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Efficacy of Acetazolamide in management of idiopathic intracranial hypertension: A systematic review and meta-analysis

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ABSTRACT

Objectives: To investigate the efficacy of acetazolamide in the treatment of idiopathic intracranial hypertension. *Methods*: We searched PubMed, Scopus, Web of Science, and Cochrane central for relevant published clinical trials. We performed the risk of bias using Cochrane's risk of bias tool. Our outcomes of interest were: SF-36 mental and physical scores, papilledema grade, diplopia, optic nerve head (ONH) volume, and 6-item listed headache impact test (HIT6). We conducted the analysis using OpenMeta Analyst Software and used mean difference (MD) with 95% confidence interval (CI) for analyzing continuous data, while risk ratio (RR) and 95% CI was used for analyzing dichotomous outcomes. *Results:* We included six clinical trials in our analysis. The results revealed that, compared to baseline, acetazolamide significantly improves the SF-36 physical score (MD=3.54, (95% CI [-2.014%, 9.107%), SF-36 mental score (MD=2.593, (95% CI [-2.238%, 7.424%), reduces papilledema grade (MD=-0.687, (95% CI [-1.795%, 0.420%), and HIT6 score (MD=-5.675, (95% CI [-14.745%, 3.395%). *Conclusion*: Acetazolamide is an effective medical treatment for idiopathic intracranial hypertension. However, more studies are still required to provide clearer evidence about the drug efficacy and safety.

Keywords: Acetazolamide, idiopathic intracranial hypertension, pseudotumor cerebri.

1. INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a syndrome characterized by elevated intracranial tension of more than 250 mm of water in the absence of any space-occupying lesion (Iacobaeus et al., 2016; Wakerley et al., 2015; Dhungana et al., 2010). The exact aetiology is still unknown. The incidence is about 0.9 per 100.000, and it is increasing among young obese (Durcan et al., 1988; Radhakrishnan et al., 1993; Kesler et al., 2001). There is no gender difference regarding the disease incidence among children; however, the female-to-male ratio is about 10:1 in adults (Kesler et al., 2002). Patients with IIH suffer from symptoms and signs of increased intracranial tension, including blurred vision, disabling headache, abducens nerve palsies, and pulsatile tinnitus without any radiological or laboratory evidence of intracranial lesion (Kesler et al., 2002; Cassano et al., 2017; Sultan et al., 2020). The cerebrospinal fluid (CSF) analysis is normal in most cases except for some evidence of increased intracranial tension. Headache is the most debilitating symptom. It occurs in about 100% of patients (Cassano et al., 2017). Visual disturbance is the second common symptom (Wall et al., 1991). Besides, visual examination reveals bilateral asymmetrical papilledema in most patients. All of these symptoms tend to resolve with treatment of IIH (Wall et al., 1998). On the Contrary, visual field defects and visual acuity may not show any improvement after the resolution of IIH. It follows a benign course in most cases. However, it may be aggressive and cause blindnessunilateral or bilateral in 8–10% (Wall et al., 1991; Wall et al., 1998; Corbett, 1987). The first diagnostic criteria were published in 1937 by Dany, and recent criteria are published in the International Headache Society 2nd edition (Dandy, 1937; Arnold, 2018).

The diagnosis of HII depends on the exclusion of other causes of increased intracranial tension. Magnetic resonance imaging (MRI) becomes the investigation of choice for the diagnosis of IIH (Skau et al., 2006; Boyter, 2019; Raoof et al., 2021). Management of IIH depends on a combination of medical treatment and weight reduction (Virdee et al., 2020). Only severe cases require surgical intervention. Several medical lines for treatment were used, such as diuretics, oral glycerol, corticosteroids, and carbonic anhydrase inhibitors (Jensen et al., 2016). Furosemide showed favorable results; however, it is much less potent than the carbonic anhydrase inhibitors. Recently, acetazolamide, a carbonic anhydrase inhibitor, is the drug of choice in the treatment of IIH. Acetazolamide reduces CSF production. However, some patients taking acetazolamide usually suffer from nausea, fatigue (Toscano et al., 2020). In resistant cases, repeated lumbar puncture, lumbo-peritoneal, and ventriculoperitoneal shunts can be used (Lueck et al., 2002). In this meta-analysis, we aim to get the efficacy of acetazolamide in treating patients with IIH.

