Analysing the Effect of Early Acetazolamide Administration on Patients with A High Risk of Permanent Cerebrospinal Fluid Leakage

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Abstract- In this study, we examined the role of early acetazolamide administration in reducing the risk of cerebrospinal fluid (CSF) leakage in patients with a high risk of permanent CSF leakage. In a randomised clinical trial, 57 patients with a high risk of permanent CSF leakage (rhinorrhea, otorrhea, pneumatocele or imaging-based evidence of severe skull-base fracture) were analysed. In the experimental group, acetazolamide, at 25 mg/kg/day, was started in the first 48 hours after admission. In the control group, acetazolamide was administered after the first 48 hours at the same dose administered to the patients in the experimental group. The following factors were compared between the two groups: duration of CSF leakage, duration of hospital stay, incidence of meningitis, need for surgical intervention and need for lumbar puncture (LP) and lumbar drainage (LD). All of the patients in the experimental group stopped having CSF leakage less than 14 days after the first day of admission, but 6 out of 21 patients (22%) in the control group continued having CSF leakage after 14 days of admission, which was a significant difference (P=0.01). This study showed that early acetazolamide administration can prevent CSF leakage in patients with a high risk of permanent CSF leak.

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Introduction

Once the integrity of the dura is violated, direct passage of CSF from the subarachnoid space to lower pressure areas may result, which may manifest as either rhinorrhea or otorrhea (1,2).

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%. Meningitis occurs in 25-50% of untreated traumatic CSF fistulas and in 10% of patients in the first week after trauma with head injury (3-7).

Certain groups of patients are considered at high risk for permanent CSF leakage following head trauma. These groups include patients who have signs of apparent pneumatocele by CT scan or those who have evidence of severe skull-base fracture on imaging (diastatic fractures, fractures toward the cranial cavity, fractures with the collection of blood and CSF in skull-base cavities), and those with apparent CSF leakage (rhinorrhea or otorrhea).

Acetazolamide, a carbonic anhydrase inhibitor, is a sulphonamide derivative. 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% (8-11).

Acetazolamide is part of the therapeutic protocol in CSF leakage, but since most leakages resolve spontaneously, some physicians delay the use acetazolamide, although there is no contraindication in its usage. As there has been no study evaluating the role of acetazolamide in patients with a high risk of permanent CSF leak, we compared the benefits of early versus late acetazolamide administration in reducing the risk of CSF leak in this group of patients.

Materials and Methods

Methodology

In this randomised clinical trial, we evaluated 57 patients with skull-base fractures who were referred to the emergency department of two main university hospitals in Esfahan, Iran, from September 2008 to

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March 2009. Of these, 28 patients were randomly assigned to our experimental group and 29 to our control group.

Using the convenience-sampling method, every patient who presented with signs of skull-base fracture was enrolled in our study until the size of the study population was acceptable. To divide our cases in two groups, we used the block randomisation method. The physician could not be blinded, but the analysers and the team who collected the data were blinded.

Our inclusion criteria were as follows: apparent CSF leakage in the form of rhinorrhea or otorrhea, presence of pneumatocele and/or evidence of severe skull-base fracture on imaging (signs of severe fractures were as follows: diastatic fractures, fractures toward the cranial cavity, fractures with the collection of blood and CSF in skull-base cavities).

Our exclusion criteria were as follows: no tolerance of oral medication, meningitis with need for treatment and documented brain death.

Patients who were referred to the emergency ward of our two university hospitals with the complaint of head trauma were examined by the physician. A complete physical examination was performed to detect any sign of leakage, and a brain CT scan was taken immediately after stabilising the patients. Those who met the inclusion criteria entered the study.

With a checklist designed for each patient, we registered and compared the following data between the two groups: demographic data, duration of CSF leakage, incidence of meningitis during admission (based on the presence of headache, fever and neck stiffness), need for surgical intervention, need for lumbar puncture (LP) and lumbar drainage (LD) and site of CSF leakage.

We defined the indication for LP and LD as the presence of CSF leak that did not stop by 7 days. In all these patients, we first performed an LP, after which a catheter was placed to continuously drain the fluid for treatment. The following criteria were chosen as the indications for surgical intervention: enlarging pneumocephalus, persistent CSF leak and meningitis. These patients underwent open surgery.

