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Stem Cell Therapy in the Treatment of Patients With Autism Spectrum Disorder: a Systematic Review and Meta-analysis

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Abstract

Objective Assess the safety and efficacy of upcoming stem cell treatments and analyze their effects on the cognitive and behavioral impairments in patients diagnosed with autism.

Methods We included controlled and noncontrolled, randomized and non-randomized trials evaluating stem cell therapy as a treatment in patients with autism spectrum disorder compared to placebo or without comparator. Data Sources: Scopus, Web of Science, MEDLINE and EMBASE. Risk of bias was assessed using Cochrane's Risk of Bias tool and the NIH's Quality Assessment Tool for Studies With No Control Group.

Results Eleven trials including 461 patients proved eligible. *ABC scale* meta-analysis showed a mean raw of -11.97 in the intervention groups (95 % CI -91.45 to 67.52, $p < 0.01$). *CARS scale* reported a mean raw of -9.08 (95 % CI -15.43 to -2.73, $p < 0.01$). *VABS scale* was reported by their domains: communication domain reported a mean raw of 2.69 (95 % CI 1.30 to 4.08, $p = 0.92$); daily living domain, 1.99 (95 % CI 0.83 to 3.15, $p = 0.51$); motor domain, 1.06 (95 % CI -0.37 to 2.48, $p = 0.20$); socialization domain, 3.09 (95 % CI 1.71 to 4.48, $p = 0.61$); adaptive behavior domain, 2.10 (95 % CI 1.04 to 3.16, $p = 0.36$). Furthermore, the most common side effects reported included fever, hyperactivity, vomit, headache, and aggressiveness; no serious adverse events were reported.

Conclusions The body of evidence suggests that stem cell therapy significantly improves scales in patients with autism spectrum disorder, hence, future studies should help us have more confidence in the results. We found no serious adverse events related to the stem cell therapy.

Keywords Stem cells · Stem cell transplantation · Autism · Autistic disorder · Systematic review · Meta-analysis

Abbreviations

ASDs	Autism spectrum disorders
MSCs	mesenchymal stem cells
BMMNC	bone marrow mononuclear cell
CBMNC	cord blood mononuclear cell
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Introduction

Autism spectrum disorders (ASDs) are a complex series of neurodevelopmental disorders [1]. Autism *per se* is the most prevalent of the ASDs. It is characterized by deficits in social communication and interaction, presence of restricted interests, repetitive and stereotypic verbal and nonverbal behaviors, with an early onset in life [2].

Despite advances in early diagnosis and behavioral therapies, no known cure or effective treatment has been established [3, 4]. Treatment approaches include psychotropic medication, behavioral, occupational and speech therapies, and specialized educational and vocational support [5–8].

When there is evidence of increased neuroinflammation and aberrant neuronal connectivity in individuals with ASD, therapeutic interventions that impact immune modulation and regulation of neural connectivity show promise in the treatment of these patients [9]. Recent findings have

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suggested that stem cell transplantation can show improvements in several neurological conditions in ASD [9–12].

Neuroprotection, neurogenesis and synaptogenesis have been described from animal research as mechanisms of action of mesenchymal stem cells (MSCs) in the nervous system [13–19]. Several studies that assessed stem cell transplantations for the treatment of children with ASD arose from these findings [11, 20–23]. Explored approaches have included autologous bone marrow mononuclear cell (BMMNC) [21, 22], allogeneic and autologous stored cord blood mononuclear cell (CBMNC), and CBMNC combined with umbilical cord MSC transplantation [11, 23], infused by intrathecal and intravenous route respectively. These studies have been broadly consistent in outcomes, reporting improvements in behavior, socialization speech and language patterns, and brain metabolism, with no safety concerns. However, there is still uncertainty over which is the best administration route, cell sources, processing, and dosage, or whether any of these variables impact the overall outcome of the treatment. Therefore, we assessed the safety and efficacy of these upcoming stem cell treatments and also analyzed its effects on the cognitive and behavioral impairments via a systematic review and meta-analysis of the available scientific literature [11].

Methods

Study Design

This study adhered to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement. This review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the following registration ID: CRD42021225190.

Eligibility Criteria

We included controlled and non-controlled, randomized and non-randomized trials evaluating stem cell therapy as a treatment in patients with confirmed autism spectrum disorder compared to placebo or without comparator. Primary outcomes of interest included: (1) improvement in clinical scales. Secondary outcomes: (2) changes in imaging studies, (3) adverse events. Studies with a language other than English were excluded.