2. METHODS

This systematic review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and adheres to the guidelines from the Cochrane Handbook (Green, 2008; Moher et al., 2009).

Eligibility Criteria

The inclusion criteria were: population: patients with pseudotumor cerebri (idiopathic intracranial hypertension), intervention: acetazolamide, comparator: placebo, included study designs: clinical trials, and primary outcomes: SF-36 mental and physical scores, papilledema grade, and diplopia. We excluded all secondary works, such as meta-analyses and reviews, all animal studies, conference abstracts, and studies with incomplete reported data.

Information Sources

We searched PubMed, Scopus, Web of Science, and Cochrane CENTRAL databases till April 2021 for articles that matched our inclusion criteria.

Search and Study Selection

We used the following search strategy in our search: acetazolamide AND (pseudotumor cerebri OR idiopathic intracranial hypertension). We screened the included articles in three steps. The first step implied importing the results from electronic databases to a Microsoft Excel sheet using End Note Software. The second step was done by two independent authors and included title and abstract screening of the articles imported to the Excel sheet. The third step was the full-text screening of the included citations from step 2. Additionally, we manually searched the references of the included papers for possible missed studies.

Data Collection

We collected three categories of data from each included study: the first category is the baseline and demographic characteristics of the included participants, such as the author, year, sample size, age, and gender. The second category included the outcomes of analysis, mainly: SF-36 mental and physical scores, papilledema grade, and diplopia. The third category included data for risk of bias assessment. The process of data collection was done using Microsoft Excel.

Risk of bias Assessment

We followed The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Guidelines in assessing the quality of this study. Two authors assessed the risk of bias among included studies using Cochrane's risk of bias tool for clinical trials (Green 2011). The tool assesses proper randomization of patients, allocation concealment, and adequate blinding through seven domains (Green 2011). Each domain is put to either "low", "unclear", or "high" risk of bias.

Analysis

We performed the meta-analysis of this study using Open Meta Analyst Software. Our study included continuous and dichotomous outcomes. We analyzed continuous data using mean difference (MD) and 95% confidence interval (CI), while dichotomous data were analyzed using risk ratio (RR) and 95% CI. The fixed-effects model was used when data were homogeneous, while heterogeneous data were analyzed under a random-effects model. To measure the presence of inconsistency among the studies, we used the I^2 and the p-value of the Chi-square tests (Green, 2008). Values of $P < 0.1$ or $I^2 > 50\%$ were significant indicators of the presence of heterogeneity. We tried to solve the inconsistency of heterogeneous outcomes using Cochrane's leave-one-out method (Green, 2008). We conducted two types of analyses, 1) a single-arm analysis to assess the incidence of diplopia and the average pooled value of the scores, and 2) a double-arm analysis comparing baseline with post results.

