L-carnitine versus Propranolol for pediatric migraine prophylaxis

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Abstract

Objective

Carnitine plays a significant role in fatty acid transportation in mitochondria and has been shown to have a prophylactic effect on adult migraine. The aim of this randomized controlled trial was to compare and evaluate the effects of L-carnitine supplementation versus propranolol in the prevention of pediatric migraine.

Materials & Methods

A total of 60 pediatric patients with episodic migraine were randomly allocated to 2 independent groups to receive either 50 mg/kg/day L-carnitine or 1 mg/kg/day propranolol as a prophylactic drug. Frequency, severity, and duration of migraine attacks and headache disability based on the Pediatric Migraine Disability Assessment Score (PedMIDAS) were studied at the baseline and after 2, 4, and 12 weeks.

Results

A total of 56 patients were evaluated in the study: 23 girls (41%) and 33 boys (59%) with a mean age of 9.7 ± 2.1 years. Frequency of migraine headaches per month reduced from 11.4 ± 7.1 to 5.34 ± 2.4 in the L-carnitine group and from 10.7 ± 6.2 to 4.96 ± 3.9 in the propranolol group by the end of the study. Headache severity score was also reduced from 19.38 ± 14 to 2.88 ± 7.4 and from 12.92 ± 13 to 0.82 ± 1.3 in the L-carnitine and propranolol groups, respectively. We found a significant decrease in frequency, severity, and duration of headache attacks in both groups ($P < 0.01$). No significant difference was observed between the efficacies of the 2 drugs.

Conclusion

This study concluded that L-carnitine supplementation can play a prophylactic role in the management of pediatric migraine.

Keywords: Migraine; Pediatrics; Prophylaxis; L-carnitine; Propranolol
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Introduction

Migraine is the most frequent type of headache in both adults and children and accounts for 75% of headaches in young children referred for neurological consultation (1, 2). Pulsating head pain accompanied by increased sensitivity to environmental stimuli, such as light (photophobia) or sound (phonophobia), and/or gastrointestinal symptoms are the main diagnostic features of a migraine attack (3).

Prevalence of migraine is reported to be around 1%–3% in 3–7 years-old and 4%–11% in 7–11 years old, which increases to 8%–23% by the age of 15 years (4), and while it may not be a life-threatening illness in the majority of patients, it can severely interfere with the daily life of a growing child, including academic performance, quality of life, and leisure activities (5, 6).

A full understanding of the pathophysiology of migraine is still not available. Besides the common vascular and neuronal theories (7-9), impaired oxygen metabolism due to mitochondrial disorders has been hypothesized since the 1980s (10-13). Since then, numerous studies have tested this hypothesis and various types of evidence (including biochemical, morphological, genetic, and therapeutic) are reported, which further supports the association between mitochondrial disorders and migraine-type headaches (14).

The treatment strategy for migraine is divided into acute and preventive therapy (15). Beta-adrenergic receptor antagonists (beta-blockers) were the first class of migraine prophylactic medications, which still have a firm place in preventive therapy and have shown to be very effective in reducing the frequency and severity of migraine attacks when used at an optimum dose (16). Beta-blockers exert their effect mainly centrally by modifying neuronal excitability. Also, there is a report that their preventive action is mediated through beta-1 adrenoceptor inhibition in nociceptive neurons in the thalamus. Antagonist effects of beta-blockers on 5-hydroxytryptamine (serotonin or 5-HT) receptors and inhibition of nitrous oxide production are other suggested mechanisms (17).

Carnitine is necessary in the mitochondrial oxidation of fatty acids and stimulates lipid-mediated energy production in the central nervous system. Any faults in this mechanism could lead to toxin accumulation, which then potentiates nociceptive triggers (14). L-carnitine, the biologically active form of carnitine, facilitates β-oxidation by helping the transport of activated long-chain fatty acids from the cytosol to the mitochondrial matrix. Due to its important role in the central metabolism of the human body, it has been used as a migraine prophylactic agent. Besides, oxidative stress along with decreased antioxidant defenses are other associated factors in the pathogenesis of migraine headache (18). Carnitine might play a prophylactic role due to its potent antioxidant activity, which protects the cells against oxidative injury (19).

