-based interventions, which had greater attrition rates than face-to-face intervention. Finally, the statistical heterogeneity was statistically significant for almost all meta-analysis of pain and psychosocial variables, and the subgroup analysis could not provide reasons for heterogeneity and, therefore, should be considered a limitation.

Clinical and Scientific Implications

The aim of the educational approach is to reverse the process of chronification through different treatments that, when combined, enhance their effect. Currently, the combination of pharmacologic and nonpharmacologic approaches is considered the gold standard in the treatment and prevention of migraines [7]. Stanos et al. concluded that the best treatment once chronic migraine is established is a multidisciplinary headache management that includes pharmacological and educational approaches [8].

From a clinical perspective, treating patients with migraines should include TPE. In this way, TPE seems to have a clinical effect at the intermediate term on disability, quality of life, and frequency of migraines. Also, there is a trend of significant improvement in other variables, such as self-efficacy and depressive symptoms. Therefore, this approach should be used for patients with these characteristics. Our results are relevant for evidence-based practice with this important population of migraine sufferers. It is important that the TPE approach should be part of a comprehensive intervention offered to patients.

BBT should include educational and activity-based approaches. The educational approach helps patient understand their symptoms from a neurophysiological point of view. Activity-based approaches help the patient return to normal activities through a thorough explanation and graded exposure or graded exercise to reduce fear and catastrophizing [44].

Indeed, there is a general consensus that BBTs are not equally suitable for all subjects. Patients who are more likely to benefit include those with chronic or refractory migraines, poor coping strategies, and psychiatric comorbidities, such as anxiety and mood disorders. Strong candidates for TPE also include children and adolescents, due to the adverse effects of pharmacological treatments, which may be particularly deleterious during growth [7,74]. It has been shown that there is a risk that an episodic migraine is transformed into chronic migraines, which can commonly be attributed to medication overuse [75]. The difference between receiving basic migraine TPE or not receiving it led to educated patients reduce three times their drug use for acute treatment and were more compliant with prophylactic medication and these permitted to reduce the medication overuse [40]. On the other hand, the attrition rate is something to bear in mind and raises concerns about whether participants dropped out of the study for reasons relating to either the exposure (website) or the outcome (improvement or worsening of migraine or related symptoms). Internet-based cognitive-behavioral interventions are being used increasingly because they are easy to manage. Some studies have a web-based registration for data collection or to have manuals where patients can review the learned concepts [32,39,76]. Internet interventions targeting pain obtained similar effect to those of face-to-face interventions [76]. However, in this case, the main problem was the higher attrition rates when compared with face-to-face intervention in some studies [36,39,77,78]. It is known that patients' adherence to treatment seems to improve with TPE.

From the first education interventions performed years ago to the current BBT, the quality of the intervention itself has been improving. This includes concepts that might help patients to better modify psychological aspects that

may be influencing or maintaining the chronic pain. Education intervention aims are also changing and that is why strategies, such as migraine neurophysiology, coping strategies, relaxation, and active exercise, are included in the behavioral approach.

On the other hand, when an intervention is directed to a patient, he or she needs to become actively involved in the therapy to be able to obtain better results.

Future research should attempt to obtain more specific knowledge about the potential risks and protective factors to better understand the full range of patient's experiences when dealing with chronic pain. We can teach better to obtain better results.

Conclusion

This systematic review and meta-analysis revealed strong evidence for intermediate-term disability improvement and decreased headache frequency after TPE in adult patients with migraines. Moderate evidence was also found indicating improvement in the quality of life, at least in the intermediate term.

More studies with higher methodological quality and using a double blind design when appropriate and feasible are needed. Future studies could investigate the long-term effects of migraine treatments using a longitudinal design.

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