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SYSTEMATIC REVIEW

Effect of Repetitive Transcranial Magnetic Stimulation in Decreasing Muscle Tone of Spastic Cerebral Palsy Kids to Improve Motor Activity – A Systemic Review and Meta-Analysis

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Author`s Contribution

[1-6] Substantial contributions to the conception or design of the work for the acquisition, analysis or interpretation of data for the work, [1-6] Drafting the work or reviewing it critically for important intellectual content, [1-6] Final approval of the version to be published, [1-6] Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Article Info.

Received: October 30, 2024
Acceptance: April 08, 2025

Conflict of Interest: None
Funding Sources: None

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Cite this article as: Subramanian P, Balasubramanian D, Mohan R. Florence J, Tamilarasan P, Xaviar S, Effect of Repetitive Transcranial Magnetic Stimulation in Decreasing Muscle Tone of Spastic Cerebral Palsy Kids to Improve Motor Activity. JRCRS 2025:13(2):69-76 https://dx.doi.org/10.53389/JRCRS.2025130202

A B S T R A C T

Background: Cerebral palsy (CP) is a neurodevelopmental disorder that predominantly affects the kids' motor activity. The mainstay of treatment for the motor deficit in CP is conventional physical therapy. Due to the advancement in medical technology, a non-invasive stimulation of brain parenchyma like repetitive transcranial magnetic stimulation (rTMS) is found to be an effective therapy for motor deficits in spastic CP kids

Objective: To assess the efficacy of repetitive transcranial magnetic stimulation in spastic CP kids.

Methodology: Data sources: PubMed and Google Scholar were systematically searched until June 2024. Study selection: The meta-analysis included all published Randomized controlled trials that investigated the efficacy of rTMS over conventional physical therapy in children up to 18 years of age. Data extraction was guided by a predetermined checklist.

Results: Data extraction was guided by a predetermined checklist using Revman 5 software. Mean and standard deviation were evaluated and analysed. A total of 8 articles were selected, of which 5 articles were assessed quantitatively and the remaining 3 articles were taken for qualitative assessment. The primary outcome (Modified Ashworth scale) favours the usage of rTMS in Spastic Cerebral palsy kids (Mean standard deviation = -0.37, 95% CI -0.64, -0.09 P < 0.00001). The secondary outcome (Gross motor function measure) included 156 patients (Mean standard deviation = - 0.62, 95% CI -0.96, -0. 27 P < 0.00001). Both primary and secondary outcomes are in favour of rTMS or its combination with conventional therapy.

Conclusion: This systematic review and meta-analysis demonstrated that rTMS has a beneficial effect in reducing spasticity in CP kids compared to the control group under conventional therapy.

Keywords: Cerebral palsy, Spasticity, Conventional therapy, repetitive transcranial magnetic stimulation, Developmental delay.

Introduction

Cerebral palsy (CP) is a neurodevelopmental disorder that leads to global developmental delay involving movement, posture, and intellectual dysfunction due to injury of the developing brain. Brain injury damages the motor and sensory nerves mainly causing motor disabilities. CP presents with different degree of motor deficits like spastic, ataxic, dyskinetic, etc., of which the common form is spastic CP.[1,2] Spastic CP presents with impairment of motor activity and imbalances. The mainstay of therapeutic approaches for a spastic CP is conventional therapies like physical therapy. Repeated physical tasks help in motor learning and in correcting abnormal postural reflexes. But in recent times newer interventions like transcranial direct current stimulation, and repetitive transcranial magnetic stimulation (rTMS) were found to be more efficient in improving the motor deficit, behavioural issues, and intellectual capacity of the spastic cerebral palsy kids.[3] Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technology that has been applied to monitor, evaluate, and treat various nervous system diseases. rTMS also helps to explore the structure and functions of the brain. As rTMS is a non-invasive technique it is gaining importance in recent therapeutic protocols along with conventional physical therapy. It is proposed that rTMS along with conventional therapy is more effective and safer in reducing the spasticity in cerebral palsy kids, by modulating the neural circuits in the brain.[4,5] Hence, this meta-analysis was planned to determine the efficacy of rTMS in improving the motor deficit in spastic CP kids.

Methodology

The study was conducted with the requirements of the reporting rules in the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines". As this work is a systematic review the presence of heterogeneity was within the acceptable range. We strictly adhered to the requirements of PRISMA guidelines.

