Original Article

A Systematic Review Of Randomized Controlled Trials Assessing The Effect Of L-Carnosine On Children With Attention Deficit Hyperactivity Disorder

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DOI: 10.47750/pnr.2023.14.02.28

Abstract

To evaluate the efficacy of L-Carnosine in children with Attention deficit hyperactivity disorder (ADHD) using existing data sources. Databases, such as PubMed, Scopus, Embase, and web of Science were searched using a comprehensive search strategy. Data were identified from randomized controlled trials (RCTs). The main outcomes were changes in inattention, hyperactivity or both based on ADHD rating scales by teachers, parents or both. Additional outcomes included improvement in sleep disorders, learning disabilities and adverse events. Jadad scale was used to assess the quality of RCTs. The risk of bias was assessed using modified Cochrane risk of bias tool. The protocol was registered with PROSPERO; registration number CRD42020209818. Two double-blinded, placebo-controlled RCTs with a total of 111 participants were selected for the review. Both the trials were methodologically of high quality as per the Jadad scale. There was a low risk of bias according to the modified Cochrane risk of bias tool. Both the studies showed no significant difference between L-Carnosine and placebo controls on majority of their outcome measures. The available data does not recommend the use of L-Carnosine in the management of children with ADHD owing to scarcity of studies. Further studies are needed to explore the effect of L-carnosine in management of ADHD.

Keywords L-carnosine . Attention deficit disorder . Hyperactivity . Neurodevelopmental disorder . Children

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition that affects children with a prevalence of 5% globally (Sayal et al., 2018). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) characterizes ADHD as age-inappropriate inattention, increased impulsivity and hyperactivity (American Psychiatric Association, 2013). The etiology of this disorder is unknown, but it could be due to heredity or environmental influences (Thapar et al., 2012). Sleep disorders, learning disabilities (LD), obsessive compulsive

disorder (OCD) and autism spectrum disorder (ASD) are medical conditions associated to ADHD and may manifest along with symptoms of ADHD (Wajszilber et al., 2018; Richardson & Puri, 2002; Brem et al., 2014; Leitner, 2014).

Although psychopharmacological therapies like methylphenidate are effective in children with ADHD, their adverse effects make them unpalatable and lowers adherence (Schachter et al., 2001; Storebø et al., 2015; Groenman et al., 2017). In the management of ADHD and other neuropsychiatric disorders, conventional therapies, such as occupational and behavioral therapies, as well as complementary and alternative medicine (CAM) have been widely employed (Mohammadi & Akhondzadeh, 2007; Narasimhan et al., 2020) . According to the literatures, CAM combined with conventional therapies can assist children with neurodevelopmental disorders for a better prognosis (Sinha & Efron, 2005; Ann Abraham et al., 2020). Reporting of adverse effects associated with CAM is essential for health care professionals and caregivers to provide evidence based therapies (Debi Ann et al., 2020).

L-Carnosine is an amino acid containing β-alanine and l-histidine, considered to be beneficial for patients with ADHD. It is known to accumulate in the sub-frontal cortex and thereby enhance the function of frontal lobes (Boldyrev et al., 2013; Hipkiss, 2009). It is also considered to have neuroprotective (Bellia et al., 2011), antioxidant (Prokopieva et al., 2016), Gamma-aminobutyric acid (GABA) modulatory (Wang et al., 2000), anti-aging (Brondino et al., 2016), anticonvulsant (Shen et al., 2010) and N-methyl-D-aspartate (NMDA) receptor antagonists properties (Shen et al., 2007). It has been used in other brain disorders such as Alzheimer's disease (Hisatsune et al., 2016), OCD (Arabzadeh et al., 2017), Parkinsons disease (Boldyrev et al., 2008), schizophrenia (Chengappa et al., 2012) and ASD (Hajizadeh-Zaker et al., 2018; Mehrazad Saber et al., 2018; Chez et al., 2002).

Despite the fact that few clinical trials have been conducted in investigating the effect of L-Carnosine as an adjuvant to pharmacological and non-pharmacological therapies in children with ADHD, there has been no systematic review on L-Carnosine's effect in children with ADHD. As a result, the goal of this study was to systematically review randomized controlled trials (RCTs) on the effect of L-Carnosine in children with ADHD and its associated medical conditions, such as sleep problems and learning disabilities, as well as adverse events, in order to identify lacunae in the literature and provide scope for future research.

