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The effect of topiramate and acetazolamide in patients with idiopathic intracranial hypertension compared to acetazolamide alone

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ABSTRACT

Background: Idiopathic intracranial hypertension (IIH) is a nervous disease characterized by increased intracranial pressure around the brain. It is induced by increased production or decreased reuptake of cerebrospinal fluid (CSF). The standard treatment of IIH includes medicines to reduce CSF production. Acetazolamide is the most commonly used drug in treating IIH and is also considered as the first-line treatment. Topiramate is used to treat obesity. Since obesity is a risk factor of IIH, topiramate is used to treat IIH. We investigated the effect of topiramate as an adjunct drug along with acetazolamide in patients with IIH who presented to Shahid Sadoughi Hospital in Yazd, central Iran.
Methods: This study was a double-blind clinical trial. Forty-eight IIH patients presenting to Shahid Sadoughi Hospital participated in the study, divided into two groups. The acetazolamide group received acetazolamide 750-1000 mg qd and the Acetazolamide+topiramate group received acetazolamide 750-1000 mg qd and topiramate 25-50 mg qd. CSF pressure, body mass index (BMI), and visual field were assessed at the beginning of treatment and 6 months after intervention. The gleaned data were analyzed with SPSS20 using statistical tests.
Results: Our findings showed significant differences in CSF pressure in acetazolamide group and CSF pressure, BMI, and visual field in acetazolamide+topiramate group at baseline and 6 months after treatment. There were also statistically significant differences between the mean score of retinal examination in IIH patients in both groups at second, fourth, fifth, and sixth months (P-value <0.05).
Conclusion: Topiramate can be used as an adjunct to acetazolamide to increase the effect of treatment in IIH patients.

Key Words: Idiopathic intracranial hypertension, Acetazolamide, Topiramate
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INTRODUCTION

IIH is a syndrome induced by increased CSF pressure without any known etiologic cause. It is also known as pseudotumor cerebri or benign intracranial hypertension.[1,2] IIH is a rare condition with, according to a study conducted in the United States, an incidence rate of 0.9 cases in 100,000 persons. It is more prevalent in obese women of child-bearing age. The common symptoms and complications of IIH include migraine headaches, nausea, vomiting, blurred vision, diplopia, papilledema, cranial nerves paralysis, and visual loss.[3,4] Since the etiologic cause of IIH is not known yet, various treatments have been offered.[5] These treatments aim at relieving headaches and preventing loss of vision.[6] The standard treatments of IIH include carbonic anhydrase inhibitor drugs that diminish CSF production. Acetazolamide is the first-line treatment and the most frequently administered drug. Acetazolamide is a carbonic anhydrase inhibitor used to treat glaucoma and sometimes tonic-colonic, myoclonic, and atonic seizures, especially in women who develop seizure at menopause or whose seizure aggravates at the time of menstrual cycle (specify which part of the menstrual cycle). Anaphylactic shock and acute pulmonary edema are among the complications of Acetazolamide.[7] Topiramate, also a carbonic anhydrase inhibitor, belongs to the second generation of antiepileptic drugs and is highly effective in treating epilepsy and headaches. It is also used to treat psychotic disorders and obesity. Since obesity is one of the risk factors of IIH, topiramate is used in treating IIH. The common unexpected side effects of topiramate are its negative effect on the identification of spontaneous glaucoma, weight loss, renal stones, and blood acidosis.[8,9] No study has yet investigated the detrimental complications of concurrent administration of topiramate and acetazolamide. This study explored the effects of topiramate used as an adjunct to Acetazolamide in IIH patients who presented to Shahid Sadoughi Hospital. The results will be used to improve the treatment of IIH.