This meta-analysis included the double-blinded, randomized controlled trial studies with two groups randomized to rTMS (alone or with physical therapy) and conventional physical therapy. The study population included children < 18 years of age with spastic cerebral palsy undergoing repetitive transcranial magnetic stimulation of any frequency considering Modified Ashworth scale score and gross motor function measure as outcomes.

The articles with other study designs like Cross – sectional, Case control, Observational and with incomplete data, targeting different study populations (Stroke patients, spinal cord injury patients, and other central nervous system disorders), using different assessment scales were excluded from the review. Animal studies were also excluded.

The literature retrieval was done by the electronic retrieval methods. The combination of Medical Subject Headings (MeSH), controlled vocabulary, and keywords were used for a comprehensive and systematic research review. The review was conducted through databases of PubMed and Google Scholar for studies till 2024. The keywords used were "Cerebral palsy", "spasticity" "conventional therapy", and "repetitive transcranial magnetic stimulation". Moreover, the relevant articles included in this review and analysis, were finalised by manual search of reference list of primary trials which was conducted.

The study selection was performed by uploading the search results into the online systematic review program Rayyan and it was done by two-stage screening process. The literature search, screening of the title, abstract and keywords of all the studies was performed by two independent authors (B.D, S.P). The selection of the studies that satisfy the eligibility criteria of our review was done independently by two authors (B.D, S.P) by screening the abstract and full text of the articles. Consultation of the third author (R.M) was obtained for any disagreements or discordances present during the entire selection process. The fourth and fifth reviewers (J.F.M, P.T.) moderated and discussed over the conflicts that arose between reviewers to agree for the joint decision. Figure 2 shows the study selection process.

Data extraction and management: The extraction of the relevant study characteristics for the review was performed by the first and co-author independently. The extraction was related to outcome measures from the included studies. The first author's last name, published year, total sample size, study design, duration of intervention, participants' age, type of intervention (rTMS), comparator, and the result scores was a predetermined checklist used for the data extraction.

The obtained data was transferred into the software Review Manager (RevMan_5.3) by the first author (P.S). The second author (B.D) double-checked for correct entry of the data by comparing the data presented in the review and included in the reports. Characteristics of included studies in shown in Figure 1 and Table 1

Outcome measure for the study: Total 5 articles were included for the assessment of the primary outcome, in which a comparison of the modified Ashworth scale in kids receiving rTMS (intervention) and conventional therapy (control) was assessed. The modified Ashworth scale score ranges from 0 – 4.[1,2,3,4,5] The gross motor function measures is the secondary outcome which was assessed in both intervention and control

groups. Only 3 articles were included for the assessment of secondary outcome. The analysis was performed according to the five domains and total score of GMFM that consists of 88 items (five domains are namely, (A) lying and rolling, (B) sitting, (C) crawling/kneeling, (D) standing, and (E) walking/running/jumping1,2,3). Three more articles were considered for qualitative assessment.[6,7,8]

Quality Assessment: The risk of bias in the selected articles and the quality review process was monitored by Revman risk-of-bias tool for randomized trials (RoB 2). The categorization of "low-risk," "some concern," or "high-risk" of bias was given for each study and is shown in Figure 3 and Figure 4

Statistical analysis: A comprehensive qualitative analysis was made. The binomial data was performed using RevMan_5.3 for quantitative Meta-analysis. Only the relevant arms were included in the analysis though some of the selected articles reported multiple arms in a single trial. A logistic-normal-random-effect model was conducted as there were heterogeneity among the studies. For study-specific and overall pooled prevalence 95% Confidence Interval (CI) was performed. I^2 statistics were used to assess the heterogeny. The p-value <0.05 or I^2>50% among the studies was considered to be significant heterogeny.