Search Strategy and Data Management

An experienced librarian (E.G.L.) with input from the study principal investigators designed and conducted the search strategy, which was also approved by all the investigators. The following electronic databases from the time of their inception to November 2020 were searched: Scopus, Web of Science, MEDLINE and EMBASE. We complemented the initial search strategy by consulting experts in the field, screening the reference lists from the eligible selected studies and grey literature to identify any potentially relevant studies that may have been missed. The full search strategy can be found on supplementary appendix (Supp A1, A2). All search results were uploaded to EndNote X8 for deduplication. The resulting studies were uploaded to Distiller Systematic Review (DSR) for both, abstract and full-text screening.

Study Selection Process

Study selection took place in two phases. Through each phase of the review, four reviewers (G.G.M., M.S.F., A.J.B.G., A.G.M.) worked independently and in duplicate to assess the eligibility of the studies. Chance adjusted inter-rater agreement was assessed using Kappa statistics. Prior to each phase, a pilot test was carried out in order to standardize the reviewers' criterion. The pilot was repeated until a kappa index of >0.70 was reached. In the first phase, title and abstracts were screened and reviewers selected the eligible studies based on the inclusion criteria. At this stage, in order to be more sensitive, if discrepancies were found between reviewers the study was included into the next phase. Following the title/abstract phase, eligibility was assessed through a full-text screening. At this stage, disagreement between reviewers was resolved by consensus.

Data Collection Process

Four independent reviewers (G.G.M., M.S.F., A.J.B.G., A.G.M.) working in duplicate collected data for all eligible articles using a web-based data extraction form. The following information was obtained for each study: study setting, title, author information, year of publication, baseline characteristics of patients (age, sex, race, comorbidities) treatment characteristics, adverse events, results from imaging studies, and reported scales for improvement evaluation. Conflicts at this phase were resolved by consensus or arbitration of a third reviewer. In studies that had a control group, we only extracted data from the intervention group.

Risk of Bias in Individual Studies

Four reviewers (G.G.M., M.S.F., A.J.B.G., A.G.M.) working independently and in duplicate assessed the risk of bias. The Cochrane's Risk of Bias 2 tool was employed for assessing risk of bias in randomized trials with a comparison group. It evaluates the following domains: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of

outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Studies were rated as high, some concerns, and low risk of bias. For single armed trials, the NIH's Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group was employed; which focuses on aspects regarding population, outcomes, intervention and other important methodological features. Studies were rated as good, fair and low. Disagreements were resolved by consensus.

Data Synthesis and Statistical Analysis

A narrative synthesis of the studies that met our inclusion criteria was conducted. When possible, meta-analyses were performed to estimate the effect of stem cells therapy on the prespecified outcomes in our PROSPERO submission. When multiple groups were available in one trial, we split the shared group into the necessary groups to include multiple independent comparisons, following the Cochrane Handbook for Systematic Reviews of Interventions [24].

For our quantitative data synthesis, we used a random effects meta-analysis of single means to calculate an overall mean and the inverse variance weighting method to pool single means for pre and post intervention scores from the intervention groups [25]. Heterogeneity was measured using Cochran's Q test (high heterogeneity determined by a p-value < 0.10) and with the I^2 statistic in which a value $< 25\,\%$ was considered low heterogeneity and a value $> 75\,\%$ high heterogeneity.

When events were evaluated, a summary of the intervention effect was reported with frequencies for categorical variables and in mean or median in case of continuous variables; Cochrane's handbook formula for combining groups was used for combining means and standard deviation (SD). When possible, a random effect meta-analysis using a generalized linear mixed effects model to calculate revision rates was performed using R (Version 4.0) with R studio (version 1.2.5001) using the package meta.

Results

Study Selection

A total of 5237 records were identified through our search, no additional records were identified. From the excluded records, some were protocols, repeated references or did not meet our inclusion criteria. Finally, 11 studies met inclusion criteria, these were single armed trials and trials with a control group. The complete flow-diagram can be observed in Fig. 1.

Study Characteristics

The trials sample sizes ranged from 12 to 180 patients, from 2 to 33 years of age and had a follow up ranging from 6 to 26 months. Main characteristics from each study are reported in Table 1. Six studies administered infusion of autologous umbilical cord blood cells [9, 23, 26–29]. Three studies administered bone marrow stem cell transplantation [11, 21, 30]. One study administered intravenous infusion of mesenchymal stromal cells. Lastly, one study administered fetal stem cell transplantation [31]. The primary outcome of most studies were efficacy and safety of stem cell therapy.

