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Role of Acetazolamide in Traumatic CSF Rhinorrhea and Otorrhea: A Randomized Controlled Trial

Shivam Madeshiya[1] Chhitij Srivastava[1] Bal Krishan Ojha[1] Anil Chandra[1] Somil Jaiswal[1] Ankur Bajaj[1] Awadesh Yadav[1]

[1] Department of Neurosurgery, King George Medical University, Lucknow, Uttar Pradesh, India

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Address for correspondence Shivam Madeshiya, MS, MCh, Department of Neurosurgery, King George Medical University, Chowk, Lucknow, Uttar Pradesh 226003, India (e-mail: shivammadeshiyaa@gmail.com).

Abstract

Background Untreated cerebrospinal fluid (CSF) rhinorrhea and otorrhea can lead to adverse complications like meningitis and hence should not be overlooked. Acetazolamide reduces CSF production by 48%. The actual role of acetazolamide in the amelioration of traumatic CSF rhinorrhea and otorrhea is not clear as, till date, very few formal studies have been conducted. Aim of the study was to determine the role of acetazolamide in traumatic cerebrospinal fluid rhinorrhea and otorrhea.

Materials and Methods A randomized controlled trial was conducted among 134 patients with head injuries presenting to the neurosurgery department of a tertiary care center in North India, with complaints of CSF rhinorrhea and otorrhea within 72 hours of traumatic injury. One-hundred thirty-four patients were randomized into intervention and control group. Comparative analysis was not possible in 58 patients as in due course they were either operated for head injury or lumbar drain was put due to excessive CSF leak; hence, forth comparative analysis was done in 76 patients. Out of these 76 patients, 44 patients belonged to the intervention group (Acetazolamide given) and 32 belong to the control group (Acetazolamide not given). The day of the stoppage of CSF Leak was the main endpoint of this study.

Result Majority of the patients were in the age group of 21 to 30 years and were predominantly males. Road traffic accident was observed in 84 (75%) patients. There was no statistically significant difference noted in the mean number of days of CSF leak whether acetazolamide was given or not ($p = 0.344$). The complication associated with CSF leak was meningitis. The percentage of patients developing meningitis was more after lumber drain insertion.

Conclusion In our study, there was no advantage of adding acetazolamide to the conservative management of traumatic CSF leak. Therefore, the practice of routinely giving acetazolamide should be reconsidered.

Keywords
- acetazolamide
- meningitis
- cerebrospinal fluid rhinorrhea and otorrhea

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Introduction

Cerebrospinal fluid (CSF) rhinorrhea and otorrhea is leakage of CSF from subarachnoid space into nasal cavity and external auditory canal via defect in dura mater, bone, and mucosa.[1] Notably, 80% of CSF leaks result from skull-base fractures following head trauma. The relationship between closed head injury with basilar skull fractures and the formation of CSF leaks ranges from 2 to 30%.[2] Depending on whether the CSF flows into the middle ear cavity or the nasal cavity, CSF leak can be classified into CSF otorrhea or rhinorrhea respectively, and both have different clinical presentations.[1]

Untreated CSF rhinorrhea and otorrhea can lead to adverse complications in such patients like meningitis and hence should not be overlooked in case of traumatic injuries. Majority of the CSF fistulae resolve spontaneously. However, some may require a longer time to stop and need surgical intervention.[3] Acetazolamide is a carbonic anhydrase inhibitor and diuretic and has shown to reduce intracranial pressure (ICP) in patients with idiopathic intracranial hypertension.[4] Following an initial dose of acetazolamide, more than 99% of brain carbonic anhydrase activity is inhibited, thus decreasing CSF production by as much as 48% thereby justifying its utility in CSF rhinorrhea and otorrhea.[5,6]

The actual role of acetazolamide in the amelioration of traumatic CSF rhinorrhea and otorrhea is not clear as, till date, very few formal studies have been conducted investigating its impact in the management of CSF fistulae following head trauma. Many clinicians delay its use due to the spontaneous resolution of these leaks.[1,7] Hence, the following study has investigated the role of acetazolamide in CSF rhinorrhea and otorrhea.