Methods

Protocol and registration

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). The study has been registered in PROSPERO, an international database of systematic reviews (CRD42020209818).

Search strategy and study selection

An extensive literature search was performed in PubMed, Scopus, Embase, and web of Science from the start of the study till June 15, 2022. The Medical Subject Heading (MESH) and non-MESH terms of L-Carnosine, Carnosine, β-alanyll-histidine, Levo-Carnosine, attention deficit hyperactivity disorder, attention deficit disorder, ADHD, ADD, learning disabilities, learning disorders, LD, learning impairments, sleep disorders, sleep disturbances, adverse effects, ADR were combined for the search strategy. References of articles with original research were also checked. Two of the authors (DAA and MGR) independently reviewed the title/abstract obtained by the search strategy and selected the studies which were relevant to our review. The full-text screening was carried out by two independent reviewers and any disagreements were resolved through mutual discussion or by discussing with another co-researcher of the team.

Inclusion and exclusion criteria

The inclusion criteria comprised RCTs in which L-carnosine is given for minimum 6 weeks alone or along with behavioral or pharmacological therapies, articles published in English, children upto 18 years of age diagnosed with

ADHD using DSM diagnostic criteria, studies which assessed the effect of L-Carnosine on ADHD symptoms by teacher or parent rating scales, other conditions, such as sleep problems, learning disabilities, and adverse events occurred. We excluded case reports, editorials, letters, reviews, animal studies; studies published before the year 2000, case reports, studies conducted on adult populations, grey literature such as thesis and conference proceedings.

Extraction of data

The data extraction form was designed prior to running the search strategy in selected databases. The relevant information from the selected studies was extracted using this data extraction form. Data was extracted and combined in preset tables by one author (DAA) and reviewed by another author (MGR) and any discrepancies were solved by discussion with other two authors. The following variables were collected: author names, year and country, number of participants, mean age, inclusion and exclusion criteria, dose of L-Carnosine, study design, study duration, adverse events, randomization, blinding and outcome measures.

Quality assessment

Jadad scale was used to assess the quality of RCTs (Jadad et al., 1996).The modified Cochrane risk of bias tool was used to assess the risk of bias. The risk of bias was assessed in the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain was classified as high risk of bias, low risk of bias and unclear risk of bias (Higgins et al., 2011; Rajanandh et al., 2018). DAA and MGR were involved in risk of bias assessment and the reviewers did not have any disagreements.

Results

Search results and study selection

The systematic review flow diagram is represented in Figure 1. The initial search resulted in 450 articles. Out of these, 410 were screened after removal of duplicates and 2 were included in the review according to preset criteria.

Study characteristics

The characteristics of the two trials included in the systematic review which were published in the year 2009 and 2018 are shown in Table 1. One RCT was conducted in Iran (Ghajar et al., 2018) and the other one in Finland (Kairaluoma et al., 2009). A total of 111 participants in which 50 and 61 children in each study were assessed for the effect of L-Carnosine on ADHD and dyslexia respectively. Mean age was approximately 10 and males and females comprised 75 and 36 respectively. One study investigated L-Carnosine as an adjuvant therapy to methylphenidate in ADHD children and another study assessed the effect of L-Carnosine as add on therapy to ethyl eicosapentaenoic acid (ethyl-EPA) in children with dyslexia. The authors used Teacher and Parent ADHD Rating Scale-IV (ADHD-RS-IV) (McGoey et al., 2007) in one study whereas reading and spelling tests and language skills were used as outcome measures in another study.

Quality assessment

The two RCTs included in the review were double-blind, placebo-controlled trials, methodologically of high quality as per the Jadad scale (Table 2). There was a low risk of bias according to the modified Cochrane risk of bias tool showed as illustrated in Figure 2.

Study findings

Table 3 depicts the outcomes and analysis of the included trials. L-Carnosine in combination with methylphenidate increased total and inattention subscales in the Parent ADHD-RS-IV but had no significant effect on Teacher ADHD-RS-IV in Ghajar et al. (2018). In terms of the secondary outcome, there was no significant effect on reading

and spelling tests as well as language skills in children with dyslexia but blood analysis showed higher plasma levels of EPA when L-Carnosine was given with ethyl-EPA (Kairaluoma et al., 2009). Ghajar et al. (2018) reported adverse events such as headache, abdominal pain, insomnia, constipation, sweating, nausea and vomiting.

