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REVIEW ARTICLE

Effects of Anti-CGRP monoclonal antibodies for episodic and chronic migraine- on migraine characteristics, disability, impact and quality of life beyond 3 months of treatment: A Systematic review and Meta-analysis

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ABSTRACT

Objective: At the time of this study, there were no systematic reviews to evaluate phase III RCT's of CGRP monoclonal antibodies on migraine characteristics, migraine related disability, impact and quality of life after 3 months. This meta-analysis is aimed to systematically review available data on the effect of anti-CGRP monoclonal antibodies on migraine characteristics, migraine related disability, impact and quality of life after 3 months of treatment. **Methods:** A systematic literature search was performed to identify phase III randomized-controlled trials on anti-GCRP monoclonal antibodies on migraine prevention. The primary outcome was the change in migraine characteristics monthly migraine days, monthly acute migraine specific medication days and 50 % responder rate. Secondary outcome was change in patient functioning and quality of life assessed through Migraine- Specific Quality of Life Questionnaire (MSQ) Migraine Disability Assessment Questionnaire (MIDAS), Headache Impact test (HIT -6) and Migraine Physical Function Impact Diary (MPFID). We calculated the mean difference (MD), standard deviation (SD), and 95 % confidence intervals for the outcomes. **Results:** Four trials showed effect of anti-CGRP monoclonal antibodies on migraine characteristics and quality of life after 3 months, named EVOLVE 1, EVOLVE 2, STRIVE, HALO_LTS. These trials present data on galcanezumab (120mg, 240 mg, monthly), erenumab (70 mg, 140 mg, monthly) and fremanezumab (225 mg, 675 mg, quarterly, monthly), respectively. The trials included 4625 patients with migraine, 3515 with episodic migraine and 1110 with chronic migraine. Just three of them were included in the meta-analysis because HALO_LTS had no placebo-controlled group. In the included trials, anti-CGRP monoclonal antibodies (galcanezumab and erenumab) were superior to placebo for MMDs, 50% reduction rate, MSQ_RFR and MIDAS beyond a 3-month treatment period. **Conclusion:** Galcanezumab and erenumab demonstrated improvement in migraine characteristics and quality of life above and beyond those seen with placebo after 3-months of treatment in episodic migraine, providing placebo-controlled evidence. There is a need to perform good RCT's to evaluate the efficacy of all anti-CGRP monoclonal antibodies on migraine characteristics, impact and quality of life on longer time frame (beyond 12 months) and on different migraine populations such as chronic migraine, medication overuse headache and refractory migraine.

Keywords: CGRP; Antibodies; Migraine; Disability

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1 INTRODUCTION

Migraine is one of the most common type of primary headache and is considered as the second cause of living with disability and the first cause of disability in people under 50 years of age[1,2]. Based on Global Burden of Disease (GBD) Survey, near 1·04 billion people all over the world suffer from migraine[3,4].

It affects women more than men and is associated with a wide range of psychological problems such as depression, anxiety, poor sleep, decreased leisure and social activities which will result in decreased quality of life and social withdrawal[5–8]. Based on the International Classification of Headache Disorders (ICHD-3), migraine could be classified as chronic migraine (CM) and episodic migraine (EM) (CM: 15 days/month of which at least in eight days the headache fulfills the diagnostic criteria for migraine with or without aura for 3 months and EM. less than 15 days/months)[9]. Patients with CM experience more disability and comorbidities compared to EM and CM is usually associated with medication overuse headache (MOH)[10].

Migraine treatment has two parts: abortive and preventive. The goal of abortive treatment is to abort the acute attack while the goal of preventive treatment is to decrease migraine intensity, frequency, outpatient and emergency department visits and total cost using oral or injectable medications, preventing migraine triggers and lifestyle modifications[11]. Although around 39% of migraine patients need preventive medications, only 13% receive preventive agents[12].

The exact duration of preventive medication is not well-defined and is variable. A wide range of medications are usually administered such as: beta-blockers, antiepileptic drugs, calcium channel blockers, antidepressants, nutraceuticals, botulinum toxin and calcitonin gene related peptide (CGRPs) monoclonal antibodies (MAbs)[11].