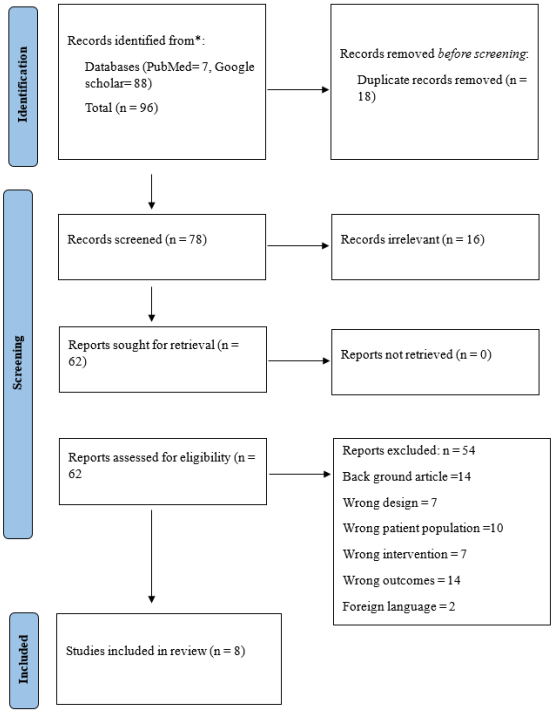

Figure 2: PRISMA flow diagram of the study selection process

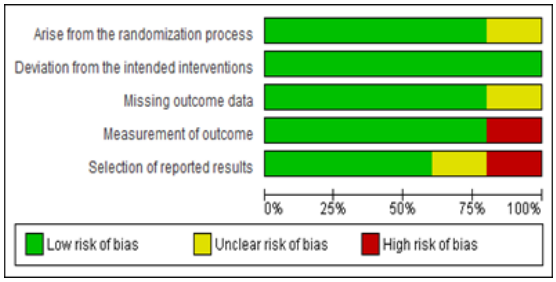

Figure 3: Risk of bias graph

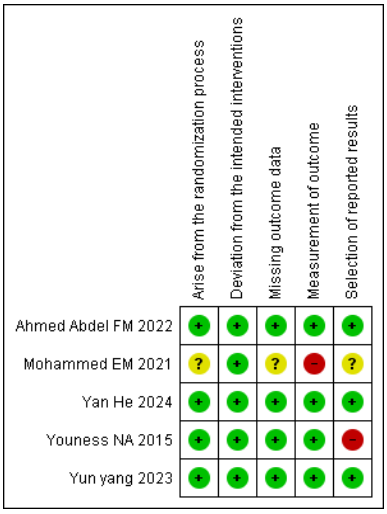

Figure 4: Risk of bias summary

Results

Study selection and characteristics: After the removal of 18 duplicates**,** 78 studies were initially retrieved, of which 16 studies were deemed irrelevant to our review. After screening, the remaining 62 studies were assessed for eligibility. Of those 62 studies, we included 8 studies for the qualitative and quantitative analysis that met the inclusion criteria. Figure 2 illustrated the PRISMA flowchart for the study selection.

The Revman risk-of-bias tool was used to assess the risk of bias among the included study. It was found that three studies had a low risk of bias and two studies had a high risk of bias**.** Though the baseline characteristics were found to be similar in both intervention and control groups in all studies, small sample size in two studies is the major limitation of this review and analysis.

Finding of the review: The primary outcome findings favour the usage of rTMS in Spastic Cerebral palsy kids (MD = -0.37, 95% CI -0.64, -0.09 P<0.00001). Figure 5 shows a significant Q statistic (p = 0.00001) indicated the presence of heterogeneity (I2 =97%). The secondary outcome assessment included 156 patients (MD = - 0.62, 95% CI -0.96, -0. 27 P<0.00001). Figure 6 shows the significant Q statistic (p = 0.00001) indicated the presence of heterogeneity (I2 =94%)

Table 1: Characteristics of the included study for Qualitative analysis						
First Author	**Year**	**Journal**	**Objective**	**Study duration**	**Results**	**Major limitation of the study**
Xin Li	2023	BMC paediatrics	This trial aims to investigate the efficacy and safety of virtual reality (VR) combined with repetitive transcranial magnetic stimulation (rTMS) for improving musculoskeletal pain and motor development in children with unilateral spastic cerebral palsy (CP).	4 Weeks	The effect of combined VR therapy with rTMS on pain and motor development in children with spastic CP is more effective than physical therapy and rTMS alone	It may be difficult to blind the intervention practitioners (physiotherapists) during the intervention process. The assessment of outcome is different from other studies
Bablu RL	2019	Annals of Indian academy of neurology	This modulatory effect of rTMS is used in this study to evaluate its effect on motor function and spasticity by increasing the number of therapy session and keeping frequency of10Hz and pulse train of 2500 constant.	4,6,8 weeks	The findings of the current study clearly demonstrated that increasing rTMS therapy sessions leads to functional gain in motor abilities	The duration of the therapies was not equal in all groups and the placebo group was not included
Bablu RL	2017	Journal of neurological disorders	The rTMS combined with rehabilitation therapy demonstrated functional improvement in motor activities of spastic cerebral palsy kids	4 weeks	The findings in this study demonstrated that high frequency rTMS is beneficial in spastic CP cases to enhance the functional hand activity	The outcome assessment scale and score were different in this study