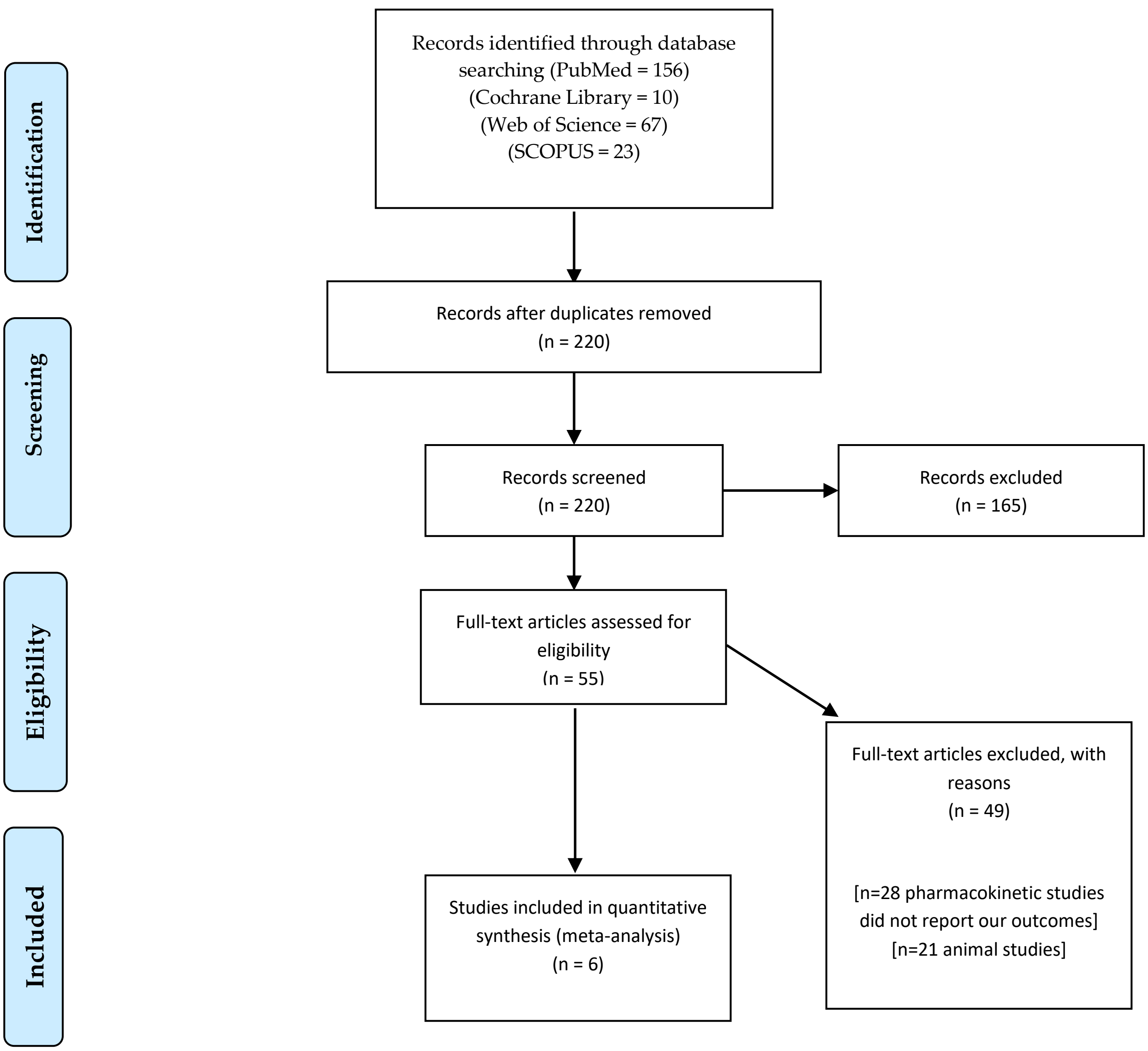

Figure 1 shows a PRISMA flow diagram of our literature search.

3. RESULTS

Summary of Included Studies

The results of our literature search are illustrated in figure 1. In our study, we performed the analysis of 297 patients with idiopathic intracranial hypertension from six studies (Celebisoy et al., 2007; Ball et al., 2011; Kupersmith et al., 2017; Sheils et al., 2018; Committee, 2014; Wall et al., 2017).

All patients received acetazolamide and were followed up to assess its beneficial effect. The average age of patients was 30.7 years. Data of included patients, their demographic data, and their BMI are described in Table 1, while baseline data of the included outcomes are illustrated in Table 2.

Table 1 A detailed summary of the included participants, their demographic data.

Study ID	Sample size, n	Age (years)	Females (%)	BMI
	ACZ	ACZ	ACZ	ACZ
Ball 2011	25	35(12.2)	88	41.8(7.8)
Celebisoy 2007	20	33.75(8.8)	85	NR
Sheils 2019	86	28.2 (6.9)	97.7	40.0 (8.5)
IIHTT 2014	86	28.2 (6.9)	97.7	40.0 (8.5)
Kupersmith 2016	44	NR	NR	NR
Michael Wall 2017	36	28.4 (7.0)	100	NR

Data is represented as mean (SD). BMI: body mass index and NR: not reported.

