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# Role of CSF Irrigation in Bacterial CSF Infection: A Randomized Controlled Trial

AHMED M.Sh. ALAKHRAS, M.D.*; MOHAMED E.M. ESMAEL, M.D.** and MOHAMED A. ABBAS, M.D.*

*The Department of Neurosurgery, Faculties of Medicine, Kafr Elshekh* & Cairo** Universities*

## Abstract

*Background:* Intravenous antibiotic administration is an essential component in the management of patients with cerebrospinal fluid (CSF) infections. However, very low concentrations reach the CSF because of the blood-brain barrier. Local irrigation with antibiotics could be a promising option to enhance the outcomes for such patients.

*Aim of Study:* In this prospective randomized trial, we evaluated whether ventricular irrigation with local antibiotics had a significant benefit in these cases.

*Patients and Methods:* Fifty patients diagnosed with CSF infections were divided into two groups; Group I included 25 patients who had CSF irrigation with local antibiotics, and Group II included the remaining patients who had external ventricular drainage (EVD) only. The main outcomes were the modified Rankin scale (MRS), the hospitalization period, and mortality.

*Results:* Preintervention demographic, clinical, and laboratory criteria were statistically comparable between the two groups. However, patients in the irrigation group showed earlier improvement in their blood leucocytes (41 vs. 71 days), CSF leukocytes (4 vs. 12 days), and CSF proteins (12.9 vs. 27.22 days) compared to the other group. There was a significant shortening in the duration of EVD placement in the irrigation group (18 vs. 60 days in the other group). Moreover, patients in the irrigation group had a lower disability scale. Twelve patients died in the non-irrigation group (48%), which was significantly higher than the mortality rate in the irrigation group (20%).

*Conclusion:* CSF irrigation with local antibiotics is associated with significantly better outcomes in patients with CSF infections.

***Key Words:*** *CSF infection – Irrigation – Local antibiotics – Outcome.*

## Introduction

**THE** cerebrospinal fluid (CSF) is formed by ultrafiltration of the plasma, and it occupies the subarachnoid spaces of the spine and cranium along with the brain ventricles **[1]**. It has multiple functions, including brain protection, nutrition, and elimination of metabolic waste products **[2,3]**. Moreover, it provides a mirror to neurosurgeons for the early diagnosis and management of several disorders, like CSF infections **[4]**.

CSF infections usually occur secondary to ventricular shunt placement, whether internal (like the ventriculoperitoneal shunt VPS), or external (like the external ventricular drain EVD). The incidence of infection after shunting procedures is high, reaching up to 29% **[5,6]**. CSF infection can also occur following transnasal endoscopic surgery **[7]**. That complication carries a substantial risk for morbidity and mortality **[8,9]**.

The management of CSF infections includes removal or exteriorization of the infected shunt (in patients with previous shunting procedures), ventricular tapping, EVD, and intravenous antibiotics **[10]**. Although antibiotic administration is crucial for the elimination of infection, it poorly penetrates the blood-brain barrier, leading to low CFS concentrations below the effective threshold level **[11]**. That may decrease the chances of patient recovery, especially because CSF is rich in glucose and poor with antibodies and immune cells, making it a good medium for bacterial growth and multiplication **[4]**.

Previous studies have highlighted the beneficial role of ventricular lavage with intraventricular antibiotic administration in patients with CSF infections **[12-14]**. However, there is a paucity of prospective trials confirming that beneficial impact in the Egyptian setting. Therefore, we conducted the current trial to evaluate if ventricular irrigation with local antibiotics could enhance outcomes in patients with ventriculitis.

***Correspondence to:*** Dr. Ahmed M.Sh. Alakhras, The Department of Neurosurgery, Faculty of Medicine, Kafr Elshekh University

## Patients and Methods

This prospective randomized trial was conducted at the Neurosurgery Departments of both Kafr Elsheikh University and Nasser Institute over a two-year duration, from November 2020 to November 2022. Before patient enrollment, the trial gained approval from the local scientific and Ethical Committee of the Kafr Elsheikh Faculty of Medicine.

The trial was designed for patients diagnosed with intracranial infection and requiring external drainage (EVD placement). The diagnosis of intracranial infection was based on the "National Health Commission" criteria **[15,16]**. These criteria include; (1) Clinical manifestations suggesting intracranial infection, (2) The presence of risk factors for infections (like previous CSF shunting, hematological malignancies, transplant patients, hereditary or acquired immunodeficiency), (3) CSF biochemical abnormalities (leucocytic count greater than $10x10^6$/L; total protein concentration greater than 450 mg/l; glucose level less than 2.25mmol/l; and chloride concentration less than 120mEq/l), and (4) The presence of bacterial organisms in CSF culture. Patients presenting the initial three criteria, or the fourth one alone, were eligible for inclusion in our trial.

We used the G*Power software to estimate the proper sample size. Using the previous data published by Al Menabbawy and his colleagues, who reported a 68.6% recovery rate in the irrigation group and a 23.5% rate in the conventional group **[12]**, a sample size of 23 patients was required in each study group to achieve a 5% alpha error and a 90% power. That number was increased to 25 patients per group to avoid possible dropouts or non-response rates.

The included patients were evaluated by the same neurosurgical team, and the evaluation included history taking (focusing on age, complaint, and the presence of risk factors for intracranial infections), a clinical examination (including, general and detailed neurological assessment), and a radiological evaluation (brain computed tomography or magnetic resonance imaging). Laboratory assessment included a complete blood count (CBC) and CSF analysis (for the leucocytic count, glucose, protein, chloride, and culture for microorganisms). The initial CSF sample was obtained via a lumbar puncture, and all initial laboratory investigations were withdrawn before antibiotic administration. The Modified Rankin Scale (MRS) **[17]** was calculated for all patients before any intervention.