Various forms of carnitine have been shown to be effective as a potent prophylactic nutraceutical agent for migraine in the adult population with minimal side effects (20, 21); therefore, we evaluated the efficacy of L-carnitine supplementation versus propranolol for the prevention of migraine in pediatric patients.

Materials & Methods

Subjects

Guidelines of the International Headache Society were considered for the design and conduct of this randomized controlled trial (22). Subjects

were chosen from those who were referred to the pediatric neurology clinics of Imam Hossein Children's Hospital and Al-Zahra Hospital, between September 2018 and February 2019, in Isfahan, Iran. All referred children between 5 and 15 years of age who met the International Classification of Headache Disorder III (ICHD-III) (23) criteria for episodic migraine with or without any history of aura were enrolled for this randomized clinical trial. All participants were newly diagnosed with at least 1 migraine attack per week. None was receiving any prophylactic drugs at the start of this study. Two expert pediatric neurologists examined all the participants in the first visit to confirm the diagnosis and inclusion criteria, from which 60 were subsequently enrolled for this trial. Children suffering from metabolic acidosis, kidney dysfunction, any serious systemic diseases, secondary headaches, or headaches other than migraine were not included.

Subjects were excluded from this clinical trial if they did not adhere to the study protocol, missed their follow-up visits, experienced any severe adverse drug reactions, experienced continuous headaches, or if the diagnosis was changed during the course of the study.

The protocol of the study was clearly explained to all parents or the legal guardian of the child and a written consent form was signed before participation.

Study design

All parents were informed about the clinical trial and that their child would either receive a drug or a nutraceutical supplement. If they consented to join, their child was assigned to group 1 or group 2 using a randomized number list created before the start of the study. The first group received L-carnitine (50 mg/kg), which was divided into 2 doses per day, and the second group received 1 dose of propranolol (1 mg/kg) daily. Participants did not take any other migraine prophylactic drugs during the course of this study. An analgesic or nonsteroidal anti-inflammatory drug was prescribed in the case of an acute attack and the patients were advised to refer to the clinic if their headache continued after 2 days.

Data gathering

A data form containing demographic data and questions regarding the headache type, severity, frequency, duration, accompanying symptoms, and headache disability was filled in the first visit. These data were collected by a neurologist, who filled in the questionnaires during a face-to-face interview with the parents of the child.

The Pediatric Migraine Disability Assessment Score (PedMIDAS) questionnaire was used for assessing headache disability and the impact of migraine headaches in children and to monitor their response to treatment (24). Follow-up appointments were arranged after 2 weeks, 1 month, and 3 months of the first visit.

Side effects

At each follow-up visit, the participating children and their parents were asked about any adverse drug events. Four patients in group 1 (receiving L-carnitine supplementation) were excluded from the study due to gastric cramps and stomachache (3 cases) and vomiting (1 case).

Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normality of the collected data. The Mann–Whitney, Friedman, and chi-square tests were

implemented to explore the differences between the groups. Statistical analysis was done using SPSS for Windows version 20 (SPSS Inc., Chicago, IL, USA) and *P*-value below 0.05 was considered as significant.

Results

A total number of 60 participants were enrolled, out of which 56 patients completed the study. A total of 31 patients received L-carnitine (group 1) and the remaining 29 patients received propranolol (group 2). Four patients of group 1 were excluded due to gastric complaints. The average age of the patients in group 1 and 2 was 9.6 ± 1.9 and 9.8 ± 2.4 years, respectively. No significant difference was observed between the groups in terms of age and gender of patients ($P < 0.01$). Table 1 shows the demographic specifications of the participants. Our study indicated that both L-carnitine and propranolol significantly lower the number of headache attacks. Mean number of migraine attacks per month was 11.4 in the L-carnitine group and 10.7 in the propranolol group, which dropped to 5.34 and 4.96, respectively, by the end of this study (Table 2).

