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Effectiveness of high-frequency repetitive transcranial magnetic stimulation (rTMS) in migraine – a systematic review and meta-analysis

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Running head: rTMS in migraine

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ABSTRACT

Objective

To evaluate the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in migraine measured by decrease in pain severity or attack frequency.

Methods

Search at the Cochrane Controlled Trials Register (CENTRAL), Medline (via PubMed), Embase, Cinahl, Web of Science and Scopus. The risk of systematic bias was rated by using the Cochrane domain-based quality assessment tool. A random-effects model was used.

Results

Of 434 identified records, eight RCTs were included in the meta-synthesis. All have employed a high-frequency rTMS targeting the left dorsolateral prefrontal cortex. The risk of systematic bias was low. The difference between rTMS and control groups in frequency of migraine days per month was 8.1 (95% CI 4.8 to 11.4) days in favor of rTMS. Respectively, for intensity of migraine pain (scaled from 0 to 100), this difference was 13.6 (95% CI 5.3 to 21.8) points in favor of rTMS. The heterogeneity was substantial with I^2=86%.

Conclusions

In chronic migraine, rTMS seems to have positive effects on both migraine pain severity and attack frequency compared to sham stimulation. While the effect on pain intensity was probably clinically insignificant, rTMS reduced pain frequency by eight days per month on average.

Keywords:

migraine; chronic pain; TMS; systematic review; meta-analysis

SUMMARY

- What is Known

  While over 30 reviews on the effect of rTMS in migraine have been published, the has been uncertainty regarding the size of that effect.

- What is New

  This meta-analysis of eight RTCs found positive effects of rTMS seems on both pain severity and attack frequency in chronic migraine compared to sham stimulation. While the effect on pain intensity was probably clinically insignificant, rTMS reduced pain frequency by eight days per month on average.

INTRODUCTION

Transcranial magnetic stimulation (TMS) non-invasively generates a magnetic field stimulating the brain cortex by producing brief magnetic pulses. These pulses may affect cortical excitability locally and produce transsynaptic effects distantly. First presented in 1985, the TMS has widely been used for diverse clinical conditions [1]. Repeatedly applying, the TMS pulses is termed repetitive TMS (rTMS). It is believed that the rTMS may affect the activity of cortical and subcortical brain structures related to pain modulation and processing. It may also reduce chronic pain by inhibiting neural pathways at a spinal level [2]. While the TMS is still especially popular in treatment of psychiatric disorders, there have been growing interest in the TMS effects on neurologic conditions and pain syndromes like neuropathic pain, fibromyalgia and complex regional pain syndrome (CRPS) [2-9]. The rTMS has been considered a safe method by all previous reviews.

For the past three decades, TMS has been used as an adjuvant therapy of migraine in situations when medication achieves only suboptimal effect [10 11]. By applying rapidly varied magnetic field, repetitive TMS (rTMS) induces weak electric field in the brain tissue. While the exact mechanism of rTMS in migraine has been debated, the interest towards this treatment method has been substantial. During the last two decades, over 30 reviews on the topic have been published [10 12-22].

While previous reviews have usually concluded that rTMS is effective in treating migraine, there has been uncertainty regarding the size of that effect in migraine prophylaxis and attacks' alleviation. A single meta-analysis conducted on the subject has concluded that rTMS might be efficient to treat migraine attack but inefficient to deal with chronic migraine [18]. That meta-analysis has been limited to five trials. The effects of rTMS have been marginally significant for migraine with aura – odds ratio (OR) of 2.3 (95% CI 1.2 to 4.5) and insignificant for chronic migraine – OR 2.9 (95% CI 0.7 to 12.2). In that study, one of the included trials, responsible for the biggest analytical weight of 37%, had employed a single-pulse TMS instead of rTMS [23], which left the results and conclusions dubious.

73 The objective was to evaluate the effectiveness of rTMS in migraine measured by decrease in pain

74 severity or attack frequency.