Table 2 Baseline values of headache, diplopia, HIT-6, ONH volume, SF-36 physical, and SF-36 mental.

Study ID	Headache (%)	Diplopia (%)	HIT-6 Score	ONH volume	SF-36 physical	SF-36 mental
	ACZ	ACZ	ACZ	ACZ	ACZ	ACZ
Ball 2011	86	16	NR	NR	NR	NR
Celebisoy 2007	100	10	NR	NR	NR	NR
Sheils 2019	81.4	23.3	60.3 (8.7)	NR	45.4 (9.8)	45.2 (11.8)
IIHTT 2014	81.4	23.3	60.3 (8.7)	NR	45.4 (9.8)	45.2 (11.8)
Kupersmith 2016	NR	NR	NR	16.5 ± 3.8	NR	NR
Michael Wall 2017	NR	NR	61.3 (8.6)	NR	43.7 (10.1	43.0 (13.4)

Data is represented as mean (SD). HIT: Headache Impact Test, ONH: optic nerve head, and NR: not reported.

Results of risk of bias

The result of the risk of bias assessments yielded an overall low risk of bias according to Cochrane's tool (Green, 2011). All the included (Celebisoy et al., 2007; Ball et al., 2011; Kupersmith et al., 2017; Sheils et al., 2018; Committee, 2014; Wall et al., 2017) were randomized trials, therefore. The randomization domain was at low risk. Regarding allocation concealment, the IIHTT study (Committee, 2014) was at low risk, but the rest of the studies did not report enough data about allocation concealment (Celebisoy et al., 2007; Sheils et al., 2018; Wall et al., 2017). The majority of the included studies (Celebisoy et al., 2007; Ball et al., 2011; Kupersmith et al., 2017; Sheils et al., 2018; Wall et al., 2017) were not blinded, and only the IIHTT (Committee, 2014) study was blinded to the participants and personnel. All the included studies (Celebisoy et al., 2007; Ball et al., 2011; Kupersmith et al., 2017; Sheils et al., 2018; Wall et al., 2017) showed a high risk of blinding of outcome assessment except for IIHTT (Committee, 2014). The remaining domains of the Cochrane tool were all at low risk of bias. Summary of the risk of bias is shown in figure 2.

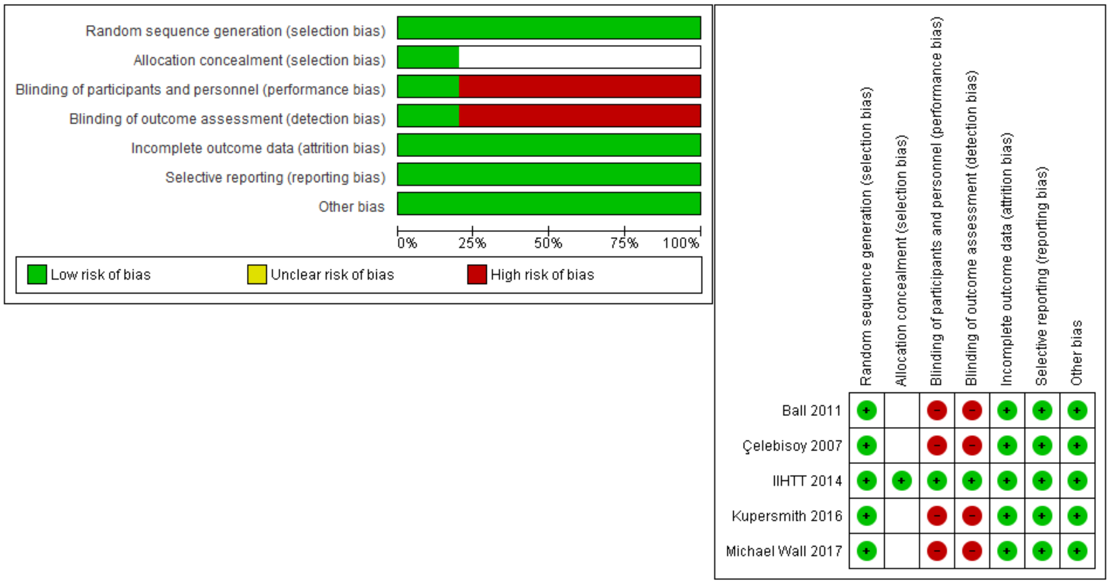

Figure 2 Summary of risk of bias assessment.