Scales

Description of Reported Scales

Fourteen scales were reported in the totality of the included articles: Autism Diagnostic Observation Schedule (ADOS), Vineland Adaptive Behavior Scales (VABS), Autism Clinical Global Impression (CGI), Expressive One-Word Picture Vocabulary Test (EOWPVT), Receptive One-Word Picture Vocabulary Test (ROWPVT), Autism Treatment Evaluation Checklist (ATEC), Childhood Autism Rating Scale (CARS), Autism Behavior Checklist (ABC), Indian Scale for Assessment of Autism (ISAA), Functional Independence Measure (FIM), Wee Functional Independence Measure (WeeFIM), Pervasive Developmental Disorder Behavior Inventory (PDDBI), Development Quotient (DQ) and Stanford Binet. A meta-analysis was made for the following scales that were reported in two or more articles: ABC scale, CARS scale, VABS scale.

ABC Scale

Two studies [11, 31] reported the ABC scale. Results from meta-analysis showed a mean raw of -11.97 points in the intervention groups (95 % CI -91.45 to 67.52, $I^2 = 99\,\%$, $p < 0.01$, Fig. 2).

CARS Scale

Three studies [11, 26, 30] reported the CARS scale. Results from meta-analysis showed a mean raw of -9.08 points (95 % CI -15.43 to -2.73, $I^2 = 88\,\%$, $p < 0.01$, Fig. 3) in the groups of intervention of these.

VABS Scale

Four studies [23, 27, 28, 30] reported the communication domain of the VABS Scale. The mean raw was 2.69 (95 % CI 1.30 to 4.08, $I^2 = 0\,\%$, $p = 0.92$, Fig. 4a) in the intervention groups. The daily living domain was reported by four studies