Materials and Methods

Study Design and Period

The study was designed as a prospective, single-center, randomized controlled trial. Data recruitment and follow-up were done during the study period of 18 months

Study Setting

The study was conducted in the Department of Neurosurgery, of tertiary care center of Northen India.

Study Participants and Inclusion Criteria

All patients with head injury presenting with CSF rhinorrhea and/or otorrhea within 72 hours of traumatic injury were included in the study after informed written consent.

Exclusion Criteria

Patients with a history of spontaneous CSF rhinorrhea and/or otorrhea, patients undergoing intracranial surgery for a head injury, patients allergic to acetazolamide, and patients undergoing lumbar drain insertion were excluded.

Sample Size

Convenient sampling was done and all the patients ($n = 134$) fulfilling the inclusion criteria were enrolled during the 18 months of the period of study.

Patient Groups, Randomization, and Blinding

The patients were randomly allocated into two groups, that is, intervention and control group A and B, respectively. Simple randomization method was used. A computerized randomization table was created by a researcher who was not involved in the study. The exact details of the treatment allocation of patients were concealed in an encrypted folder of the computer system. In the intervention group, acetazolamide (dose: 15 mg/kg) was administered to the study subjects. The control group was not given any form of such treatment. The rest of the management like bed rest, sedation, and flat head was decided by senior consultants who were blinded to the study and was similar in both the groups. The follow-up and assessment of outcome were blinded, as they were done by clinicians who were not a part of the study. Every effort was made to minimize any form of bias in the study.

Outcome

The day of stoppage of CSF Leak was the main endpoint of this study. First assessment was done after 7 days and second assessment was done after 1 month.

Comparative analysis was done in all the enrolled patients who filled the inclusion criteria except in patients who died before a reasonable assessment could be done, patients who took leave against medical advice, patients who were undergone lumbar drain procedures, and patients who had undergone surgery for CSF leak.

Statistical Analysis

The data was analyzed using SPSS version 24.0. Descriptive summary using frequencies, percentages, graphs, mean, and standard deviation has been used to present the study results. Probability (p) was calculated to test statistical significance at the 5% level of significance. Categorical variables were compared between the two groups using chi square test. Continuous variables have been analyzed between the two groups using independent *t*-test.

Results

In this study, 134 patients were enrolled with head injuries who presented with CSF rhinorrhea and/or otorrhea within 72 hours of injury. Out of these, 58 patients were excluded from the comparative analysis as their proper assessment was not possible because 15 patients underwent lumbar drain insertion, 22 patients underwent surgery for CSF leak/trauma, 9 patients left the department against medical advice, and 12 patients expired during follow-up. All the comparative analysis was done on the findings of the 76 patients. Patients were randomly allocated into two groups, that is, 44 in the intervention (acetazolamide, dose -15 mg/kg) and 32 in the control group (no acetazolamide or placebo), by simple randomization method.

Table 1 Baseline characteristics of the study participants in both the groups

Variables		Diamox given/not given				*p*-Value
		Given ($n=44$)		Not given ($n=32$)		
		n	%	*n*	%	
Age intervals (y)	0–10	3	6.8	1	3.1%	0.637
	11–20	2	4.5	2	6.2%	
	21–30	19	43.2	10	31.2%	
	31–40	8	18.2	11	34.4%	
	41–50	8	18.2	6	18.8%	
	51 to 60	4	9.1	2	6.2%	
Gender	Male	40	90.9	26	81.2	0.219
	Female	4	9.1	6	18.8	
Mode of injury	Assault	5	11.4	5	15.6	0.441
	RTA	36	81.8	22	68.8	
	Fall from height	3	6.8	4	12.5	
	Hit by animal	0	0	1	3.1	
Site of CSF leak	CSF Rhinorrhea	31	70.5	16	50.0	0.192
	Left CSF otorrhea	6	13.6	7	21.9	
	Right CSF otorrhea	7	15.9	9	28.1	
Hospital stays (d)	Up to 5	12	27.3	12	37.5	0.587
	6–10	24	54.5	16	50.0	
	11–15	8	18.2	4	12.5	
Time since injury (h)	Up to 24	33	75.0	26	81.2	0.706
	25–48	4	9.1	3	9.4	
	49–72	7	15.9	3	9.4	
CT scan timing since injury (h)	Up–24	38	86.4	29	90.6	0.768
	25–48	3	6.8	2	6.2	
	49–72	3	6.8	1	3.1	

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; RTA, road traffic accident.