Analysis of outcomes

SF-36 physical

Two studies have reported the SF-36 physical outcome (Committee, 2014; Wall et al., 2017). The SF-36 physical score had improved significantly compared to baseline (MD=3.54, (95% CI [-2.014%, 9.107%). Data was heterogeneous (I^2=82.26%, p=0.018) figure 3a. We could not solve the heterogeneity. The results of the single-arm analysis revealed an overall pooled mean of 51.876 (95% CI [50.273%, 53.480%). The analysis was homogenous (I^2=0%, p=0.718), figure 3b.

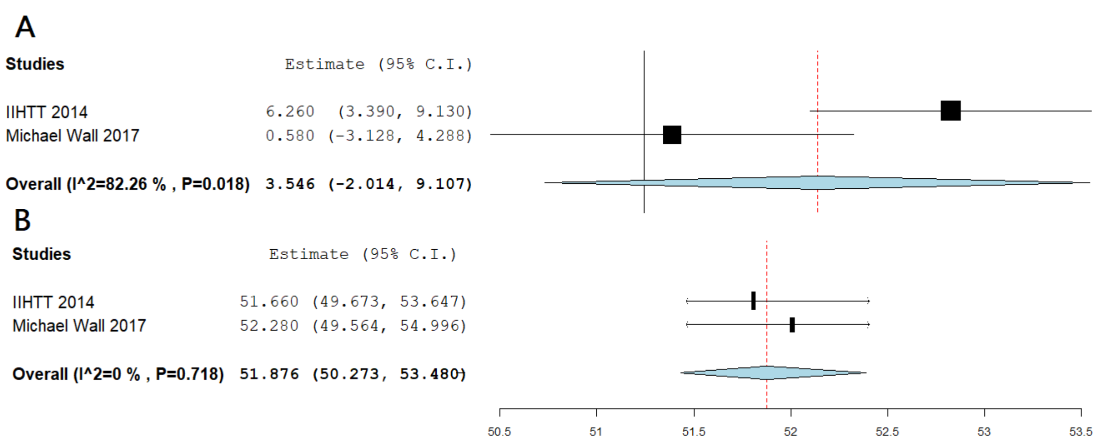

Figure 3 a, b meta-analysis of SF-36 physical outcome.

SF-36 mental

SF-36 score was reported by two studies (Committee, 2014; Wall et al., 2017). The analysis showed a significant improvement in SF-36 mental score in the treatment group compared to baseline (MD=2.593, (95% CI [-2.238%, 7.424%), the combined analysis was heterogeneous (I^2=74.59%, p=0.047) figure 4a. Heterogeneity could not be solved. The results of the single-arm analysis showed an overall pooled mean of 50.514 (95% CI [48.780%, 52.248%). The analysis was homogenous (I^2=0%, p=0.701), figure 4b.