												Age		Sample size		Intervention		Control		Intervention		Control		Side effects	
First Author	**Year of publication**	**Journal**	**Study setting**	**Study design**	**Blinding**	**Study period**	**Study population**	**Sampling strategy**	**Intervention group**	**Type of comparator**	**Type of analysis (PP/ITT)**	**Intervention (mean and SD or median (IQR))**	**Control (mean and SD or median (IQR))**	**Intervention**	**Control**	**Pre GMFM**	**Post GMFM**	**Pre GMFM**	**Post GMFM**	**Pre MAS**	**Post MAS**	**Pre MAS**	**Post MAS**	**Intervention**	**Control**
Yan He	2024	BMC Paediatrics	Hospital	A randomized controlled clinical trial	Double blind	4 weeks	3 - 12 years	Randomization	rTMS	PT (Physical Therapy)	Not mentioned	6.47 ± 2.42	7.38 ± 2.92	15	16	78.44 ± 6.95	78.44 ± 6.95	76.69 ± 7.09	87.13 ± 5.76	0.76 ± 0.16	0.93 ± 0.05	0.78 ± 0.09	0.87 ± 0.09	NIL	NIL
Yun Yang	2023	Journal of Radiation Research and Applied Sciences	Hospital	A randomized controlled trial	Not mentioned	4 weeks	2- 6 years	Randomization	rTMS + SA	SA (Scalp acupuncture)	ITT	2.87 ± 0.74	3.21 ± 1.08	30	30	13.33 ± 4.42	14.70 ± 4.56	12.61 ± 5.03	14.10 ± 5.30	2.80 ± 0.41	1.50 ± 0.57	2.87 ± 0.53	2.87 ± 0.53	NIL	NIL
Ahmed Abdel Fattah Muhammad	2022	Neurology	Hospital	A randomized controlled trial	Not mentioned	4 weeks	4 - 18 years	Randomization	rTMS + PT	PT (Physical Therapy)	ITT	8.47 ± 2.76	9.52 ± 3.9	40	25	2.83 ± 0.74	1.1 ± 0.74	2.88 ± 0.83	2.12 ± 0.9	2,20 ± 0.85	0.83 ± 0.67	2.12 ± 0.83	1.44 ± 0.91	NIL	NIL
N. A Youness	2015	Trends in applied science research	Hospital	A randomized controlled trial	Not mentioned	12 weeks	6 - 9 years	Randomization	rTMS + PT	PT(Physical Therapy)	Not mentioned	Not mentioned	Not mentioned	20	20	NA	NA	NA	NA	4.015 ± 0.664	3.24 ±0.76	4.05 ± 0.654	3.14 ± 0.36	NIL	NIL
Mohamed Serag EM	2021	Clinical schizophrenia and related psychosis	Hospital	A randomized controlled trial	Single blind	4 weeks	7 - 14 weeks	Randomization	rTMS	PT (Physical Therapy)	Not mentioned	10.7 ± 3.4	10.4 ± 3.5	15	15	NA	NA	NA	NA	0.4665 ± 0.0943	0.7309 ± 0.1212	0.4877 ± 0.0879	0.5887 ± 0.0933	NIL	NIL