METHODS

Data sources and search

Criteria for considering studies for this review were based on PICO (Population, Intervention, Comparison, Outcome):

- Patients and trials: Adults with migraine. Excluding psychiatric disorders. Study design – randomized controlled studies. Abstract available, published in English, no time restrictions.
- Intervention: Repetitive transcranial magnetic stimulation (rTMS).
- Comparison: Placebo or sham
- Outcome: Any quantitative outcome regarding pain intensity or its frequency

Cochrane Controlled Trials Register (CENTRAL), Medline (via PubMed), Embase, Cinahl, Web of Science and Scopus databases were searched in April 2021. The search clauses are presented in Table 1. In order to avoid missing relevant studies, the use of limits was restricted and further selection was conducted manually. The references of identified articles and reviews were also checked for relevancy. The review protocol, registered on Prospero database, is available on demand from the corresponding author. This study conforms to all PRISMA guidelines and reports the required information accordingly (see Supplementary Checklist).

Study selection

Two independent reviewers screened titles and abstracts of articles and assessed full texts of potentially relevant studies, and rated the risk of systematic bias of the included trials (Fig 1). Disagreements between reviewers were resolved by consensus.

Data extraction and assessment of risk of systematic bias

Data needed for meta-analysis were extracted from the included trials using a standardized form based on recommendations by the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, part 7.6 9 [24]. The extraction form contained i.e., study year, country, group size, gender

and age distributions, inclusion and exclusion criteria, follow-up, main outcome measures and main results.

The risk of systematic bias of the included trials was rated by using the Cochrane domain-based quality assessment tool [25]. Each study was rated as having 'low', 'high', or 'unclear' risk of systematic bias in seven domains. Domains were assessed in the following sequence: 1) selection bias (randomized sequence generation and allocation concealment); 2) allocation concealment; 3) performance bias (blinding of participants and personnel); 4) detection bias (blinding of outcome assessment); 5) attrition bias (incomplete outcome data e.g., due to dropouts); 6) reporting bias (selective reporting); and 7) other sources of bias. Disagreements between the reviewers were resolved by consensus or by the third reviewer.

Data synthesis and analysis

The test for heterogeneity was conducted using the Q test considering heterogeneity being present if Q was greater than the degree of freedom (number of studies – 1). The I^2 statistic described the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A random-effects model was used if the heterogeneity was present. The results were accompanied by 95% confidence intervals (95% CIs). A weighted mean difference (WMD) between groups in change of mean estimates was calculated for each included study and for the pooled sample. Two types of reported continuous data were entered in the model: a) pre/post mean estimates and standard deviations and b) mean changes in outcomes along with standard deviations. As the correlation between pre- and post-estimates within groups was not reported, the coefficient of pre/post correlation was set at 0.6. The sensitivity tests included setting pre/post correlation coefficient at 0.0 and 0.8 and by removing one study at a time assessing the consequence of that removal on a pooled estimate. The risk of publication bias was assessed graphically by using a funnel plot and numerically by employing the Egger's test of significance. All the calculations for the meta-

123 analysis were performed using the Comprehensive Meta-Analysis CMA software, Version 3.0,
124 available from www.meta-analysis.com.

RESULTS

Of 434 identified records, eight RCTs were included in the meta-synthesis. The group size varied from six to 50 for rTMS and from five to 50 for shame (Table 2). All the samples were predominated by women – from 64% up to 100%. The patients were relatively young and the age varied between 31 and 47 years. The duration of follow-up varied from immediate measurement after the last session up to two months. The intensity of rTMS varied between three and 12 sessions and the duration of intervention from three days to eight weeks. All of the included RCTs have employed a high-frequency rTMS targeting the left dorsolateral prefrontal cortex (DLPFC). All but one study included patients with chronic migraine only. The study by AbdElkader et al. included patients with chronic daily headaches together with migraine. All eight RCTs have concluded that rTMS is effective treatment approach for migraine. The frequency and doses of rTMS varied widely from 1 Hz to 20 HZ and from 600 to 1,500 pulses per session (Table 3). The rates of drop-outs were low. The inclusion criteria were similar for all the studies with greater diversity in exclusion criteria especially concerning the presence of depression. Of the included studies, three have explicitly excluded patients with depression [26-28] and one study has reported absence of patients with clinical depression [29]. Additionally, three RCTs have excluded patients with severe psychiatric comorbidity [30-32]. One study has not mentioned the presence or absence of psychiatric disorders [33].