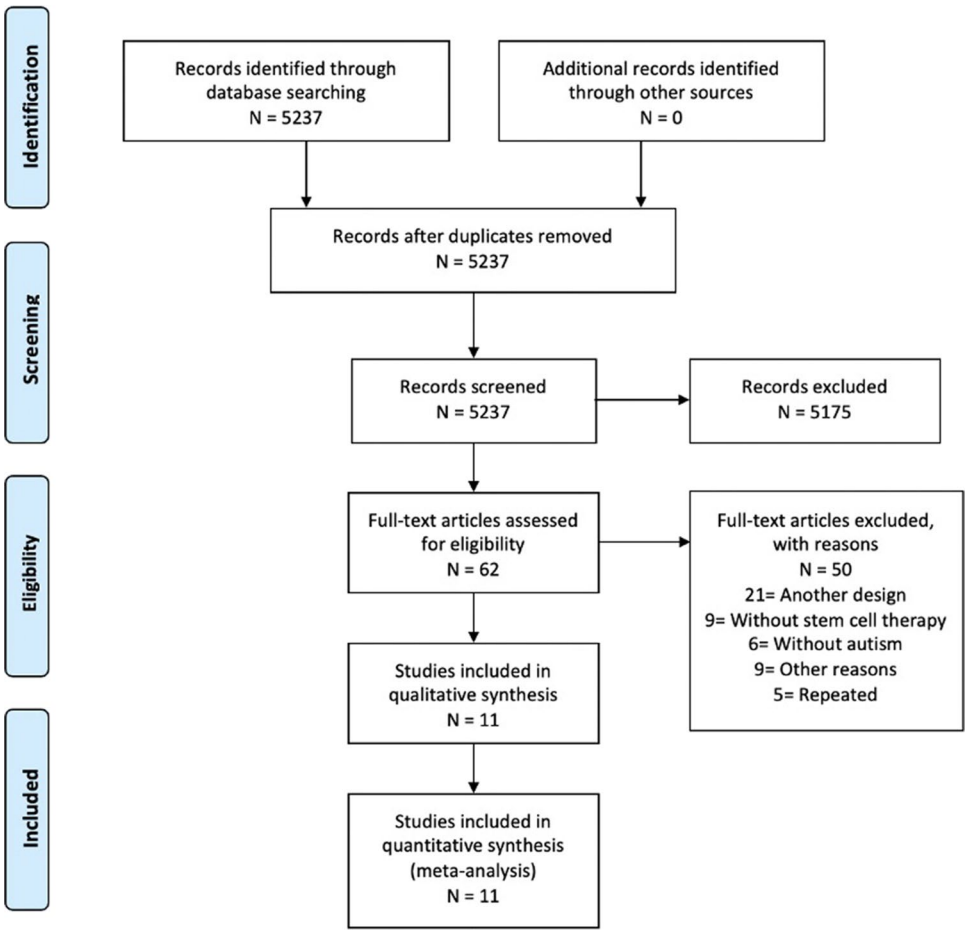


Fig. 1 PRISMA flow chart

[23, 27, 28, 30]. In this domain our meta-analysis showed a mean raw of 1.99 (95 % CI 0.83 to 3.15, $I^2 = 0$ %, p = 0.51, Fig. 4b). The motor domain was reported by four studies [23, 27, 28, 30]; our meta-analysis showed a mean raw of 1.06 (95 % CI -0.37 to 2.48, $I^2 = 28$ %, p = 0.20, Fig. 4c). The socialization domain of this scale was reported in three studies [23, 28, 30]; our meta-analysis showed a mean raw of 3.09 (95 % CI 1.71 to 4.48, $I^2 = 0$ %, p = 0.61, Fig. 4d) in the intervention groups. Three studies [23, 27, 28] reported the VABS adaptive behavior domain; our meta-analysis showed a mean raw of 2.10 (95 % CI 1.04 to 3.16, $I^2 = 9$ %, p = 0.36, Fig. 4e) in the intervention groups.

Adverse Effects

Proportion meta-analysis was performed in five studies reporting adverse effects with the use of stem cell therapy. Four studies reported fever as an adverse effect 31 % (p = 0.02 $I^2 = 61$ %), three studies reported headache 13 % (p = < 0.001$I^2 = 78.6$ %), four studies reported vomit 25 % (p = < 0.001, $I^2 = 72$ %). Hyperactivity was reported by three studies of 27 % (p = 0.07, $I^2 = 46.3$ %) and three studies reported aggressiveness with an overall proportion of 14 % (p = 0.39, $I^2 = 0.0$ %)(Fig. 5).

Imaging Results

Six studies reported imaging results. One study [9] used an MRI to associate improvements in behavior with increased neuronal connectivity in limbic, frontal, temporal and basal ganglia neural networks, which has been previously implicated in the pathophysiology of autism. Another study [21] used PET-CT scan in eight patients and showed the following changes. After cellular therapy, glucose metabolism in the form of FDG uptake were observed in the frontal and parietal lobes of six patients, occipital and temporal lobes of five patients and cerebellum of four patients; amygdala, hippocampus, and parahippocampus of three patients; and cingulate, paracingulate area, and basal ganglia of five patients. PET-CT scan before intervention showed reduced FDG uptake in the areas of frontal lobe, cerebellum, amygdala, hippocampus, parahippocampus, and mesial temporal lobe. Six months after intervention comparison showed increased FDG uptake in these same areas. EEG was used in one study [27] to show abnormalities. There was specific

Table. 1 Study characteristics

Author, year	Design	Country	Age	n	Intervention group	Control group
Carpenter et al., 2019	Randomized controlled trial	USA	4.49 ± 1.08	25	Autologous Umbilical Cord Blood Cells	Non intervention arm
Riordan et al., 2019	Randomized controlled trial	Panamá	10.25 ± 2.81	20	Allogeneic Umbilical Cord Blood Mesenchymal Cells	Non intervention arm
Yong-Tao Lv et al., 2013	Randomized controlled trial	China	6.43 ± 2.36	37	Allogeneic Umbilical Cord Blood Mesenchymal and Mononuclear Cells	Control group
Sharma et al., 2013	Randomized controlled trial	India	10.5 ± 5.6	32	Autologous Bone Marrow Mononuclear Cells	Non intervention arm
Dawson et al., 2017	Randomized controlled trial	USA	2–5	25	Autologous Umbilical Cord Blood	Non intervention arm
Chez et al., 2018	Randomized controlled trial	USA	2–6	30	Autologous Umbilical Cord Blood	Control group
Thanh et al., 2020	Uncontrolled clinical trial	Vietnam	5.6 ± 0.9	30	Autologous Bone Marrow Mononuclear Cells	Non intervention arm
Dawson et al., 2020	Randomized controlled trial	USA	5.47 ± 1.65	180	Autologous/Allogeneic Umbilical Cord Blood	Placebo
Sun et al., 2020	Uncontrolled clinical trial	USA	4–9	12	Allogeneic Umbilical Cord Blood Mesenchymal Stromal Cells	Non intervention arm
Murias et al., 2018	Randomized controlled trial	USA	2–6	25	Autologous Umbilical Cord Blood	Non intervention arm
Bradstreet et al., 2014	Uncontrolled clinical trial	International	6.94 ± 0.89	45	Allogeneic Fetal Stem Cell Transplantation	Non intervention arm