Figure 1: Characteristics of the included study for Quantitative analysis

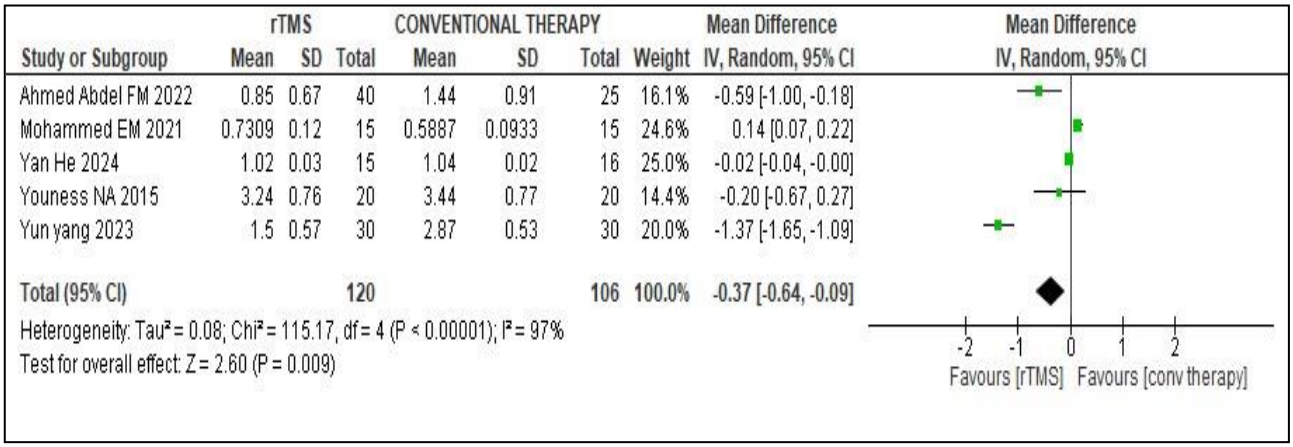

Figure 5: Forest plot for Modified Ashworth scale assessment

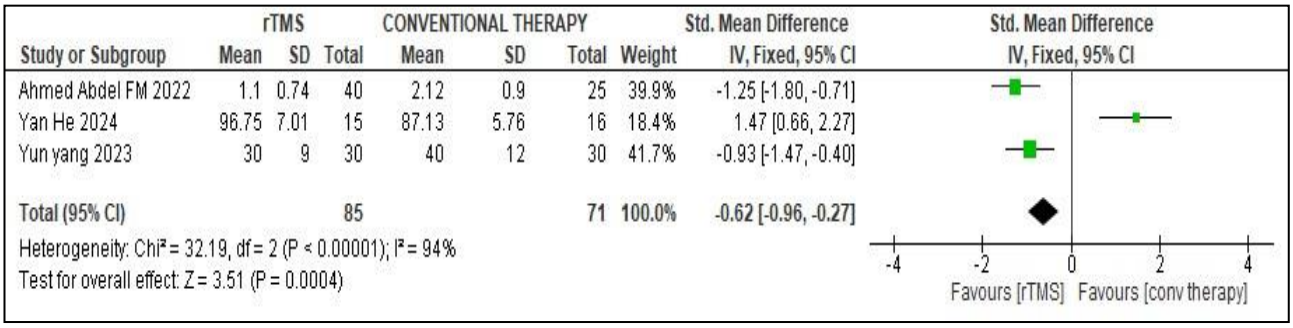

Figure 6: Forest plot for Gross motor function measure assessment

Discussion

Cerebral palsy is a clinical syndrome that leads to motor deficit and postural abnormalities. The aetiology of the clinical syndrome is an insult to the infant brain before or after birth leading to global developmental delay of various degrees according to the level of insult to the central nervous system.[9,10] There is no curative treatment for the motor deficit in cerebral palsy kids, but there is a wide range of interventions like physiotherapy, Acupuncture, Occupational therapy, Speech & language modulation techniques, and selective dorsal rhizotomy procedures for intense spasticity. All these rehabilitative measures bring about a reasonable outcome by modulating the cortical plasticity. The advancement in technologies has paved the way for newer interventions like Transcranial direct current stimulation and transcranial magnetic stimulation.[11] These newer techniques modulate the spasticity and motor function in children with spastic CP by controlled neural excitation and inhibition of the concerned circuits that bring about the normal muscle tone. The change brought about by conventional therapy in the control group was expected to be slow[12,13,14] and short lived as they work only on the muscles and don't affect motor pathways. This is also substantiated by the study which was published in 2003 in the journal of neuroscience, that the efficacy of rTMS is long-lasting in children than in the adult brain as the paediatric brain is more plastic in nature.[6,13]

Rajak BL in the year 2017 published the study that proved the efficacy of Repetitive Transcranial Magnetic Stimulation in improving the hand Function of Spastic Cerebral Palsy Children. In this study, he concluded that these interventions induce long-lasting neuronal plasticity compared to the traditional approaches.[7]