There was no significant difference between the two groups for age, gender, mode of injury, site of CSF leak, hospital stays (days), time since injury (hours), and computed tomography scan timing since injury (hours). Both the groups were age and sex-matched (►**Table 1**).

There was a negative correlation found between number of days of CSF leak and the age of patients in study groups. There was a positive correlation found between number of days of CSF leak and the age of patients in control groups. However, there was no statistically significant correlation seen between the age of the patients of the study and control groups and the number of days of CSF leak (►**Table 2**).

There was a significantly positive correlation found between number of days of CSF leak and hospital stay in both study and control groups. The majority of patients ($n=64$)

Table 2 Correlation between number of days and demographic/hospital stay factors

Parameters	No. of days of CSF leak			
		Given	Not given	
	Pearson correlation	*p*-Value	Correlation coefficient	*p*-Value
Age	−0.243	0.112	0.200	0.271
Hospital stay	0.642	0.0001	0.393	0.026

Abbreviation: CSF, cerebrospinal fluid.

Table 3 Frequency distribution of patients according to number of days of CSF leak in the study and control group

No. days of CSF leak (d)	Acetazolamide given/not given			
	Given		Not given	
	n	%	*n*	%
01	01	2.27	01	3.125
02	02	4.54	03	6.25
03	09	20.45	06	18.75
04	08	18.18	04	12.5
05	05	11.36	04	12.5
06	07	15.90	05	15.62
07	02	4.54	09	28.12
08	05	11.36	00	00
09	02	4.54	00	00
10	03	6.81	00	00
Total	44	100.0	32	100.0

Abbreviation: CSF, cerebrospinal fluid.

Table 4 Comparison of number of days of CSF leak in the study and control group

Diamox	No. of days of CSF leak		
	Mean ± SD	*t*-Value	*p*-Value
Given	5.30 ± 2.37	10.783	0.344
Not given	4.81 ± 1.89		

Abbreviations: CSF, cerebrospinal fluid; SD, standard deviation.

Table 5 Comparison of the site and number of days of CSF leak in the study and control group

Diamox		No. of days of CSF leak		
		Mean ± SD	*t*-Value	*p*-Value
Given	CSF rhinorrhea	5.19 ± 2.36	14.563	0.655
	CSF otorrhea	5.54 ± 2.47		
Not given	CSF rhinorrhea	4.94 ± 1.88	17.812	0.715
	CSF otorrhea	4.69 ± 1.96		

Abbreviations: CSF, cerebrospinal fluid; SD, standard deviation.

were discharged within 10 days of admission. Twelve patients had prolonged hospital stay due to associated injuries (►**Table 2**).

Among the 44 patients of CSF rhinorrhea and otorrhea who were given acetazolamide, mean number of days of CSF leak was 5.3 days, while out of 32 patients who were not given acetazolamide, mean number of days of CSF leak was 4.81 days (►**Table 3**). However, there was no statistically significant difference noted in the mean number of days of CSF leak whether acetazolamide was given or not ($p = 0.344$; ►**Table 4**).

Among the patients with CSF rhinorrhea, mean number of days of CSF leak who received and not received acetazolamide was 5.19 and 4.94 days, respectively. Similarly, among those with CSF otorrhea, the mean number of days of CSF leak who received acetazolamide was 5.54 days and those who did not receive acetazolamide was 4.69 days. However, there was no statistically significant difference in the mean number of CSF days leak between the CSF rhinorrhea and otorrhea in the intervention group as well as the control group, respectively (►**Table 5**).