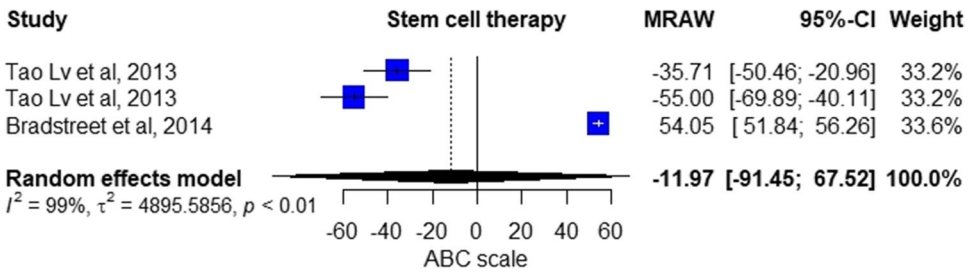


Fig. 2 Forest plot of ABC scale

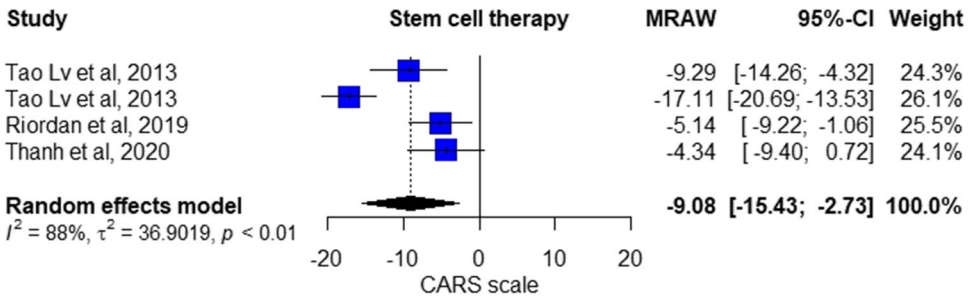


Fig. 3 Forest plot of CARS scale

bifrontal predominant generalized or focal spike wave activity that predominated in the temporal central parietal regions. One study [30] used the PET SCAN to show metabolism improvement in the parietal lobe, frontal lobe, and anterior cingulate gyrus. These areas were severely hypometabolic before the intervention. However, these changes were not statistically significant. No abnormalities on MRI or EEG were observed in any of the patients. Another study [28] used an EEG to reveal a main effect between treatment groups. Participants with intervention showed significantly lower beta2 powerposterior/social. However, there was also a significant NVIQ-by-treatment group interaction. Their