Based on clinical and para-clinical evidence gained during the last three decades, CGRP is understood to play a key role in the pathogenesis of the migraine disease. During last decade monoclonal antibodies against CGRP has been shown to be effective for controlling migraine with particular advantages such as high target specificity, not crossing blood-brain barrier (BBB), 3-6 weeks half-life, and clearance by reticuloendothelial system[13]. As they are large molecules, they need parenteral administration and could not cross the BBB, so central nervous system side effects are less[13]. As the half-life of these antibodies are 3-6 weeks, they could be administered monthly or every three months[13]. Up to now, four anti - CGRP monoclonal antibodies are introduced which are different regarding their route of administration, bioavailability, their IgG subtype, and the presence of murine proteins. Eptinezumab (ALD403), Galcanezumab (LY2951742), and Fremanezumab (TEV-48125) target the CGRP ligand while Erenumab (AMG 334) targets CGRP receptor[13].

Several clinical trials have been conducted to evaluate efficacy and safety of these medications on episodic and chronic migraine, on migraine-related disability, impact and health related quality of life. Galcanezumab (120 mg and 240 mg) has been studied in phase III RCT's on prevention of episodic migraine (EVOLVE 1, EVOLVE 2 and PERSIST-ongoing/NCT 03963232)[14,15], chronic migraine (REGAIN)[16] and treatment resistant migraine (CONQUER/NCT 03559257). Eptinezumab (30 mg, 100 mg, 300 mg) has been studied in phase III RCT's on prevention of episodic migraine (PROMISE 1)[17], chronic migraine (PROMISE 2)[18] and acute migraine treatment (RELIEF/NCT 04152083). Fremanezumab (225 mg, 675 mg) has been studied in phase III RCT's on prevention of episodic migraine (HALO EM/NCT 02621931), chronic migraine (HALO CM/NCT 02629861) and both episodic and chronic migraine on longer term (HALO_LTS/NCT 02638103)[19]. Erenumab (70 mg, 140 mg) has been studied in phase III RCT's on prevention of episodic migraine (ARISE, STRIVE, EMPOwER-finished, no results/NCT 03333109)[20,21] with failed treatment (LIBERTY-ongoing/NCT 03096834). Most of these studies had short follow ups up to 12 weeks and used different tools to measure migraine related disability (MIDAS), impact (HIT-6, MPFID, PGI-S) and health related quality of life (MSQ, SF -36, EuroQoL- 5D).

The aim of the study was to systematically review the available data on the effect of anti-CGRP monoclonal antibodies on migraine characteristics, migraine related disability, impact and quality of life in phase III RCT's after 3 months.

Exploratory literature search revealed that there are some systematic reviews and meta-analysis on RCT's that analyze the efficacy, safety and tolerability of anti-CGRP monoclonal antibodies on migraine prophylactic treatment: on episodic migraine[22,23], chronic migraine[24], episodic and chronic migraine[25,26], with galcanezumab[27–30], fremanezumab[31] or erenumab[32] but just one systematic review analyzed the migraine related disability, impact and health related quality of life in migraine patients treated with galcanezumab[27]. One systematic review and meta- analysis that present data on anti- CGRP monoclonal antibodies after 3 months but include phase 2 RCT's[26]. At the time of writing this article, there were no systematic reviews to evaluate phase III RCT's of CGRP monoclonal antibodies on migraine characteristics, migraine related disability, impact and quality of life after 3 months.

2 METHODOLOGY

2.1 Search strategy

The meta-analysis and systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Two groups of reviewers (Group 1: OG, PT, MP, JB & Group 2: NY, AR, NS) independently searched PubMed, ClinicalTrial.gov, Embase, Google Scholar, Cochrane Library and Web of Science for RCT's.

The search strategy was developed according to research question on PICOS format: Population - patients with chronic and episodic migraine, Intervention-anti-CGRP monoclonal antibodies, Comparator-placebo, Outcome-migraine characteristics and quality of life, Study type-Randomized Controlled Trial design (RCT) and time frame of the treatment arm-more than 3 months. The search terms were: 'migraine', 'episodic migraine', 'chronic migraine', 'CGRP monoclonal antibodies', 'erenumab', 'galcanezumab', 'fremanezumab', 'eptinezumab', 'LY2951742', 'ALD-403', 'LBP-101/TEV-48125', 'AMG 334', 'phase III trial', 'RCT', 'QoL'. The searches were limited to human studies published in any language from inception of the databases to 25th September, 2020.