METHODS

Forty-eight IIH patients who presented to Shahid Sadoughi Hospital located in Yazd, Iran, during (date) (add the date at which this study was

conducted) participated in this double-blind clinical trial. (add the sampling method) They were assigned randomly to two groups and were not aware of their treatment protocols. The inclusion criteria were: age 15-45 years, obesity (BMI>25 kg/ m2), no renal stones, and normal magnetic resonance imaging (MRI) results. In the case of presence of pregnancy, coagulation problems which interfere with performance of LP, and the complications of administered drugs (Topiramate and Acetazolamide) in the patients under study, they were excluded from the study à consider rephrasing into "Patients who were pregnant, had coagulation problems which could interfere with lumbar puncture (LP) and complications of administered drugs (topiramate and acetazolamide) were excluded from this study". One group underwent treatment with acetazolamide 750-1000 mg qd and the second group received both acetazolamide 750-1000 mg qd and topiramate 25-50 mg qd (unnecessary). Both groups were assessed twice for a six-month period. The first assessment was done at the beginning of treatment, while the second one was performed six months after intervention. The assessments were performed by an ophthalmologist who was blind to the study. These assessments included measurement of CSF pressure (with a normal range of 10-18 cmH_2O) via LP. During LP, the patient lies in the left lateral decubitus position to equalize the intraspinal canal and the intracranial pressure. Usually, a physician assistant (PA) bends the spinal column to open the lumbar intervertebral spaces dorsally (you need to specify whether this technique was done in your study. If yes, erase "usually"). After prepping the intended site, a needle of suitable size is inserted through the space between the L3 and L4 until the needle penetrates into the paraspinal space. To measure the CSF pressure, after the spinal needle enters the inferior end of the spinal cord, it is attached to a vertical glass tube, which the end is open to air. Then, the fluid is allowed to climb up in the tube as high as possible. If the fluid rises 136 mm above the needle level, it is said that its pressure is 136 mmH_2O. In this study, we measured the CSF pressure using the unit cm H_2O. Other assessment measures were BMI measurement and visual field (VF) examination. Perimetry was used to examine visual field by an ophthalmologist. This test uses two methods (consider changing into "Two methods were used"): kinetic perimetry in which light spots move within the perimeter, and static perimetry in which the light spots are fixed and the observer is asked to press a key to observe the light spots. The results of VF tests were reported as normal or abnormal. Moreover, the retinal examination was performed . every month for a 6-month period the results were reported as 0-4 scores. Scoring in direct ophthalmoscopy(in terms of papillary edema) has been as follows: score 1: mild,score 2: moderate,score 3: sever,score 4: Very severe with bleeding around the disc. Finally, the data culled were compared to investigate the effect of topiramate as an adjunct to acetazolamide. The gleaned data were analyzed with SPSS20.

RESULTS

In this study, 48 patients were investigated in acetazolamide group (21 patients), and acetazolamide+topiramate group (27 patients). The results after 6 months of follow up showed that the mean CSF pressure in the acetazolamide group was 363.68 ± 43.16 mmHg at the beginning and 205.5 ± 39.79 mmHg six months after intervention. The mean CSF pressure in the acetazolamide+topiramate group at baseline and 6 months was 364.82 ± 57.34 and 185.6±55.92 mmHg, respectively. A significant

Table 1 **Mean of CSF pressure at the intended times in the two groups under study**

	Time		Group	
	Number	Acetazolamide	Number	Acetazolamide+topiramate
Before intervention	20	363.68±43.16	29	364.82±57.34
6 months after intervention	20	205.5±39.79	25	185.6±55.92
P-value	0.000		0.000	

Table 2 **Mean BMI at the two intended times in both groups under study**

	Time		Group	
	Number	Acetazolamide	Number	Acetazolamide+topiramate
Before intervention	21	27.04±1.34	21	27.73±1.19
6 months after intervention	21	26.84±1.27	21	25.96±1.06
P-value	0.000		0.095	

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Table 3 Mean score of the patients' dorsal ocular exams at different times in both groups under study

	Mean±SD of mean scores of dorsal ocular examinations in terms of groups			
Time of Assessment	Group 1 (N=21)	Group 2 (N=26)	Total (N=47	P-value
First month	0.81±3.47	0.76±3.23	0.78±3.34	0.245
Second month	0.70±3.09	0.64±2.53	0.72±2.78	0.009
Third month	0.67±2.47	0.79±1.92	0.78±2.17	0.10
Fourth month	0.72±2.14	0.57±1.38	0.74±1.72	0.000
Fifth month	0.48±1.66	0.67±0.69	0.76±1.12	0.000
Sixth month	0.74±1.38	0.54±0.30	0.83±0.78	0.000

statistical difference between mean CSF pressure at the two times (consider to specify the two times: baseline and six months) was observed in the two groups (P-value >0.05) (Table 1).