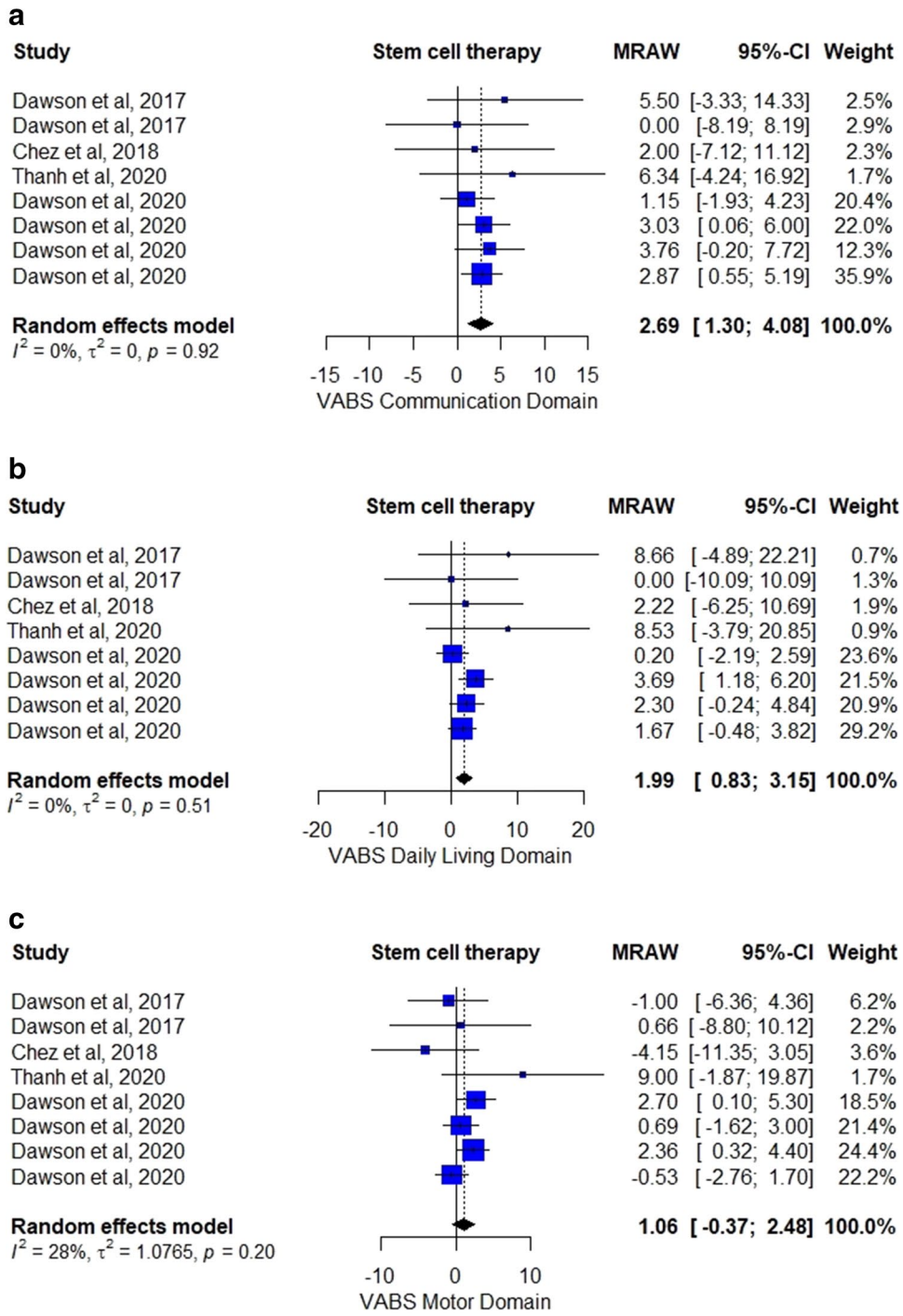


Fig. 4 Forest plot of VABS scale domains. **a)** VABS communication domain; **b**) VABS daily living domain; **c**) VABS motor domain; **d**) VABS socialization domain; **e**) VABS adaptive behavior domain

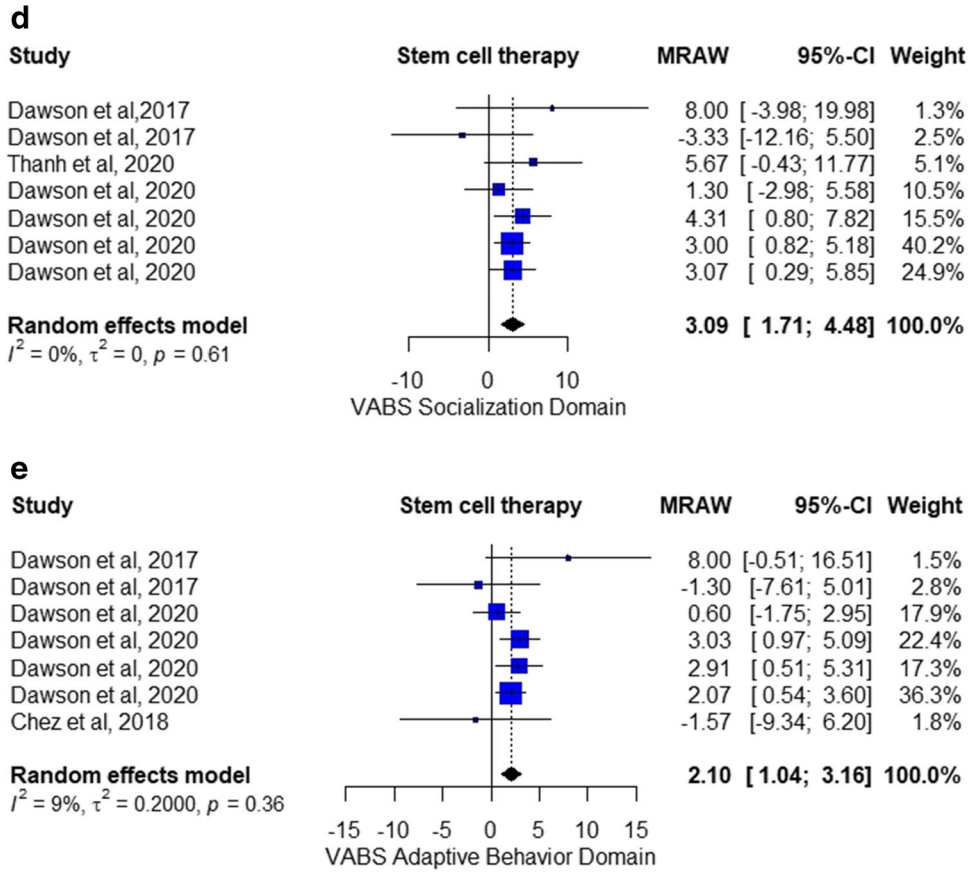
results indicated that the subgroup of participants with lower NVIQ who received CB exhibited significant reductions in beta2 powerposterior/social.

The last study [29] showed significant changes in EEG power that was reflected in a normalization of the EEG spectral characteristics 12 months after infusion. Higher baseline EEG beta 2 power was associated with a greater degree of improvement in social communication symptoms. Baseline measures of EEG beta 2 power and NVIQ together were highly predictive of treatment response. This highlighted the potential of EEG as a tool to discriminate between children with different degrees of improvement after treatment with autologous umbilical cord blood.