The risk of systematic bias was low for seven out of eight studies and unclear for one (Table 4). Pooling eight RCTs with 166 patients in rTMS groups and 173 patients in sham groups, the pooled difference in frequency of migraine days per month was -8.09 (95% CI -11.4 to -4.79) days in favor of rTMS (Figure 2). The heterogeneity was substantial with Q=56 and degree of freedom=7, I^2=87%. Pooling six RCTs with 136 patients in rTMS groups and 121 patients in sham groups, the pooled difference in intensity of migraine pain (scaled from 0 to 100) was -13.56 (95% CI -21.8 to -5.32) points in favor of rTMS (Figure 3). The heterogeneity was substantial with Q=36 and degree of freedom=5, I^2=86%.

When setting pre/post correlation to 0.8, the pooled difference in intensity of migraine pain did not change much: -13.76 (95% CI -22.13 to -5.39) points in favor of rTMS. Respectively, the pooled difference in frequency of migraine days per month was -8.10 (95% CI -11.38 to -4.81) days in favor of rTMS. Similarly, when setting pre/post correlation at 0.0, the pooled estimates were -12.76 (-20.67 to -4.86) and -8.09 (95% CI -11.40 to -4.77), respectively. Also, when removing one study at a time, both pooled estimates remained significant in favor of rTMS (Supplemental Digital Content 1). There was not a significant risk of publication bias – the Egger's test 2-tailed p-value 0.820 and 95% CI -6.06 to 5.0 (Figure 4).

DISCUSSION

This meta-analysis pooled the data reported by eight RCTs. The overall risk of systematic bias was considered low. The included RCTs were predominated by women and the average age ranged between 30 and 50 years. Meta-analyses were performed for pain severity and for the number of days with headache during the past month. Both analyses resulted in statistically significant pooled estimates in favor of rTMS over sham stimulation. The pooled effect for pain intensity was below the minimal clinically important difference for pain visual analogue scale, which is usually placed around $\geq$20 out of 100 points. The pooled effect for pain frequency was eight days with lower 95% confidence limit of five days. Both analyses showed substantial heterogeneity, most of which came from heterogeneity in true effect (I^2 statistic 90%).

When generalizing the results, it should be kept in mind that meta-analysis is always approximation. Observed substantial variation in true effect points at the probable substantial differences in RTCs' samples and rTMS intensity. The age distribution of the pooled sample may weaken inferences amongst people who are younger than 30 or older than 50 years. The samples were small – five out of eight studies have applied rTMS at less than 20 patients. Only half of the studies have mentioned the absence of depression amongst patients' comorbidities. The presence of depression might affect both the genuine effect of rTMS on migraine and the psychometric properties of the outcome scales used by the original research. The publication bias was assessed even if there were less than 10 RTCs available. While the number of studies was close to 10, a cut-off recommended by the Cochrane, analysis on a such a small number of studies might result in a situation when the risk of publication bias is not seen even if there is one and vice versa.

The results are in line with the majority of previous reviews on the subject, which have reported positive effects of rTMS in migraine [10 12-22]. Instead, the results were controversial to a previous meta-analysis that reported on effectiveness of rTMS in dealing with migraine attack but found no evidence on rTMS effectiveness in chronic migraine [18]. This difference may be explained by the fact that that

previous meta-analysis was smaller (five versus eight RCTs) and mixed rTMS with a very different form of TMS – single-pulse TMS. A single-pulse TMS has usually been used not for the purpose of treatment but rather as a diagnostic or research tool to assist in localizing a lesion and helping to characterize the nature of that lesion [34].

Further research may focus on the safety and cost-effectiveness of rTMS that was left outside the scope of the present review. While previous studies have found rTMS to be a safe procedure, a comprehensive meta-analysis on the rTMS safety profile is needed. The cost-effectiveness of rTMS in migraine should be established in different settings. Further research on bigger samples may reveal the dose-dependent effects of rTMS as well as regression coefficients of that effects by the time since the last intervention session.

Conclusions

In chronic migraine, rTMS seems to have positive effects on both migraine pain severity and attack frequency compared to sham stimulation. While the effect on pain intensity was probably clinically insignificant, rTMS reduced pain frequency by eight days per month on average.