Severity score of attacks (based on the PedMIDAS questionnaire) decreased in both groups, from 19.38 to 2.8 in the L-carnitine group and from 12.92 to 0.82 in the propranolol group (mean ± SD). This reduction in severity of headache attacks was statistically significant in both groups (Table 3).

At the beginning of the study, about 15% of participants in both groups suffered migraine attacks, which lasted for more than 6 hours. This number was reduced to zero after 1 month of prophylactic therapy. In general, both drugs significantly lowered the duration of headache attacks (Table 4).

This research project demonstrates that both L-carnitine and propranolol significantly reduce the average headache frequency, duration, and severity in pediatric patients. However, no significant difference was observed between the efficacies of the two drugs during the course of the study.

Table 1. Comparing age distribution of participants between the two groups.

Age groups (year)	L-carnitine group	Propranolol group	Total
5-8	4 (15%)	5 (17%)	9 (16%)
8-11	12 (44%)	11 (38%)	23(41%)
11-15	11 (41%)	13 (45%)	24(43%)
Total	27	29	56

Data is presented as N(%).

Table 2. Comparing migraine headache frequency per month between the two groups at baseline and each visit.

Group	Baseline	After 2 weeks	After 4 weeks	After 12 weeks	P-value
L-carnitine	11.4 ± 7.1	7.84 ± 4.1	6.42 ± 3.5	5.34 ± 2.4	< .01
Propranolol	10.7 ± 6.2	6.71 ± 3.5	7.35 ± 4.4	4.96 ± 3.9	< .01

Data is presented as mean ± standard deviation. The difference in headache frequency between the two groups at each visit was not statistically significant ($p > 0.1$).

Table 3. Comparing migraine headache severity score based on PedMIDAS questionnaire between the two groups at baseline and each visit.

Group	Baseline	After 2 weeks	After 4 weeks	After 12 weeks	P-value
L-carnitine	19.38 ±14	3.23 ± 3.7	1.8 ± 3	2.88 ± 7.4	< .001
Propranolol	12.92 ±13	2.32 ± 3.2	1.5 ± 2.2	0.82 ± 1.3	< .001
P-value	0.055	0.254	0.919	0.767	

Data is presented as mean ± standard deviation.

Table 4. Comparing migraine headache duration between the two groups at baseline and each visit.

	L-carnitine group					Propranolol group				
	No headache	< 1 hour	1-2 hours	2-6 hours	> 6hours	No headache	< 1 hour	1-2 hours	2-6 hours	> 6hours
Baseline	0	2(7.7%)	10(38.5%)	10(38.5%)	4(15.4%)	0	7(25%)	10(35.7%)	7(25%)	4(14.3%)
After 2 weeks	1(3.8%)	12(46.2%)	6(23.1%)	6(23.1%)	1(3.8%)	5(17.9%)	11(39.3%)	6(21.4%)	4(14.3%)	2(7.1%)
After 4 weeks	8(30.8%)	9(34.6%)	6(23.1%)	3(11.5%)	0	9(32.1%)	11(39.3%)	5(17.9%)	3(10.7%)	0
After 12 weeks	8(30.8%)	8(30.8%)	8(30.8%)	2(7.7%)	0	7(25%)	15(53.6%)	4(14.3%)	2(7.1%)	0

Data is presented as N(%). Both l-carnitine and propranolol significantly decreased headache duration in the two groups ($p < 0.001$). The difference in headache duration between the two groups at each visit was not statistically significant ($p > 0.1$).

Discussion

It is reported that up to 75% of children experience headaches by the age of 15 years, from which migraine headache is the most frequent type and occurs in up to 28% of teenagers (25). This debilitating ailment has a significant effect on the social and academic life of a child, which will be even more aggravated if there are any other psychological co-morbidities like depression or anxiety. It causes absenteeism in school, exclusion from social interactions, and also exerts a great economic burden on the parents as a result of increased healthcare and admission costs.

Different pharmacologic regimens are advised for migraine prophylaxis, but the safety of the prescribed drugs in pediatric patients is still not clear (3), and there are even some reports that question the risk–benefit ratio of such preventive therapies (6). In recent years, the focus has shifted toward nutraceutical agents that have a role to play in the cellular metabolic chain. The efficacy of such agents has been studied in adult patients (20, 21), but this effect needs to be assessed and confirmed in pediatric patients because childhood and adult migraines exhibit slightly different behaviors (26). From this list, carnitine is a potential complementary approach and has shown evidence of efficacy (19, 27).