BMI in the first group was 27.04 ± 1.34 kg/m2 before intervention and 26.84 ± 1.27 kg/m2 six months after intervention. In the second group, BMI before and six months after intervention were 27.73±1.19 kg/m2 and 25.96 ± 1.06 kg/m2, respectively. Furthermore, there was no statistically significant correlation between mean BMI before and after intervention in the first group, while in the second group significant correlation was demonstrated (P-value >0.05) (Table 2).

VF was not significantly different in the first group at the two intended times (P=0.687). On the other hand, the second group demonstrated significant VF differences at baseline and 6 months (avoid repetitive sentences) (P=0.002). The mean dorsal ocular examination score in the first month in the acetazolamide and acetazolamide+topiramate group was 3.47±0.81 (add the unit used) and 3.23±0.76, respectively. Statistical test showed significant retinal examination mean score difference in both groups in the first, fourth, fifth, and sixth months (P-value>0.05) (Table 3).

DISCUSSION

This study investigated the effect of topiramate as an adjunct to acetazolamide in idiopathic intracranial hypertension patients. Many studies have been conducted over recent years exploring the effects of drugs in IIH patients, such as acetazolamide and topiramate. All studies used acetazolamide as the standard treatment of IIH. A systematic review in 1991 introduced acetazolamide as the first line of treatment for IIH.[10] The results of another study (2013) indicated the suppressive effect of acetazolamide on intracranial pressure,.[11] The findings of these studies were consistent with our results which showed that acetazolamide alone reduced CSF pressure significantly after 6 months of treatment. Presupposing that topiramate can decrease BMI in obese patients,[12] some studies were performed to prove this postulation. In a study in 2005, the effect of topiramate on decreasing weight in bipolar patients was investigated and it was found that this drug exerted a significantly positive effect.[13] Moreover, a systematic review in 2009 introduced topiramate as a safe and effective medicine to treat obesity induced by excess alcohol drinking.[14] Considering that obesity is rendered as a risk factor of IIH,[15] some studies were conducted to examine the effect of topiramate on improving IIH by diminishing their BMI. The study in 2007 which compared the effect of topiramate and acetazolamide in IIH patients found significant difference in the rate of healing in the two groups indicating that topiramate is useful in treating IIH patients.[16] Another systematic review carried out in 2013 revealed that both topiramate and acetazolamide are effective in treating IIH.[17] The results of these two studies are consistent with our findings that the combination of topiramate+acetazolamide leads led to significant decrease in CSF pressure. Also, our study suggested that the effect of topiramate was greater during the fourth to sixth months. Additionally, there was a significant difference in acetazolamise+topiramate group after 6 months of intervention which is consistent with the results of 2007 study.[16]

Note: please elaborate about the BMI and retinal examination findings.

CONCLUSION

It may be concluded that the acetazolamide alone or in conjunction with topiramate are effective in treating IIH. However, considering the greater reduction in CSF pressure in the second group, it can be inferred that the combination of Acetazolamide+topiramate exerted a greater effect in improving IIH. Furthermore, the significant decrease in BMI in the second group and lack of significant decrease of this variable in the first group after 6 months of intervention indicated that topiramate improves IIH patients through diminishing

BMI. Moreover, the statistical significance of Visual Field status in the second group patients and lack of its significance in the first group after 6 months of treatment demonstrates that topiramate has not only improved the IIH patients to a greater degree but also exerted a positive effect on the Visual Field of the patients leading to improved VF in patients after 6 months. Consequently, it may be concluded that the combination Acetazolamide+topiramate is the best combination for treating IIH patients and it should replace treatment with Acetazolamide alone. (more suitable to be written in the discussion)

Note: consider simplifying the conclusion. You can elaborate more in the discussion section. To conclude, you can say "Topiramate improves IIH through diminishing BMI, and has also positive effects on visual field"

SUGGESTIONS FOR FURTHER RESEARCH

We recommend further studies be conducted with more sample, variables, complications researched, and in longer time intervals. Moreover, future studies may explore more drugs to be used for treatment of IIH.

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