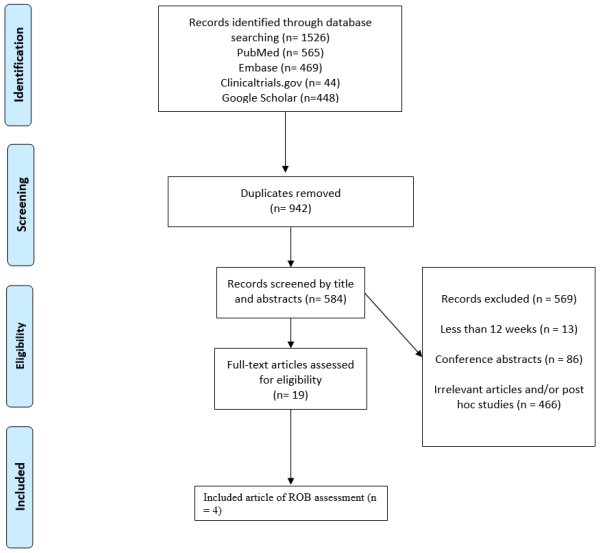

Fig. 1: Flow diagram of study selection

2.2 *Inclusion and exclusion criteria:*

The articles were included in the systematic review if they met the following criteria: (1) double blinded, randomized controlled trials (RCT's) evaluating the efficacy of anti-CGRP monoclonal antibodies for episodic and chronic migraine versus placebo, any form, dose or administration methods as per treatment group and control group respectively, (2) RCT's conducted on adult population of both sexes, (3) presence of outcomes like migraine characteristics and quality of life after 3 months and (4) no restriction on publication status. Studies were excluded when one of the following situations occurs: (1) RCT's with intervention arm of less than 6 months duration, (2) CGRP small molecule antagonists, (3) Non-double blinded RCT's, (4) no outcomes of migraine-related disability, impact and health related quality of life.

2.3 *Study selection*

All references found by all the authors from the databases, were pooled, the duplicates were removed. The relevant studies were reviewed to determine possible qualification. Studies were screened according to title and abstract to determine eligibility by two authors (OG & NY). In the second step the full text of the qualified studies was assessed. In case of a disagreement, 3rd independent author JS's judgement was used to make a decision. The flow chart of the included studies is presented in Figure 1.

3 RISK OF BIAS IN INDIVIDUAL STUDIES

The quality of the included studies was assessed independently by two investigators (OG and NY) using the 7-item criteria in Review Manager Software version 5.4 provided by the Cochrane Collaboration. The 7-item criteria mainly contained: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting and (7) other bias. Each item involved assigning a judgment of high, low, or unclear risk of material bias. Detailed criteria for making judgments about the risk of bias from each of the items in the tool are available in the Cochrane Handbook. Discrepancies were reconciled by discussing with the corresponding author PT. The risk of bias summary is presented in Figure 2.

Fig. 2: The risk of bias summary

3.1 Outcomes

- Efficacy evaluation on migraine characteristics: Monthly headache days (MHD's), Monthly migraine days (MMD's), monthly acute migraine specific medication days (MSMD's), headache days of at least moderate severity, headache days of any severity, use of acute headache medication, use of migraine specific acute headache medication, 50%, 75%, 100% responder rate.
- Functional measurement- migraine - related disability, impact and health related quality of life was measured with MIDAS (Migraine Disability Assessment Questionnaire), HIT-6 (Headache Impact Test), MSQ (Migraine-Specific Quality of Life Questionnaire), PGI-S (Patient Global Impression of Severity), MPFID-Migraine Physical Function Impact Diary.

4 DATA ANALYSIS

Continuous outcomes were analyzed using mean differences (MD) and 95% confidence intervals (CI), dichotomous outcomes-using relative risk and 95% CI. Chi-square test was used to assess the statistical heterogeneity. If I^2 < 50% was used fixed-affect model, I^2 >50% heterogeneity was regarded as unacceptable and a random-affect model was used. All data analyses were performed using Review Manager 5.3.