The site of CSF leakage was divided in the following groups based on the presenting signs of the patient: otorrhea; rhinorrhea; otorrhea & rhinorrhea; evidence of severe skull-base fracture on imaging; pneumatocele; otorrhea & evidence of severe skull-base fracture on imaging; otorrhea & pneumatocele; rhinorrhea & evidence of severe skull-base fracture on imaging; rhinorrhea & pneumatocele; evidence of severe skull-base fracture on imaging & pneumatocele; rhinorrhea, evidence of skull-base fracture on imaging & pneumatocele; and otorrhea, rhinorrhea, evidence of skull-base fracture on imaging & pneumatocele (Table 2).

In the experimental group, treatment with acetazolamide tablets, 25 mg/kg/day, was initiated during the first 48 hours after admission of the patient to the emergency ward. It was administered after the first 48 hours with the same dose and the same method in the control group. Conservative treatment was started for both groups at the same time and just after admission. The acetazolamide tablets used, for the patients in both groups, were a product of the Daroo Pakhsh pharmaceutical factory in Iran. Acetazolamide was continued for 48 hours after clinical cessation of the leakage. For the patients with skull-base fracture but no clinical sign of CSF leakage, acetazolamide was continued for the first 48 hours. Patients who had become NPO (non per oral) because of the need for other types of surgery following trauma or those who could not tolerate the drug because of severe vomiting were removed from the study.

All the patients were visited by the physician once a day and the checklist was completed daily for every patient. In the mean time, if any of the patients had recurrent leakage, the treatment was considered a failure, and another treatment was started.

Statistical analysis

SPSS 14 was used for data analysis. To determine the correlation between our quantitative data, we used the independent t-test, Mann-Whitney test and Fisher's exact test. For our qualitative data, we used the Chi-square test. We considered the correlations in our study statistically significant if their *P*-value was less than 0.05.

Ethical issues

Our research proposal was reviewed and approved by the research committee of the Esfahan University of Medical Sciences.

Results

The minimum and maximum ages were 16 and 60 in the experimental group and 9 and 53 in the control group. The t-test showed that the mean age in our two groups (30±14 in the experimental group and 24±9 in the control group) did not differ significantly (*P*=0.08).

The gender distribution of the patients in the two groups was homogenous; we had 24 male and 4 female

patients in our experimental group and 24 male and 5 female patients in our control group. This was not significantly different using the Chi-square test (P=0.5).

Two of our patients in the control group were excluded afterwards because they had died from complications of head trauma after 60 and 96 days.

CSF leakage resolved in all of the patients in the experimental group less than 14 days after the first day of admission, while 6 out of 27 patients (22%) in our control group continued to exhibit CSF leakage after 14 days of admission. Fisher's exact test showed a significant relationship between the early use of acetazolamide and the CSF leakage termination time (P=0.01).

We then compared the duration of CSF leakage between the groups of patients in whom the leakage stopped within 14 days. Twelve patients in the experimental group never had leakage and less than half of this group (11 patients) had leakage for more than 2 days, while in the control group, among the 10 patients that presented with no apparent CSF leakage, most started having CSF leak in a few hours; only 6 patients had leakage lasting for ≤ 2 days. The mean termination day was 2.2±2.4 days in our experimental group and 3.8±2.4 days in our control group. These values were significantly different by *t* test (P=0.02).

The mean durations of admission were 6.7±4.7 and 6.8±5 days in the experimental and control groups, respectively. The maximum durations of stay were 20 and 22 days for the experimental and control groups, respectively (Figure 1). The Mann-Whitney test did not reveal a significant difference (P=0.9).

A total of 4 patients were diagnosed with probable meningitis (headache, fever and neck stiffness) during our study: one patient in our experimental group and three in the control group (Table 1). Fisher's exact test did not show any significant difference between the groups in terms of the incidence of meningitis (P=0.3).