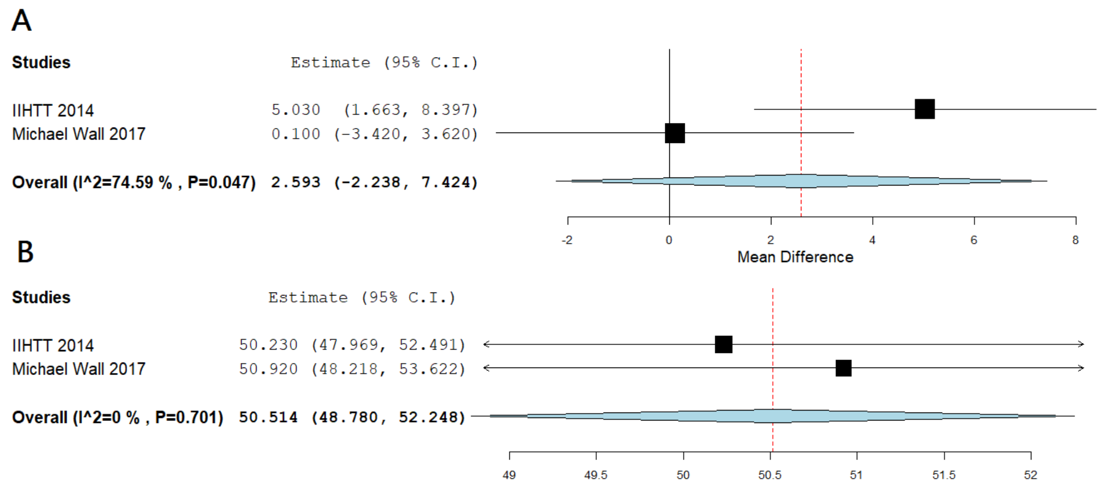

Figure 4 a, b meta-analysis of SF-36 mental outcome.

Papilledema grade

Two studies (Committee, 2014; Wall et al., 2017) have reported papilledema grade. The combined mean difference showed a significant decrease in papilledema grade after treatment (MD=-0.687, (95% CI [-1.795%, 0.420%), Data was heterogeneous (I^2 =96.72%, p=0.001) figure 5a. we could not solve the heterogeneity. The single-arm analysis results showed an overall combined mean of 0.914 (95% CI [-0.134%, 1.963%). The analysis was heterogeneous (I^2 =98.02%, p=0.01), figure 5b.

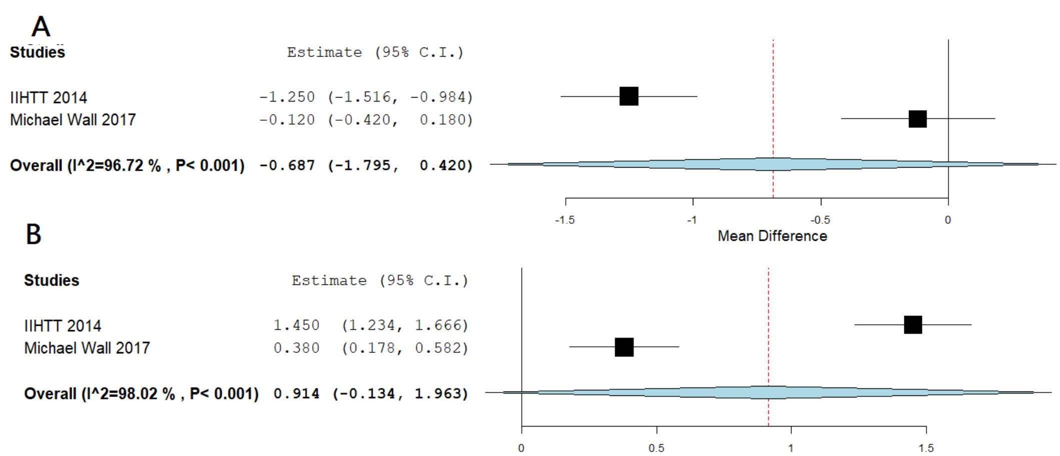

Figure 5a, b meta-analysis of Papilledema grade.

Headache Impact Test (HIT6)

HIT6 outcome was reported by two studies (Committee, 2014; Wall et al., 2017). HIT6 score was significantly decreased in the treatment group compared to baseline (MD=-5.675, (95% CI [-14.745%, 3.395%), the overall analysis was heterogeneous (I^2 =92.27%, p=0.001), figure 6a. The results of the single-arm analysis revealed an overall pooled mean of 50.340 (95% CI [48.628%, 52.052%), Pooled analysis was homogeneous (I^2 =0%, p=0.729), figure 6b.