5 RESULTS

5.1 Selection and characteristics of studies

After repeated filtering in the systematic review was included 4 RCT's that present the outcomes on migraine characteristics, migraine-related disability, impact and health related quality of life beyond the 3-month period: EVOLVE 1 and EVOLVE 2 on galcanezumab, STRIVE on erenumab and HALO_LTS on fremanezumab. No RCT's on eptinezumab to present data after 3 months were detected. The summary characteristics of the studies are presented in table nr. 1. Baseline patient demographics and disease characteristics are summarized in table nr. 2. The included trials covered 4576 patients with chronic and episodic migraine.

5.2 Efficacy evaluation on migraine characteristics

In the EVOLVE-1 randomized controlled trial, Stauffer et al. randomly assigned 858 patients with episodic migraine into monthly placebo, galcanezumab 120 mg, and galcanezumab 240 mg groups for 6 months and followed up for 4 months after treatment cessation. The mean MHDs reduced 4.7, 4.6 and 2.8 days in 120, 240 and placebo groups. Monthly MHDs with acute medication use decreased -4, -3.8 and -2.2. More than 50% response rate was significantly higher in 120 and 240 mg groups (62.3% and 60.9%) than placebo group (38.6%) as well as 75%, and 100% response rates.

In a phase 3, global, double-blind, 6-month study of patients with episodic migraine (EVOLVE-2 trial), Skljarevski et al. randomized 915 patients to monthly subcutaneous injections of galcanezumab 120 mg (N=231) or 240 mg (N=223) or placebo. The decrease in mean monthly migraine headache days was 4.3, 4.2 and 2.3 in the galcanezumab 120 and 240 mg and placebo groups. Decrease in monthly MHDs ≥50% were reported in 59% and 57% of patients in the galcanezumab 120 and 240 mg groups and 36% in placebo group.

Galcanezumab 120 mg and 240 mg achieved reduction in monthly headache days during treatment, including both patients who received and not received a preventive migraine treatment in the previous 5 years and those with frequent acute medication use. The reduction during 6 months of treatment translates in 8 weeks (EVOLVE1) and 7 weeks (EVOLVE 2) of additional migraine-free days over the course of a year. The treatment effect is rapid and continued through month 6. Treatment with both dose regiments of galcanezumab was associated with decrease in the days of use of acute migraine medications.

In a study which was conducted by Goadsby et al., (STRIVE), long term effects of erenumab were assessed and 955 patients with episodic migraine were randomly assigned into 70 mg, 140 mg and placebo groups for 24 weeks while the mean monthly days with migraine was 8.3 in overall population which was reduced by 3.2, 3.7 and 1.8 days in 70 mg, 140 mg, and placebo group. On the other hand, ≥50% reduction from baseline in migraine days per month was achieved in 43.3%, 50% and 26.6% of 70 mg, 140 mg, and placebo groups. The mean change of the days of use of acute migraine-specific medication per month reduced more in 140mg group (1.6) than 70 mg (1.1) and placebo groups (0.2). Their results could show that long term treatment with erenumab will decrease MMD's more than short term treatment with this medication. Migraine preventive treatment with erenumab resulted in reduction in the frequency of migraine days, use of acute migraine specific medications.

Goadsby, 2020 (STRIVE 1 year)-included 845 patients randomly assign to 70 mg (nr- 421) and 140 mg (nr 424) 24-week dose blinded active treatment phase to complete 52-week study duration. The percentage of patients achieving >50% response at week 52 were higher than for 24 weeks, suggesting that response to treatment may be greater with longer term treatment.

In a recent study conducted by Goadsby et al., (HALO_LTS) which was a multicenter, randomized, double-blind, parallel-group study, 551 patients with CM and 394 with EM received quarterly fremanezumab and 559 with CM and 386 with EM received monthly medication for 52 weeks. Their results showed that reduction of monthly migraine days from baseline to week 52, was -7.2, -8, -5.2, -5.1 in CM quarterly, CM monthly, EM quarterly, EM

monthly, respectively. The reduction of headache days of at least moderate severity was -6.4, -6.8, -4.4, -4.2 in four groups, respectively from baseline to 12 months[19]. This study of long-term efficacy and safety of fremanezumab demonstrated that during the 12 months of treatment, improvement in MMD's, headache days and disability caused by headache were sustained.