Four of the patients required surgical intervention because they met the aforementioned criteria. Of these patients, one was in the experimental group and underwent surgery because of meningitis, while the other three were in the control group and needed surgery because of meningitis (one patient) or persistent CSF leaks (two patients) (Table 1). However, Fisher's exact test showed no significant difference between the two groups in the incidence of surgical intervention (P=0.3).

The number of cases that required lumbar puncture and lumbar drainage was statistically different between the groups. While just 2 patients needed LP and LD in the experimental group, 31% (9) of cases in the control group eventually needed LP and LD (Table 1). This difference was significant by chi-square test (P=0.01).

The presenting signs of the patients in the two groups are shown in table 2.

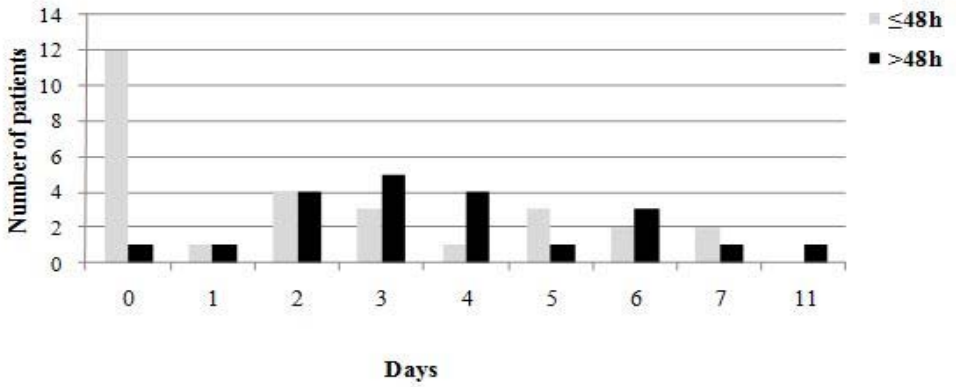

Figure 1. Bar graph comparing the duration of leakage in the two groups.

Table 1. The incidence of meningitis, surgical intervention and LP or LD in the two groups.

	Group ≤48 h	Group >48 h	*P*-value
Meningitis	1 (3.6%)	3 (10.3%)	0.3
Surgical Intervention	1 (3.6%)	3 (10.3%)	0.3
LP and LD	2 (7.1%)	9 (31%)	0.01

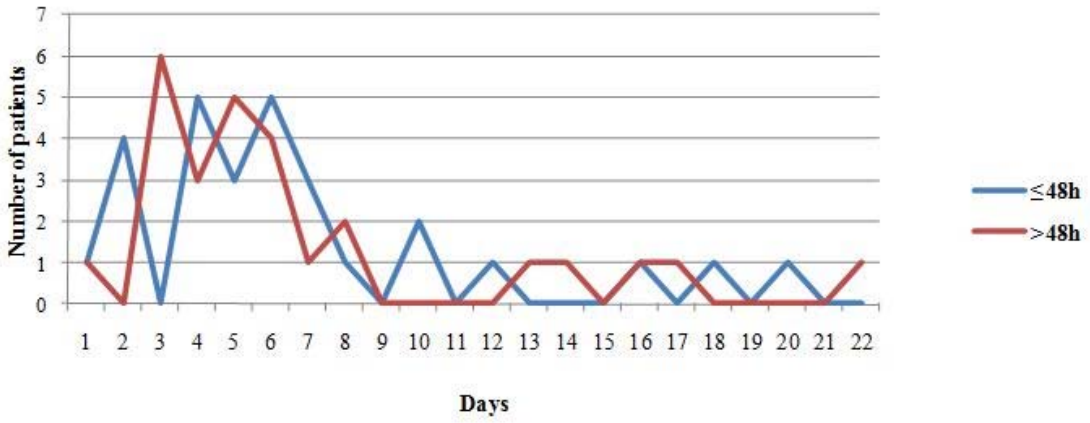

Figure 2. Bar graph comparing admission days between the groups.

Table 2. Signs presented by the patients in both groups.