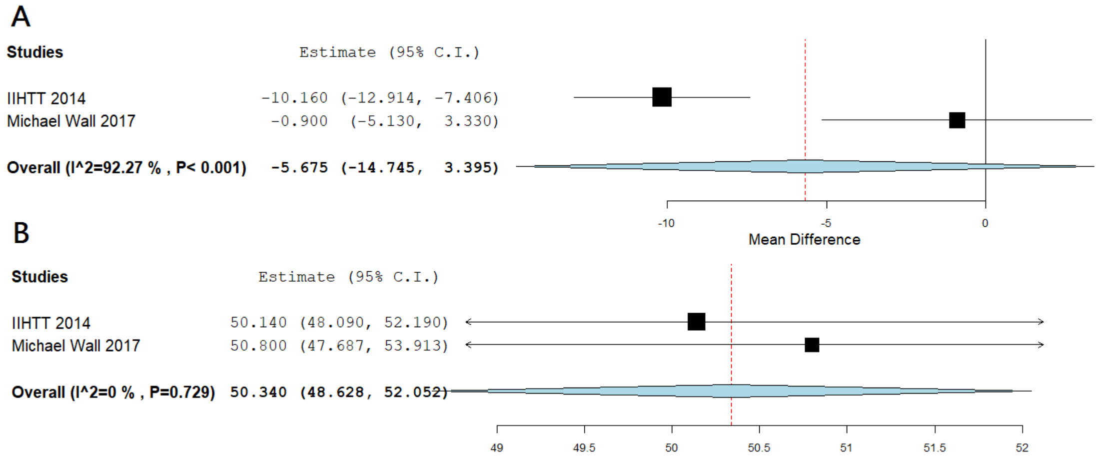

Figure 6 a, b meta-analysis of Headache Impact Test.

Diplopia

Two studies (Celebisoy et al., 2007; Ball et al., 2011) reported diplopia outcome. We found that the overall pooled proportion was 3.1% (95% CI [-2.1%, 8.3%). Data was homogeneous (I^2=0%, p=0.63), figure 7.

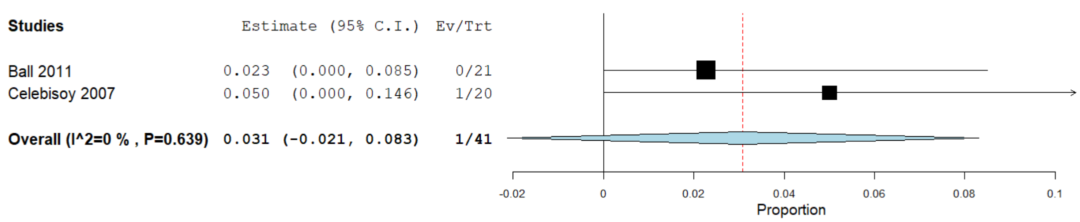

Figure 7 meta-analysis of Diplopia.

ONH volume

ONH volume was reported by two studies (Kupersmith et al., 2017; Sheils et al., 2018). We found an overall mean ONH volume of 12.677, (95% CI [10.758%, 14.596%). Data was heterogeneous (I^2=93%, p=0.001), figure 8.

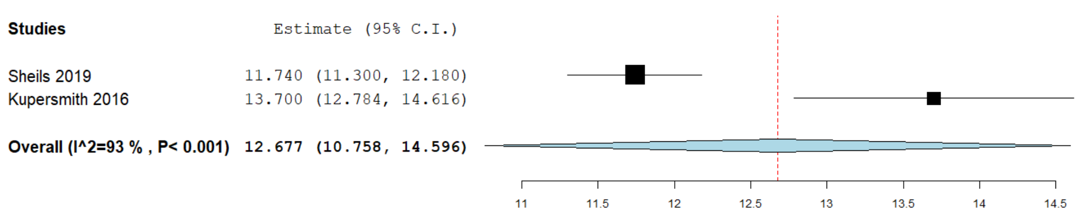

Figure 8 meta-analysis of ONH volume.