5.3 Monthly migraine days (MMD's)

There was notable heterogeneity in the overall results ($P<0.00001$, $I^2 = 99\%$). Studies in our meta-analysis revealed the reduction in MMD's for anti- CGRP monoclonal antibodies (galcanezumab and erenumab) vs. placebo at a statistically significant level (MD -1.82, 95% CI -2.05 to -1.58; participants = 2704; studies = 3; $I^2 = 99\%$) **(fig. 3)**.

5.4 50% responder rate

Compared to placebo group, patients with anti- CGRP monoclonal antibodies treatment (galcanezumab and erenumab) are more likely to present an increase of 50% in responder rates of the reduction from the baseline in MMDs (RD 0.27, 95% CI 0.18 to 0.36; participants = 2685; studies = 3; $I^2 = 83\%$).

5.5 Functional measurement

MSQ (4-week recall period) is a self-administered instrument that address physical and emotional limitations of people with migraine. It consists of 14 items that measures three dimensions: how migraine attacks limit daily social and work- related activities (role function-restrictive MSQ-RFR) and how they prevent these activities (role function-preventive MSQ-RFP) as well as the emotions associated with migraine attacks (MSQ-EF). It is considered reliable, valid and sensitive to changes in migraine effects (Cole, 2007, Rendas-Baum, 2013). Minimally important differences from baseline (individual level, within group) have been established for MSQ-RFR = ±10.9, MSQ-RFP = ±8.3, MSQ-EF= ±12.2.

MPFID-Migraine Physical Function Impact Diary-a patient reported outcome tool to evaluate the benefit of migraine interventions on the average daily impact on patient's impairment and everyday activities.

MIDAS (3 months) and mMIDAS (modified monthly)-4-week recall period to reduce recall bias and improve the accuracy. Assesses absenteeism (complete disability) and presenteeism (reduced participation) in several domains, including work, school, family, social and leisure activities. A higher value is indicative of greater disability: Grade I-little or no disability (0-5), grade II-mild disability (6-10), grade III-moderate disability (11-20), grade IV-severe disability (>21). The instrument is valid and reliable, corelates with clinical judgments on medical care.

HIT-6-(4 week recall period) is a six- item tool that assesses the impact of headache, including the frequency of headache pain severity, headaches limiting daily activity, wanting to lie down when headache is experienced, feeling too tired to work or do daily activities because of headache, feeling fed up or irritated because of headache, and headaches limiting ability to concentrate or work on daily activities.

EVOLVE 1 = Change in PGI-S (Patient Global Impression-Severity) was -1.3 for the placebo group and -1.6 for both 120 mg and 240 mg galcanezumab groups, MSQ R-FR increase was 32.4, 32.1 and 24.7 in three groups respectively.

EVOLVE 2= The reduction of MIDAS total score was -21.2 in 120 mg and -20.2 in 240 mg group in comparison with placebo which was -12. The mean MSQ RF-R (Migraine-Specific Quality of Life Questionnaire Role Function-Restrictive) increased 28.5 and 27 scores in 120, 240 mg groups as well as 19.7 in placebo group[33]. Daily functioning scores (all domains of MSQ) were increased which reflects functional improvement and reduce the migraine related impairment in functioning. Both dose regiments of galcanezumab significantly improved the patient's global impression of severity of disease (PGI-S) relative to placebo.

STRIVE=Patient-reported physical functioning in the study groups were measured using the Migraine Physical Function Impact Diary (MPFID) scores. The reduction in the every-day activity domain score (MPFID-EA) was reported to be 5.5, 5.9 and 3.3 in the 70 mg, 140 mg and placebo groups respectively. Physical impairment domain score (MPFID-PI) was reduced by 4.2 and 4.8 in the erenumab 70 mg and 140 mg groups, compared to 2.4 in the placebo group[34].

HALO_LTS = For assessing headache related disability, HIT-6 questionnaire was administered for CM groups and MIDAS questionnaire for EM groups. The reduction in the HIT-6 score from baseline to 12 months was -7.8 in CM quarterly group and -8.4 in CM monthly group and mean change in MIDAS score during 12 months of treatment was -26.0 for EM quarterly and -27.4 for EM monthly groups.

The summary results of the outcomes measured in the studies are presented.

Anti-CGRP monoclonal antibodies included in the meta-analysis (galcanezumab and erenumab) led to a greater improvement in MSQ_RFR scores compared to placebo (MD 7.15, 95% CI 5.65 to 8.65; participants = 2662; studies = 3; $I^2 = 100\%$) that indicates the reduction in functional impairment.