Rajak BL in another study that was published in the year 2019 concluded that rTMS regulates the neurotransmitter γ-aminobutyric acid (GABA) and glutamate which is found to be lower and higher respectively in spastic CP compared to healthy individuals. This further supports that rTMS modulates the level of neurotransmitters also.[7]

In the present study, five Randomised controlled trials included in this meta-analysis showed that the newer intervention rTMS is very efficient in reducing the muscle spasticity in CP kids by assessing the primary outcome (Mean standard deviation = - 0.37, 95% Confidence Interval-0.64, -0.09 P<0.00001), heterogeneity (I2 = 97%). The secondary outcome assessment of gross motor function measures[1,2,3] was done for three studies as there

was insufficient data in the other two. The meta-analysis of secondary outcome also proved to be in favour of newer intervention rTMS (Mean standard deviation = - 0.62, 95% Confidence Interval -0.96, -0. 27 P<0.00001), heterogeneity (I2 = 94%). Conventional therapy of scalp acupuncture (Yun Yang et al) was taken as a comparator in one of the five studies as we aimed at any conventional therapeutic method Vs rTMS. The combination of rTMS with conventional physical therapy was considered as an intervention (Ahmed Abdel FM et al, Youness NA et al) rather than rTMS alone. The duration of the therapy and intervention remains the same (4 weeks) in all studies except the one by N. A Youness et al[4] (12 weeks) which also adds on to the significance of our outcome.

The other three studies [6,7,8] which we considered for the qualitative analysis also proved to have the better outcome with rTMS than the conventional therapies used to treat spasticity in CP children.

The study conducted by Xin Li et al in the year 2023 combined rTMS with fully immersed virtual reality environment which will guide the children to perform active motions like touching or grasping specific objects etc. according to the child's motor action, had a better outcome on motor deficit and musculoskeletal pain. The parameter taken for outcome analysis is different from the other five articles considered for meta-analysis.[6,15]

Department of Biomedical Engineering from North Eastern Hill University, Meghalaya published the study in the year 2019 in which they concluded that increasing the session of rTMS therapy like 20, 30, 40 gives a better outcome in the motor deficit [7,16,17] of kids with spastic cerebral palsy by causing significant reduction in spasticity in both upper and lower limb muscles.

In addition to improving the motor deficit in CP kids, the non-invasive technique is also useful in improving motor disability caused by stroke.[18,19]

Bablu LR et al published an article in the year 2017, in the Journal of Neurological Disorders in which the motor activity of the upper limb was assessed in contrast to the assessment of lower limbs in the other studies that were considered for meta–analysis. Though the outcome assessment scale and score are different, the conclusions were in favour of rTMS as the intervention for motor disabilities in CP kids.[8,20,21,22]

The rTMS is also found to be efficient in improving the language development [23,24] in CP kids which was assessed by Sign-Significant relation for diagnosing language delay. The parameters of the assessment included language comprehension, language expression, basic learning ability, and attitude of communication. rTMS was also found to be beneficial in neuropsychiatric disorders[25,26] like mania, Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder, and schizophrenia. rTMS is used as therapeutics in depression. The neuro-modulatory effect of rTMS is an effective and safe treatment approach for treating spastic CP patients by reducing muscle spasticity and in facilitating motor memory and learning functions. rTMS have also proven to be safe in cerebral palsy kids who are prone to develop epilepsy.[26,27]

The inclusion of good quality double-blinded randomized controlled trials is the strength of our study. Despite this inclusion of only five trials with limited sample size is the major limitation of our systematic review.

Conclusion

Motor disability in children due to cerebral palsy is a big challenge for the clinicians to treat. Although it is a non-progressive insult, it leads to significant spasticity and mobility impairment affecting the quality of life.[28,29] Conventional physical therapy is effective if followed rigorously. As per this meta-analysis, it has been found that rTMS improves the motor activity in spastic cerebral palsy kids, which is indicated by the assessment of motor activity scores like Gross motor function measure, Fine motor function measure, Modified Ashworth scale, Interactive balance measure, Barthel index, CP quality of life scale before and after the intervention in multiple studies. In order to assess the intensity of pain during the sessions Faces pain scale, Face legs activity cry and consolability measures has been considered in recent studies. Hence rTMS can be considered as a safe and potential treatment option wherever feasible.[30]

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