4. DISCUSSION

We present the results of a meta-analysis on the use of acetazolamide in the treatment of idiopathic intracranial hypertension patients. The results of our analysis revealed that the incidence of diplopia is 3.1%. We also found a significant improvement in the mean SF-36 physical and mental scores by 3.54 and 2.59, respectively. Regarding the 6-item headache impact test, we show that acetazolamide reduced the HIT6 score by -5.67, and finally, we found that the drug reduces papilledema grade by -0.68. The only previous systematic review before this one was conducted by Cochrane (Piper et al., 2015) and included only two studies. Their main results are consistent with ours as they found a reduced papilledema grade of -0.70 (95% CI -1.00 to -0.40) as assessed by fundus photographs, and -0.91 (95% CI -1.27, -0.54) by clinical grading. Regarding previously published trials, the IIHTT study reported significant effects of acetazolamide in improving HIT6 score, SF-36 mental, and SF-36 physical scores, and reducing papilledema grade compared with baseline values (Committee, 2014). In contrast to Wall et al., (2017) where they reported no significant favouring of acetazolamide in improving any efficacy endpoint.

IIH has many proposed mechanisms for its pathogenesis with no single confirmed theory. The most important pathogeneses include oversecretion of the cerebrospinal fluid (CSF), impaired drainage of the CSF, increase in the intravenous pressure inside cerebral sinuses, and obesity. Over secretion of the CSF has been first proposed by Donaldson et al., (1979) where they reported that patients with pseudotumor cerebri experience excess increase in CSF production evidenced by serial measuring of CSF volume. However, and after 13 years, a long-term study by Malm et al., (1992) came out to provide stronger evidence that disagrees with Donaldson’s findings. Moreover, magnetic resonance imaging (MRI) findings revealed normal-sized ventricles, contrary to other conditions of CSF over secretion (such as choroid plexus papilloma), where the ventricles are enlarged in size (Eisenberg et al.,1974). Impaired drainage of the CSF leads to increased intracranial tension, which is supported by isotope imaging modalities conducted on patients with IIH revealing impaired CSF drainage (Malm et al., 1992; Johnston, 1973). Riggeal et al., (2013) reported an association between patients with IIH and transverse sinus stenosis, which subsequently leads to increased ICT.

While acetazolamide stands till now as the medical treatment of choice (Ahmad et al., 2019), several other therapeutic modalities are present. Topiramate, a weaker drug with a similar mode of action to acetazolamide (inhibition of carbonic anhydrase enzyme), has been shown to exert similar efficacy findings to a one-gram dose of acetazolamide (Celebisoy et al., 2007). Recently, a very recent animal trial reported that topiramate is more effective than acetazolamide in reducing intracranial pressure (Scotton et al., 2019). No sufficient data to confirm this on humans till now. Schoeman et al., (1994) found that the use of furosemide in adjunct to acetazolamide leads to reduced CSF pressure. However, these results have been only reported in children.

Strengths and Limitations

This paper has many strength points, 1) we included a good sample size of 297 patients, 2) we only included clinical trials and avoided all observational evidence to provide stronger evidence, 3) we included six clinical trials and conducted an additional subgroup analysis to assess the mean scores and incidence of diplopia. 4) A good support of our data is the homogeneity of most of our outcomes in single-arm analysis, which supports the evidence we provide.

The main limitation of this paper is the high risk of bias, especially attrition bias. Additionally, most of the outcomes analyzed in comparison with baseline values revealed substantial heterogeneity. However, this inconsistency could not be solved by the leave-one-out or sensitivity analysis.

5. CONCLUSION

Acetazolamide is an effective medical treatment for idiopathic intracranial hypertension patients. However, more studies are still required to provide more clear evidence about the drug efficacy and safety.

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Author contribution

Author Abdulmajeed and Mohammed designed the study. Authors Alanoud and Mawaddah performed the statistical analysis. Authors Omayrah, Aljawharh and Asayel took part in literature survey. Authors Shuruq, Sarah and Faisal managed the data extraction and Interpretation of data. Authors Abdulmajeed and Bader wrote the original draft. Authors Tarek, Fatimah, Omar, Hezam wrote, reviewedand edited the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data associated with this study are present in the paper.

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