197 Table 1. Search strategy

Database	Search strategy
Medline	("Transcranial Magnetic Stimulation"[Mesh] OR tms[TI] OR rtms[TI] OR "transcranial magnetic"[TI] OR "magnetic stimulation"[TI]) AND ("Migraine Disorders"[Mesh] OR "Headache"[Mesh] OR migraine[TI] OR headache*[TI] OR "head pain"[TI] OR Cephalodynia*[TI] OR Cephalalgia*[TI] OR "Cranial Pain" [TI]) AND Randomized Controlled Trial[ptyp] AND hasabstract[text] AND English[lang]
Embase	('transcranial magnetic stimulation'/exp OR tms:ti OR rtms:ti OR 'transcranial magnetic':ti OR 'magnetic stimulation':ti) AND ('headache and facial pain'/exp OR migraine:ti OR migraine:ti OR migraine:ti OR headache*:ti OR "head pain":ti OR Cephalodynia*:ti OR Cephalalgia*:ti OR "Cranial Pain":ti) AND 'article'/it AND 'randomized controlled trial'/de
Central	([mh "Headache Disorders, Primary"] OR [mh "Headache"] OR migraine:ti OR migraine:ti OR migraine:ti OR headache*:ti OR "head pain":ti OR Cephalodynia*:ti OR Cephalalgia*:ti OR "Cranial Pain":ti) AND ([mh "Transcranial Magnetic Stimulation"] OR tms:ti OR rtms:ti OR "transcranial magnetic":ti OR "magnetic stimulation":ti) in Trials
Scopus	(TITLE-ABS-KEY (tms) OR TITLE-ABS-KEY("transcranial magnetic") OR TITLE-ABS-KEY ("magnetic stimulation")) AND TITLE-ABS-KEY(migraine) AND TITLE-ABS-KEY(randomi*) AND TITLE-ABS-KEY(control*) AND (LIMIT-TO (DOCTYPE, "ar")) AND LIMIT-TO(SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA, "NEUR") OR LIMIT-TO (SUBJAREA , "PSYC") OR LIMIT-TO (SUBJAREA, "HEAL")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SRCTYPE ,"j"))
Web of Science	(TS=tms OR TI=tms OR TS=rtms OR TI=rtms OR TS="transcranial magnetic" OR TI="transcranial magnetic" OR TS="magnetic stimulation" OR TI="magnetic stimulation") AND (TS=migraine OR TI=migraine) AND (TI=rct* OR TS=rct* OR TI=randomi* OR TS=randomi*) Refined by: LANGUAGES: (ENGLISH) AND DOCUMENT TYPES: (ARTICLE)
Cinahl	((MH "Transcranial Magnetic Stimulation") AND (MH "Migraine")) OR ((TI "tms") OR (AB "tms") OR (TI "Transcranial Magnetic") OR (AB "Transcranial Magnetic") OR (TI "Magnetic Stimulation") OR (AB "Magnetic Stimulation")) AND ((TI "migraine") OR (AB "migraine")) AND ((TI "randomi*" OR (AB "randomi*"))

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Table 2. Main characteristic of the included studies.

Study, year, country	N, cases / controls	Women, %	Age, years	Follow-up	rTMS intensity
AbdElkader 2021, Egypt[26]	16/11	81/82	34/34	Last session	12 sessions/2 weeks
Brighina 2004, Italy[27]	6/5	64	47	2 months	12 sessions/2 weeks
Conforto 2014, Brazil[29]	9/9	100/100	41/36	Last session	23 sessions/8 weeks
Kumar 2020, India[28]	10/10	60/50	33/33	1 month	10 sessions/2 weeks
Misra 2013, India[33]	50/50	88/88	36/35	1 month	3 sessions
Misra 2017, India[30]	24/47	75/81	35/34	1 month	3 sessions
Teepker 2010, Germany[31]	14/13	93/69	31/41	2 months	5 sessions
Todorov 2020, Bulgaria[32]	37/28	81/79	39/37	2 months	5 sessions