Risk of Bias

Three studies were evaluated using the Cochrane Risk of Bias tool. One study was considered as low risk of bias [11],

Fig. 4 (continued)



one study was considered as some concerns [27], and one at high risk [28]. Most studies that were classified as some concerns exhibited deficits in the randomization process while most studies that were classified as high risk demonstrated concerns in the randomization process and deviations for intended interventions. The full risk of bias assessment is shown in Fig. 6.

Eight studies were evaluated using the NIH's Quality Assessment Tool [5, 9, 21, 23, 26, 29–31]. Six studies were considered as fair [5, 9, 21, 23, 26, 29] and two studies as good [30, 31].

Discussion

Main Findings

This comprehensive review summarizes the currently available evidence from clinical trials comprising the effect of stem cell therapy against placebo or without comparator. The body of evidence suggests that stem cell therapy significantly improves scale scores in patients with autism spectrum disorder. The most commonly reported side effects included fever, hyperactivity, vomit, headache and aggressiveness; no serious adverse events were reported. Another important finding was the improvement in imaging results, one study reported increased neuronal activity detected on MRI, two studies found hypermetabolic areas before intervention and an improvement after stem cell therapy using PET-CT, three studies using EEG reported a highly predictive response to treatment.

Comparison with Previous Studies

To our knowledge, this is the first systematic review and meta-analysis summarizing the safety and efficacy of stem cell therapy in patients with autism spectrum disorder. Hence, some trials included in our study are non-randomized and do not include a direct comparison group which can lead to inadequate or incomplete study methods. Siniscalco et al. (2018) performed a comprehensive up-to-date review focusing on the use of stem cells in treating autism, he found that there is a potential benefit and important advances for the use of stem cell therapy in ASDs and an encouraging positive effect in relief of ASD symptoms. However, authors of this study concluded that further complete and exhaustive investigations will be needed to claim definitive results.