In our study, a maximum number of patients (61.8%) were having CSF rhinorrhea followed by right CSF otorrhea (21.1%) and then left CSF otorrhea (17.1%).

Lumber drain insertion was done in 15 patients. Meningitis was diagnosed in three patients in the intervention group, one patient in the control group, and six lumber drain patients.

Discussion

CSF rhinorrhea and otorrhea are serious complications of head injuries and should be part of the neurological

assessment. Even though most of the CSF fistulas resulting in rhinorrhea and otorrhea resolve spontaneously, few may need surgical management. Acetazolamide seems to be a promising noninvasive modality for treating CSF leakage, but the evidence is still conflicting and needs vivid insight.

In this study, majority of the patients with CSF rhinorrhea and/or otorrhea were in the age group of 21 to 30 years and were predominantly males. Similar age and male predominance were reported by Junaid et al in their study.[8] Road traffic accident was the most frequent mode of injury in this study followed by assault. Road traffic accident was observed in 84 (75%) patients. Oh et al reported in their study that CSF leaks were very common in traumatic head injuries and seen in approximately 10 to 30% of skull base fractures. They also emphasized that early diagnosis and proper management are imperative for traumatic CSF leakages as it is strongly associated with a better long-term prognosis for the patients.[9]

CSF leakages in the form of rhinorrhea and otorrhea can be managed both conservatively and surgically. Surgical interventions are done when the CSF leakage fails to resolve spontaneously or does not respond to a CSF diversion. Conservative management is mainly done to reduce the active flow of CSF, decrease the CSF pressures, and allow healing of the defect/leak.[10,11] Few researchers have identified the role of acetazolamide in reducing the CSF leak due to its ability to reduce CSF production. They have used it in cases of spontaneous CSF leakage or in cases of raised ICP.[12,13] But there is a paucity of evidence regarding the role of acetazolamide in traumatic CSF rhinorrhea and otorrhea.

In our study, there was a negative correlation found between number of days of CSF leak and age in study groups and a positive correlation was found between number of days of CSF leak and age in control groups.

However, as the age of the patient increases, there is atrophy of brain parenchyma with secondary enlargement of the sulci. So, in patients with atrophied brains, there is an increased risk of prolonged/delayed CSF leak.[8] This misleading contradicting negative correlation between age and number of days of CSF leak in our study was of no clinical significance and could be explained by the fact that most young patients in our study were usually irritable and had associated injuries due to which they were not following commands of hospital staff.

In our study, there was no significant difference in the mean number of CSF leak days in both the intervention and control groups. This finding contrasted with the study by Gosal et al who observed that acetazolamide did not significantly reduce the duration taken for the resolution of CSF rhinorrhea thus proving that there is no advantage in the prophylactic administration of acetazolamide in an attempt to reduce the duration of traumatic CSF rhinorrhea.[1] But the results of our study are in concordance with a study by Abrishamkar et al who reported by Fisher's exact test that significant relationship between the early use of acetazolamide and CSF leakage termination time ($p = 0.01$).[2] Still, there is a need for more studies to get a better understanding of the management of this condition as side effects have also been reported while using acetazolamide like metabolic acidosis and hyperkalemia.[14]

The following study has both strengths and limitations. The following study unravels the conflicting role of acetazolamide in managing patients of CSF rhinorrhea and otorrhea and generates important evidence that will play a crucial role in the clinical decision-making of such patients. However, there are a few limitations. Simple randomization has resulted in an unequal number of participants in both groups and there was no attempt made to determine the CSF leak in terms of volume or size of bony defect that could have given better visibility for acetazolamide in managing CSF rhinorrhea and otorrhea.

Conclusion

There was no statistically significant difference noted in the mean number of days of CSF leak whether acetazolamide was given or not ($p = 0.344$). Similarly, there was no statistically significant difference in the mean number of CSF days leak between the CSF rhinorrhea and otorrhea in the intervention group as well as the control group, respectively. Role of acetazolamide in CSF leak is controversial. In our study, there was no advantage in adding acetazolamide to the conservative management of traumatic CSF leak.

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Conflict of Interest
None declared.

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