205 Table 3. Risk of systematic bias

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome measurement (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other	Overall risk
AbdElkader 2021[26]	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Brighina 2004[27]	Low	Unclear	Low	Low	Low	Low	Low	Low
Conforto 2014[29]	Low	Low	Low	Low	Low	Low	Low	Low
Kumar 2020[28]	Low	Low	Low	Low	Low	Low	Low	Low
Misra 2013[33]	Low	Low	Low	High	Low	Low	Low	Low
Misra 2017[30]	Low	Low	Low	High	Low	Low	Low	Low
Teepker 2010[31]	Unclear	Unclear	Low	High	Low	Low	Low	Low
Todorov 2020[32]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

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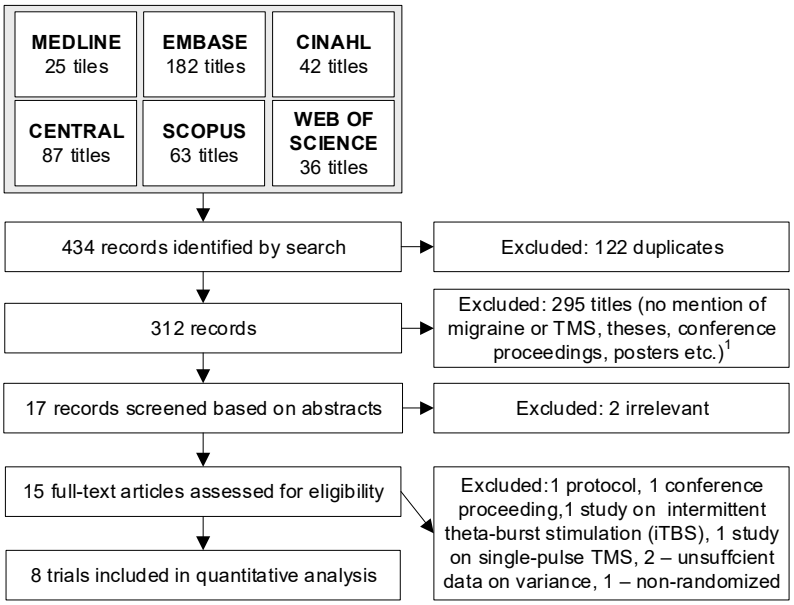
208 Figure 1. Search flow



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210 [1] Exclusion performed using the filtering engine of Endnote® software and a pre-agreed list of
211 excluding terms