Anti-CGRP monoclonal antibodies (galcanezumab and erenumab) presented reduction in the MIDAS scores compared to placebo (MD -7.29, 95% CI -9.02 to -5.57; participants = 2704; studies = 3; $I^2 = 99\%$) which indicate improvement in functional disability.

6 DISCUSSION

The systematic review evaluated the availability of phase III RCT's that measure the efficacy of anti-CGRP monoclonal antibodies on migraine prophylaxis, migraine-related disability, impact and health related quality of life beyond the time frame of 3 months. Systematic search revealed that there are a little or no good RCT's that evaluate the migraine characteristics and quality of life after the 3 months period. The suitable RCT's for analysis was on galcanezumab (EVOLVE 1 and EVOLVE 2), erenumab (STRIVE) and fremanezumab (HALO _LTS) but in the last trial the placebo control is missing. The majority of trials examine episodic migraine patients and just HALO_LTS included chronic migraine patients.

All the trials included in the systematic review show good efficacy of anti- CGRP monoclonal antibodies on migraine characteristics after 3 months by reducing monthly migraine days, migraine days with acute migraine-specific medications, monthly headache days, headache days with moderate severity or headache with any severity.

There is a lot of heterogeneity among studies based on the tools that was used to measure migraine-related disability, impact and health related quality of life. The most used was MSQ, MIDAS and HIT-6. Some published post-hoc analysis revealed the effect of anti-CGRP monoclonal antibodies on patient functioning and disability[21,35,36]. However these systematic reviews confirm that anti- CGRP monoclonal antibodies are useful in improving patient functioning, quality of life by reducing the impact of migraine and changing patient's impression on the severity of disease.

The meta-analysis evaluated the efficacy of the galcanezumab and erenumab on migraine treatment, migraine-related disability and quality of life of the patient after 3-month period. Our meta-analysis included 3 phase III RCT's and 2803 patients with episodic migraine treated with galcanezumab and erenumab. According to our results galcanezumab and erenumab was effective for the prevention of the episodic migraine. The use of galcanezumab and erenumab was associated with a reduction in the mean migraine and headache days and increased proportion of 50% responders after 3-month period. Treatment with galcanezumab and erenumab reduced the migraine related disability and quality of life compared to placebo after 3-month period.

To our knowledge, at the time of this study, no other meta-analysis was done on phase III RCT's that evaluate the efficiency of anti- CGRP monoclonal antibodies on migraine prophylaxis, migraine related disability and quality of life after 3-month period.

7 LIMITATIONS

The present systematic review and meta - analysis has limitations: the includes studies are restricted to the eligibility criteria and therefore included just episodic migraine patients treated with galcanezumab and erenumab only. Tools used to measure migraine related disability and quality of life like mMIDAS, HIT-6 and MSQ are prone to recall bias because they are monthly assessments, mMIDAS is not yet validated and may underestimate the patients' actual burden. There is a large variability in outcome measures used and reported in different trials that limit the capacity to pool the data and present strong results. There are also contextual/placebo effects noted in CGRP treatments.

8 CONCLUSION

Galcanezumab and erenumab demonstrated improvement in migraine characteristics and quality of life above and beyond those seen with placebo after 3-months of treatment in episodic migraine, providing placebo-controlled evidence.

There is a need to perform good RCT's with uniform outcome measures to evaluate the efficacy of all anti-CGRP monoclonal antibodies on migraine characteristic, migraine-related disability, impact and quality of life on longer time frame (beyond 12 months) and on different migraine populations (chronic migraine, MOH and refractory migraine).

9 AUTHORS' CONTRIBUTIONS

OG, PT, MP, JB as a group and NY, AR, NS as a group independently searched PubMed, ClinicalTrial.gov, Embase, Google Scholar, Cochrane Library and Web of Science for RCT's. Studies were screened according to title and abstract to determine eligibility by two authors (OG & NY). The full text of the qualified studies was assessed. In case of a disagreement, 3rd independent author JS's judgement was used to make a decision. The risk of bias from each of the items in the tool are available in the Cochrane Handbook. Discrepancies were reconciled by discussing with the corresponding author PT. The first draft was prepared by OG.

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