Details of the excellence in research work for which the Sun Pharma Research Award is claimed, including references and illustrations.

Background of the current research work

I work along with my research team in finding the efficacy and safety of various complementary and alternative medicines (CAM) for autism spectrum disorder (ASD). ASD is a heterogeneous neurodevelopmental disorder with increasing prevalence worldwide. ASD is a complex neurodevelopmental condition that manifests as deficits in social and communication behaviors and the presence of restricted, repetitive behaviors. There is no definite cure for ASD. Thus, therapeutic interventions that aim to alleviate the symptoms of ASD have been widely used (i.e., occupational therapy, speech therapy, behavioral interventions, educational interventions). CAMs are widely used in ASD. These are found to ameliorate symptoms of ASD in some children as each child manifests symptoms very different from the other. We have chosen few CAMs and assessed their effects on ASD children.

Findings 1

We aimed to determine the effect of Pyridoxine – Magnesium sulphate on ASD children. Pyridoxine was reported to improve speech and language in some children with ASD. Few studies had recognized that larger dose of pyridoxine produce several undesirable side effects such as irritability and enuresis. To counter act these undesirable effects, Pyridoxine – Magnesium sulphate combination is preferred. We designed a clinical trial to determine the effectiveness of pyridoxine-Mg as adjunctive therapy in the management of ASD for 6 months. Children were randomly allocated to either standard care or an intervention care arm. The standard care arm involved occupational and speech therapies; the intervention care arm involved administration of 20mg pyridoxine hydrochloride and 40-mg magnesium sulfate for 3-year-old children and 30mg pyridoxine hydrochloride and 60-mg magnesium sulfate for 4- to 6-year-old children along with the standard care therapy. The study was approved by the Institutional Ethical Committee of Sri Ramachandra Institute of Higher Education and Research and the study was registered in the Clinical Trial Registry India (CTRI).

The parents of the first 2 children allocated in the pyridoxine-Mg arm for the trial had withdrawn their consent after 2 months of ingestion of drugs due to hyperactivity in their

children. Both parents withdrew their consent to participate in the trial. Adverse drug reactions monitored was reported to Pharmacovigilance committee and the study was terminated.

Reference:

Debi Ann A, Udayakumar N, Senta C, **Rajanandh MG**. Pyridoxine and Magnesium Administration-Induced Hyperactivity in Two Children With Autism Spectrum Disorder: Case Reports From a Clinical Trial. Clin Ther. 2020 Nov;42(11):e250-e258. doi: 10.1016/j.clinthera.2020.09.010.

Findings 2

We choose another CAM, namely L-carnosine, an amino acid containing β-alanine and l-histidine which has been proposed to have neuroprotective, antioxidant and anti-convulsive properties that may benefit ASD children. To the best of our knowledge, no study is conducted in Indian population, and therefore, the present study aims to determine the efficacy of L-carnosine as an adjunctive therapy to standard treatment approaches on disease severity, sleep pattern and gastrointestinal problems in children with ASD.

The study was designed as a randomized, parallel-group clinical trial. The study was approved by the Institutional Ethical Committee of Sri Ramachandra Institute of Higher Education and Research and the study was registered in the Clinical Trial Registry India (CTRI). Treatment with L-carnosine (10–15 mg/kg) as adjunctive therapy for occupational and speech therapy did not statistically improve the total score of Childhood Autism Rating Scale, Second Edition – Standard Version (CARS2-ST), Autism Treatment Evaluation Checklist (ATEC), and other evaluated parameters.

Reference

Ann Abraham D, Narasimhan U, Christy S, **Muhasaparur Ganesan R**. Effect of L-Carnosine as adjunctive therapy in the management of children with autism spectrum disorder: a randomized controlled study. Amino Acids. 2020 Dec;52(11-12):1521-1528. doi: 10.1007/s00726-020-02909-1.

We also performed meta analysis of our topic to compare our data with other clinical trial data.

Reference

Abraham DA, Undela K, Narasimhan U, **Rajanandh MG**. Effect of L-Carnosine in children with autism spectrum disorders: a systematic review and meta-analysis of randomised controlled trials. Amino Acids. 2021 Apr;53(4):575-585. doi: 10.1007/s00726-021-02960-6.

Findings 3

Since we found no significant difference in autism severity measured by Childhood Autism Rating Scale (CARS2-ST) and Autism Treatment Evaluation Checklist (ATEC) before and after supplementation with L-carnosine, we planned to estimate the plasma levels of L-carnosine in children with ASD before and after supplementation to know whether the dose of L-carnosine was sufficient enough to produce an effect. To the best of our knowledge, no studies have investigated the level of plasma L-carnosine in children with ASD before and after supplementation with L-carnosine in Indian population. We developed and validated a bio analytical method for estimation of L-carnosine in plasma. A prospective single group pre-post comparison trial was conducted. As per the selection criteria, children were enrolled for the study. Commercially available brand of L-carnosine was administered at a dose of 10-15mg/kg in two divided doses along with their standard therapies such as occupational and speech therapy for 2 months. Blood samples were collected before and after supplementation into 5 ml EDTA tubes in the morning before the 1^{st} dose of L-carnosine (day 0) and on the day after the last dose (day 60). The blood samples were centrifuged at 12800 rpm for 5 minutes to separate plasma. They were transferred into airtight containers and stored at -20˚C until analysis. Plasma L-carnosine levels before and after supplementation of L-carnosine were 33.7± 0.2 ng/ml and 34.7± 0.1 ng/ml respectively with no statistical significant difference (p>0.05).

We are writing manuscript for publication. Once the journal is chosen, we may submit to journal within this month end.

In pipeline

Our next target on this topic is to measure the level of enzyme carnosinase activity with different doses of L-carnosine.

Signature of the applicant

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