Presenting sign	Group ≤48 h	Group >48 h	Total
1- Otorrhea	6 (21.4%)	5 (17.2%)	11 (19.3%)
2- Rhinorrhea	6 (21.4%)	8 (27.6%)	14 (24.6%)
3- Otorrhea & rhinorrhea	0	2 (6.9%)	2 (3.5%)
4- Skull-base fracture*	8 (28.6%)	7 (24.1%)	15 (26.3%)
5- Pneumatocele	3 (10.7%)	2 (6.9%)	5 (8.8%)
6- Otorrhea & skull base fracture	1 (3.6%)	0	1 (3.5%)
7- Otorrhea & pneumatocele	1 (3.6%)	0	1 (1.7%)
8- Rhinorrhea & skull-base fracture	1(3.6%)	2 (6.9%)	3 (5.3%)
9- Rhinorrhea & pneumatocele	0	1 (3.4%)	1 (1.7%)
10- Skull-base fracture & pneumatocele	1 (3.6%)	1 (3.4%)	2 (3.5%)
11- Rhinorrhea, skull-base fracture & pneumatocele	1 (3.6%)	1 (3.4%)	2 (3.5%)
12- Otorrhea, rhinorrhea, skull-base fracture & pneumatocele	0	0	0

* Evidence of severe skull-base fracture in imaging.

Discussion

In this randomised clinical trial, which occurred over the course of 6 months in two university hospitals in Esfahan, we evaluated 57 patients with skull-base fracture. Twenty-eight of the patients were randomly assigned to the experimental group and received acetazolamide in the first 48 hours of their admission, as opposed to the control group where the patients received the drug after 48 hours. In the follow-up of our cases, we recorded the duration of CSF leakage, period of hospitalisation, and incidence of meningitis.

While all of our cases in the experimental group stopped having CSF leakage in the first 14 days after admission, 22% of the patients continued having leakage after 14 days in the control group.

The mean number of days of leakage in our experimental group was 2.2 days compared to 3.8 days in our control group.

However, we did not find any significant difference in the duration of hospitalisation between groups. This finding was probably the case because of co-treatments in some of the cases for complications other than CSF leakage, such as limb fractures or surgical procedures following trauma.

We recorded the signs of meningitis in our cases and found no significant difference between groups in the incidence thereof, nor did we find any significant difference in the number of patients who needed surgical intervention for the termination of CSF leakage. However, 31% of the patients in the control group ultimately needed LP and LD in their treatment process in comparison to 2 patients in the experimental group, which was a significant difference (P=0.01).

Although most of the cases of CSF leakage resolve with conservative measures, there are some controversies in the literature. While the rate of spontaneous cessation has been reported to be 80-95% in some studies (12,13), it was only 53% in a study by Friedman *et al*., who also concluded that those leaks that persist for longer than 24 hours have a relatively high rate of requiring surgical repair. They also reported a 27.5% incidence of meningitis (4). In this study, we showed that despite some earlier studies that have tried acetazolamide for the treatment of CSF leakage with minimal success (10,14,15), early acetazolamide administration as part of the conservative measures in patients with skull-base fracture can be useful in preventing CSF leakage and shortening the duration of leakage in patients who already have either otorrhea or rhinorrhea.

There were nonetheless some shortcomings in our study, as the physician could not be blinded and the number of our cases was limited. Furthermore, we could not precisely determine the duration of hospitalisation due to head trauma because of concurrent problems such as multiple fractures or surgical interventions. Also, our diagnosis for meningitis was based on clinical signs instead of microbial culture, and the presenting signs of the cases that entered the study were various; some patients had skull-base fracture or pneumatocele without active leakage, while other patients had otorrhea, rhinorrhea or both. However, the presenting signs were similar in both groups of patients.

In spite of the results of previous studies that revealed a minimal role for acetazolamide in the reduction of CSF leakage, this study showed that early acetazolamide usage in patients with skull-base fracture can help both to prevent CSF leakage and to shorten the period of leak in those with active leakage after trauma. Even so, this study did not show any decrease in the incidence of meningitis or in the number of patients who needed surgical intervention to terminate the leakage. We propose that further studies with more cases and fewer potentially confounding factors be performed to examine the role of acetazolamide in preventing CSF leakage in patients with a high risk of permanent CSF leak.

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