Tarighat et al evaluated the effects of magnesium, L-carnitine, and concurrent magnesium–L-carnitine supplementation in migraine prophylaxis. L-carnitine supplementation was shown to significantly decrease migraine duration, frequency, and severity (20). There is also a report that patients with carnitine palmitoyltransferase II deficiency suffer migraine-type headache, which is alleviated by carnitine supplementation (21). Despite the above-mentioned studies, in a triple-blind crossover study, Hagen et al did not observe any significant differences in headache outcomes between acetyl-carnitine and placebo (28).

On the other hand, propranolol is a nonselective beta-blocker that is highly lipid soluble and can easily reach the central nervous system to exert its effect. Propranolol was the first beta-blocker that was used for prophylactic migraine therapy, and its effect compared to placebo has been confirmed by several trials (29, 30). Favorable efficacy of propranolol is tested in pediatric studies; Eidlitz-Markus et al measured the effects of low-dose propranolol versus amitriptyline for treating severe pediatric migraine. This study showed that the response rate was higher than previously reported results for placebo, and both drugs were effective on reducing migraine headache frequency. However, propranolol should be preferred due to its lower risk of side effects. Response to propranolol was also significantly better in those who experience migraine headaches without aura compared to migraine with aura (31). In another randomized clinical trial by Togha et al, the prophylactic efficacy and safety of cinnarizine was compared to propranolol. Cinnarizine reduced the baseline headache frequency by more than 50% in 74.6% of patients, and more than 50% reduction of the baseline headache frequency was seen in 72.5% of patients in the propranolol group. No significant difference was seen between the 2 groups (32). or sodium valproate (33) in reducing the frequency, severity, and duration of migraine attacks.

A majority of patients who are placed on a migraine preventive treatment will require long-term therapy. Therefore, it is very important to select the safest available medicine with the least critical potential adverse side effects. Beta-blockers are associated with impaired glucose tolerance and

an increased risk of new-onset diabetes (34-35). Hypotension, depression, and dizziness are the most common reported side effects of propranolol, and it should be avoided in children with asthma or liver pathology (17-36). This indicates the need for new treatment modalities in migraine prophylactic approaches.

In this randomized controlled trial, we assessed the prophylactic effects of L-carnitine supplementation on migraine headache compared to propranolol in a sample of pediatric patients. Current findings showed a positive prophylactic role for L-carnitine in pediatric migraine, which is in agreement with the previous reports on adult population (20, 21). Frequency, severity, and duration of the migraine attacks were reduced in both groups, but the difference between the efficacies of the 2 drugs was not significant.

A total of 4 out of 31 patients treated with L-carnitine manifested side effects (3 cases of gastric cramps and stomachache and 1 case of vomiting), who were subsequently excluded. No serious or life-threatening drug adverse effects were reported during the course of this study.

The main limitation of this research was that our study design was not blinded and we did not have a placebo group due to ethics considerations. We believed it is ethically wrong to administer placebo to children who suffer from recurrent debilitating pain.

In Conclusion

Current study indicated that L-carnitine supplementation at 50 mg/kg/day could be used as an effective complementary therapy for pediatric migraine prophylaxis. It was well tolerated and had a significant effect on increasing the quality of life of children who suffer from migraine. However, patients' compliance and preferences must be considered before prescribing this agent and studies with bigger sample size and longer follow-up time are recommended.

Acknowledgement

This study was approved by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1397.245) and is registered in the Iranian Registry of Clinical Trials (IRCT20190128042533N1).

Author's Contribution

Omid Yaghini designed the study and participated in sample recruitment. Mohammadreza Ghazavi and Nahid Aslani contributed to sample recruitment. Patients' interview and follow up, data gathering, data analysis and writing of the initial manuscript was done by Laya Amini. All authors have read and approved the final submitted manuscript

Conflict of interest

None declared

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