212 Figure 2. Forest plot – frequency of migraine days per month

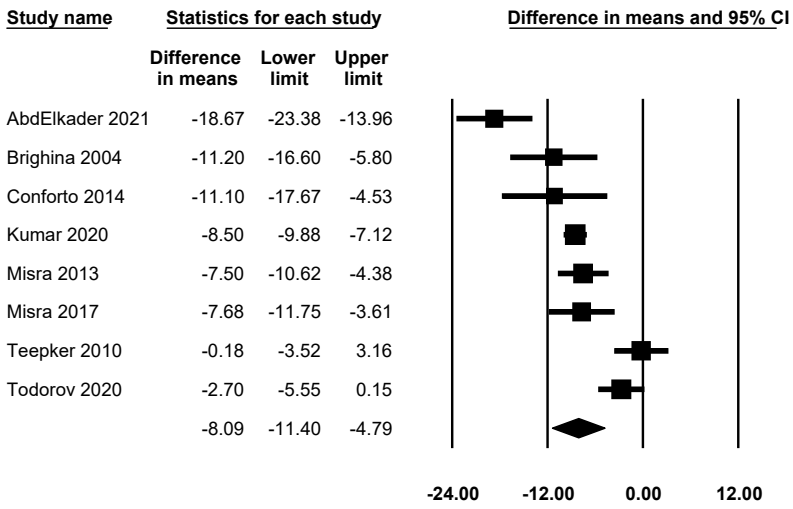

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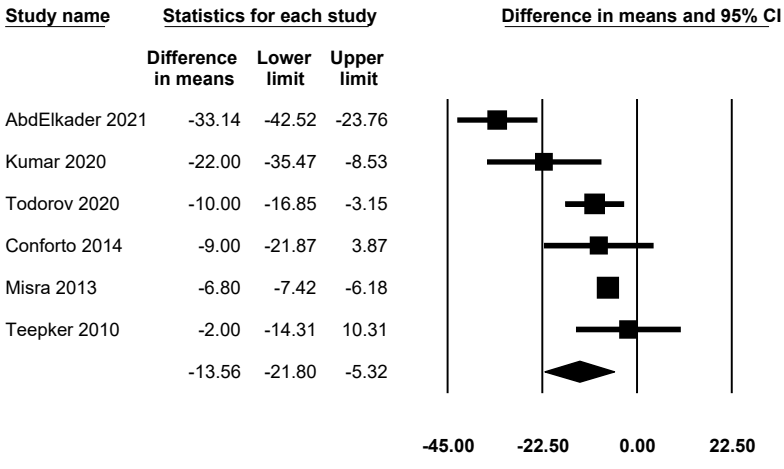
Figure 3. Forest plot – intensity of migraine pain (converted to 0 – 100 visual analogue scale units)



218 Figure 4. Difference in means with one study removed

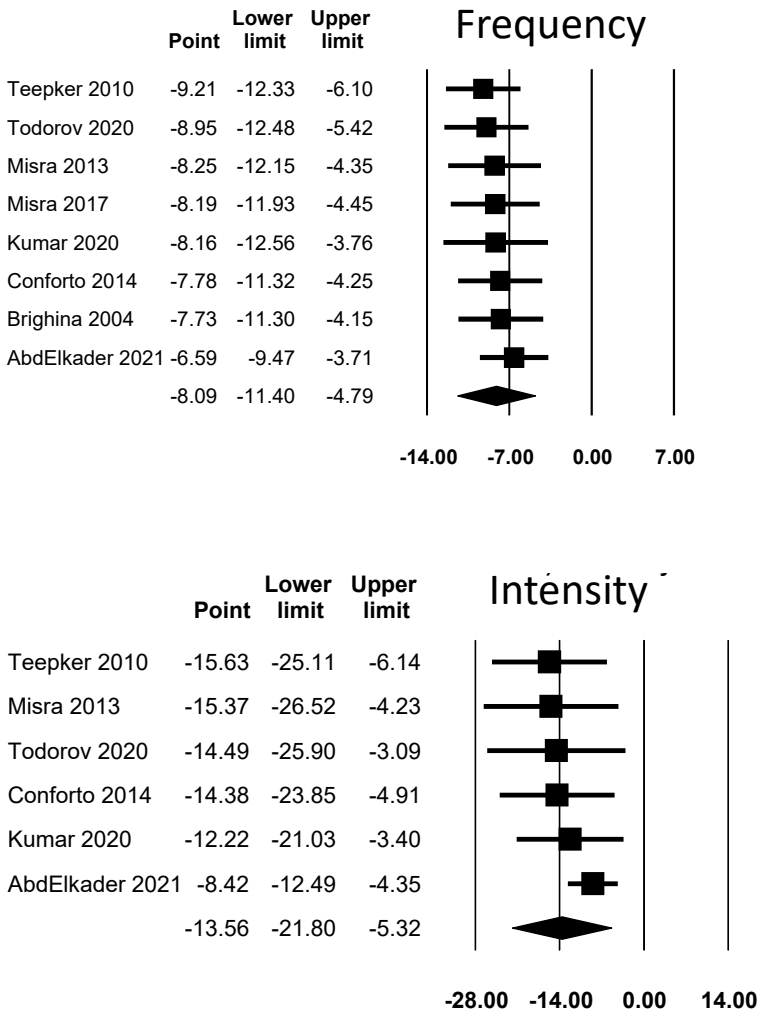


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FIGURE LEGENDS

Figure 1. Search flow

[1] Exclusion performed using the filtering engine of Endnote® software and a pre-agreed list of excluding terms

Figure 2. Forest plot – frequency of migraine days per month

Figure 3. Forest plot – intensity of migraine pain (converted to 0 – 100 visual analogue scale units)

Figure 4. Risk of publication bias. Funnel plot of precision by difference in means.

Supplemental Digital Content 1. Sensitivity analysis – effect of removing one study at a time on a pooled difference in means