Discussion

We systematically reviewed two trials with a total of 111 participants in children with ADHD and dyslexia. L-Carnosine does not exert any significant effect in treatment of children with ADHD as there is only small number of participants and studies. Males were more affected than females which are consistent with previous research (Rucklidge, 2010). Sleep disorders, learning disabilities are medical conditions which commonly co-occur along with ADHD (Hvolby, 2015; Pham & Riviere, 2015). Combination of CAM therapies along with psychotherapies has shown beneficial effects in psychiatric disorders (Barnett & Shale, 2012). One study evaluated L-Carnosine along with methylphenidate in children with ADHD for a period of 8 weeks (Ghajar et al., 2018) whereas the other study evaluated L-Carnosine as adjuvant therapy to ethyl-EPA in children with dyslexia for a period of 90 days (Kairaluoma et al., 2009). The dosage of L-Carnosine varied from 400mg to 800 mg in dyslexia and ADHD respectively. There was significant difference in the Parent ADHD-RS-IV but not in the Teacher ADHD-RS-IV when L-Carnosine was given along with methylphenidate. Jadad scale revealed the RCTs as methodologically of high quality and there was a low risk of bias according to the modified Cochrane risk of bias tool.

No animal studies were reported on L-Carnosine supplementation in ADHD. L-Carnosine has been employed in other brain disorders, such as ASD, OCD, schizophrenia etc (Schon et al., 2019). Two studies which reported L-Carnosine's effect on sleep disorders was conducted on children with ASD who had sleep disturbances (Ann Abraham et al., 2020; Mehrazad-Saber et al., 2018) but there were none conducted in ADHD. Learning disabilities such as dyslexia had no improvement on treatment with L-Carnosine and ethyl EPA (Kairaluoma et al., 2009). Adverse events such as headache, abdominal pain, insomnia, constipation, sweating, nausea and vomiting which were reported in one study (Ghajar et al., 2018) maybe due to effect of methylphenidate as L-Carnosine has not reported any side effects except for hyperactivity in other trials (Abraham et al., 2021). The duration of L-Carnosine in the studies varied from 8 to 12 weeks but no significant effect was obtained in supplementation for longer periods.

A systematic review and meta-analysis conducted in children with ASD did not recommend the use of L-carnosine in ASD as there was no sufficient data (Abraham et al., 2021). A systematic review on complementary and alternative medicine use for pediatrics with ADHD proposed the use of omega-3 fatty acids and zinc supplements and not of L-carnosine (Searight et al., 2012). Polyunsaturated fatty acids were also reviewed to have insufficient evidence for use in children with specific learning disorders (Tan et al., 2016).

Strengths and limitations

This is the first systematic review to report the effect of L-carnosine in children with ADHD and other associated medical conditions, such as sleep problems and learning disabilities. In spite of this, few limitations exist. There was a paucity of data and a meta-analysis could not be performed due to insufficient data and heterogeneity in the studies. An objective measure in this review was only blood analysis of EPA after supplementation. We could not derive a conclusion if L-carnosine produced a significant effect on Parent ADHD-RS-IV as it was given along with methylphenidate. Recall bias may be present as the studies relied on parent reports alone.

Future directions

Assessment of L-Carnosine levels in blood will help to determine if supplementation with L-Carnosine is required in children with ADHD. L-Carnosine can be given as add on therapy to conventional therapies in children with ADHD as the latter has been considered safe and reliable. Safety and efficacy of L-Carnosine should also be monitored in trials with long duration. More RCTs with long term follow-up must be employed investigating the effect of L-

Carnosine in ADHD. Caregivers and health care professionals must be vigilant on the occurrence and reporting of adverse events in CAM therapies.

Conclusion

This systematic review does not advance the use of L-Carnosine in children with ADHD owing to scarcity of trials. Future research can be conducted with larger number of participants, longer duration of trials and varied dosages of L-Carnosine.

Acknowledgements

We acknowledge the support provided by Sri Ramachandra Founder Chancellor Shri N.P.V Udayar Research Fellowship. We thank Dr. Krishna Undela, Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Guwahati, India for his guidance in writing the proposal.

Author contributions

MGR: Conceptualization of the study, methodology, supervision, validation, writing–review and editing; DAA: Conceptualization of the study, data curation, formal analysis, investigation, methodology, validation, writing–original draft preparation, writing– review and editing; PS: Investigation, writing–review and editing; AK: Investigation, writing–review and editing; All authors reviewed and approved the final study draft. MGR is guarantor for this paper.

Conflict of interest

The authors declare no conflict of interest regarding this article.

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