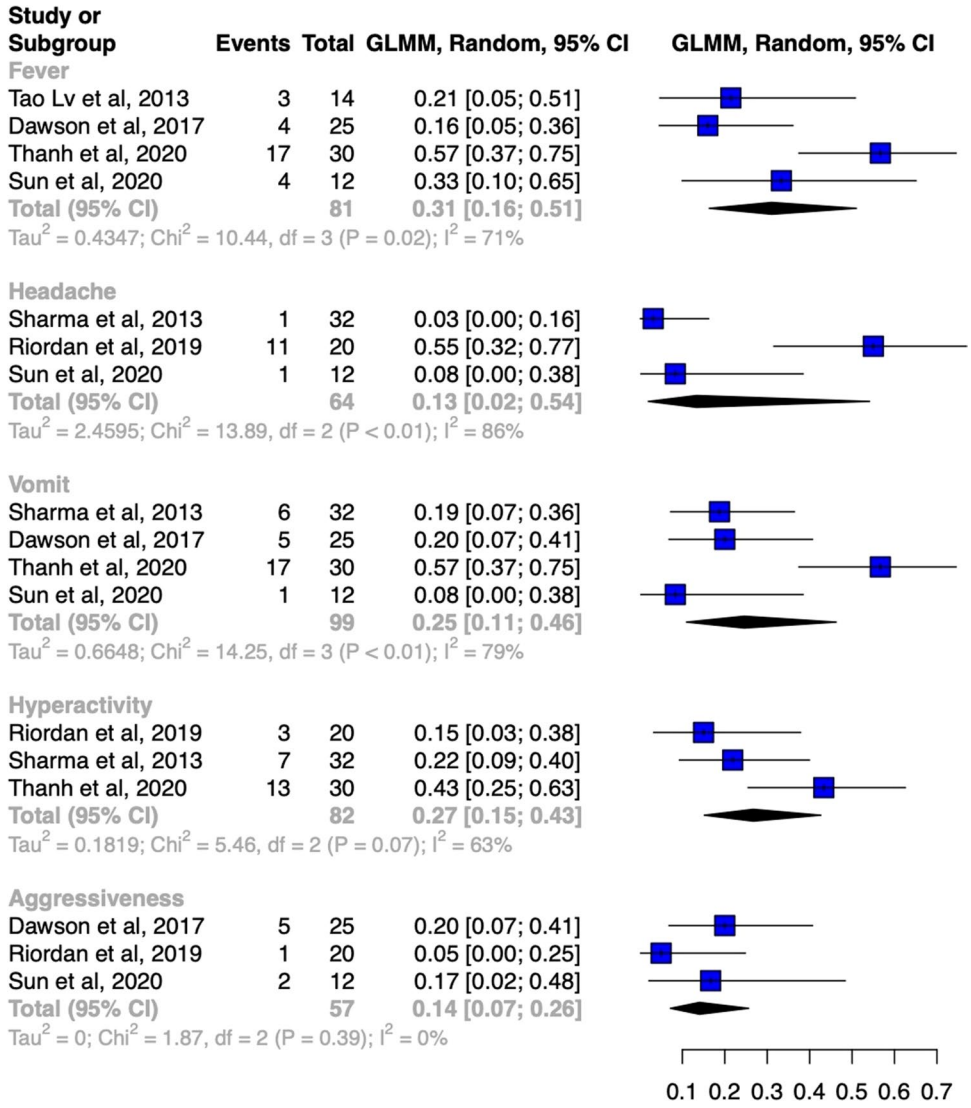


Fig. 5 Forest plot of adverse events

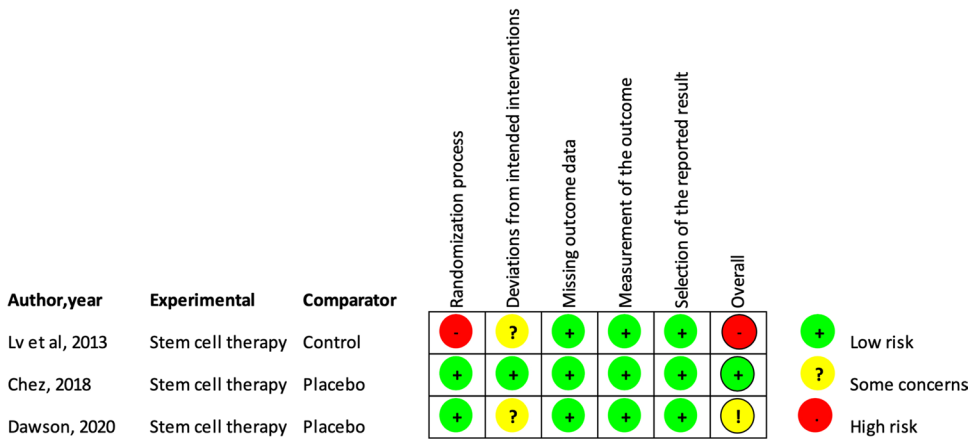


Fig. 6 Overall risk of bias

Additionally, our study showed a clinical improvement, however due to a lack of comparators in most of our included studies, fails to render enough confidence in the estimates. Further studies could either validate or refute this finding.

Strengths and Limitations

Strengths of our review include the strict inclusion criteria, and the evaluation of the risk of bias of each individual study, providing a wide information about the certainty of available evidence. The greatest limitation of our study is that most studies had a small sample size, wide heterogeneity across results, and inadequate or incomplete study methods. Finally, the moderate to fair quality, making it difficult to deduce conclusions.

Implications for Research and Practice

This comprehensive review should aid clinicians make more informed decisions regarding the use of stem cell therapy in autism. Given the dearth of evidence about stem cell therapy in patients with autism spectrum disorder, clinicians and patients should also take into account the adverse events, which for stem cell therapy seem to be inconsequential. Future studies should help us have more confidence in results.

Conclusions

Stem cell therapy and regenerative medicine have been studied recently for the management of diseases that have no other choice of treatment. To this day, autism is a condition for which there is no curative treatment, therefore, management options are limited. Our study examined the safety and efficacy of SCT in patients with ASD diagnosis. We found no serious adverse events related to the intervention. The body of evidence suggests that stem cell therapy clinically improves patients with autism spectrum disorder, regardless of the cell source, dosage and delivery routes. Therefore, any kind of SCT reviewed in this study is safe and should be considered for patients with ASD. To date, this is the most comprehensive review that has been done. It should help patients and clinicians consider the benefits and know that there are minimal risks. This will help them make more informed decisions regarding the use of stem cell therapy in patients with ASD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12015-021-10257-0.

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Author Contribution All authors were involved, in the conceiving of the research idea and elaboration of the research protocol. LVM supervised the project fulfillment. EGL designed the search strategy and performed the literature search. GGM, MSF, AJBG, AGM screened studies for eligibility. GGM, MSF, AJBG, AGM assessed the risk of bias. GGM, MSF, AJBG, AGM performed data extraction. MSF performed the statistical analysis. MOC, DARS, MSF, AJBG, AGM contributed in the design, interpretation of data and drafting of the work. All authors were involved in the elaboration and approval of the final version of the manuscript. LVM is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Conflicts of Interest/Competing Interest The authors have no conflicts of interest to declare that are relevant to the content to this article.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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