After proper patient evaluation, patients with intracranial tumors or bleeding diathesis were excluded. We also excluded patients who hadinfection spread to surrounding tissues like the epidural space, dura, bone, subcutaneous, and cutaneous tissues.

The enrolled 50 patients were allocated into two groups using the computer-based method; Group I included 25 patients who had CSF irrigation with local antibiotics, and Group II included the other 25 patients who had EVD without irrigation.

All patients received broad-spectrum antibiotic therapy till the appearance of cultures and sensitivity tests. An EVD was inserted in all patients in the two groups under complete aseptic conditions, and all patients with infected shunts had their shunts removed during the procedure. In Group A, an additional ventricular catheter was inserted into the other side of the infected ventricle for fluid and antibiotic injection. The first irrigation episode was done intraoperatively using 500ml saline mixed with 500mg of vancomycin. The irrigation fluid was injected through the ventricular catheter, to be drained through the EVD. The irrigation procedure was performed over half an hour. We made sure to exteriorize the EVD about ten cm superior to the ear tragus, to decrease the risk of low intracranial pressure and the development of pneumocephalus.

The patients were then transferred to the neurosurgical ward, where close monitoring was done. Both groups were commenced on the same broad-spectrum antibioticsuntil the results of the culture and sensitivity tests appeared. Then, the proper antibiotics were prescribed. In the irrigation group, irrigation with 500ml saline with vancomycin 500mg was performed daily over a four-hour duration. Vancomycin was replaced by the specific antibiotic when culture results were available.

In all patients, CBC and CSF analyses were done at three-day intervals. We made sure to withdraw the CSF sample in the irrigation group 12 hours after the injection episode to avoid false results due to sample dilution. A significant improvement of anyCBC or CSF parameter was established when we obtained normal values on three subsequent CSF analyses. The EVD was removed within a week after the significant improvement, and a new shunting procedure was performed via a new burrhole. The MRS was also calculated after receiving treatment in both groups.

The main outcome of our trial was the degree of patient recovery measured by the MRS, while other outcomes included the duration until significant improvement of CSF parameters, the duration of EVD placement, the duration of hospitalization, and the mortality rate.

We used the SPSS software for data tabulation and analysis. We expressed normally distributed numerical data as means and standard deviations, while medians and ranges were used to express the abnormally distributed data. The student- *t* and Mann-Whitney tests were used to compare the previous data types between the two groups, respectively. Furthermore, categorical data were expressed as numbers and percentages and compared using the Chi-square or Fisher Exact tests between our two groups. Any *p*-value less than 0.05 was considered significant.

## Results

Patients in Group I had an age rangeof 8 and 78 years (median=45), while the age of Group II patients ranged between 13 and 75 years (median=44). Men formed 64% of Group I patients, and 56% of Group II patients, while the remaining patients were women. Previous VPS and type II diabetes mellitus were the most prevalent risk factors for intracranial infections, with prevalence rates of 28% and 32%, respectively, in either group. Other risk factors are shown in Table (1).

Regarding their clinical presentation, all patients had a fever. Other manifestations included fatigue, headaches, nausea, vomiting, and a disturbed consciousness level. Preintervention blood leukocytes had mean values of 21.5 and 20.54x$10^9$/L in groups I and II, respectively. CSF leukocytes ranged between 1050 and 9100/$mm^3$ in the first group, while it ranged between 1400 and 10000 in the latter. The previous demographic and clinical characteristics showed no significant difference between the two groups.

The significant improvement in blood leukocytes, CSF leukocytes, and CSF protein was significantly earlier in Group I ($p$<0.001). Additionally, the duration of EVD placement ranged between 11 and 24 days in the irrigation group, while it ranged between 36 and 100 days in the other group ($p$<0.001).

The duration of hospitalization showed a significant prolongation in the non-irrigation group (81 vs. 59 days in the irrigation group - $p$=0.007). In addition, 12 patients died in the non-irrigation group, with a mortality rate of 48%, which was significantly higher than the other group (20%) (Table 2).

As shown in Table (3), although both groups had comparable MRS values before the intervention ($p$=0.188), patients in the irrigation group had significantly lower scores after the intervention compared to the non-irrigation group, indicating less disability in association with irrigation ($p$=0.013).

Table (1): Preintervention data in the two groups.

| | Group I (n=25) | Group II (n=25) | $p$-value |
|---|---|---|---|
| Age (years) | 45 (8-78) | 44 (13-75) | 0.946 |
| *Gender:* | | | |
| - Male | 16 (64%) | 14 (56%) | 0.564 |
| - Female | 9 (36%) | 11 (44%) | |
| *Risk factors:* | | | |
| - Acute myeloid leukemia | 2 (8%) | 0 (0%) | 0.149 |
| - Chronic liver disease | 0 (0%) | 2 (8%) | 0.149 |
| - Craniopharyngioma surgery | 2 (8%) | 2 (8%) | 1 |
| - Immune diseases | 1 (4%) | 0 (0%) | 0.144 |
| - Intraventricular | 0 (0%) | 2 (8%) | 0.149 |
| ependymoma surgery | 0 (0%) | 1 (4%) | 0.312 |
| - Liver abscess | | | |
| - Lung abscess | 4 (16%) | 2 (8%) | 0.384 |
| - Ommaya reservoir | 2 (8%) | 2 (8%) | 1 |
| - Diabetes mellitus type I | 0 (0%) | 2 (8%) | 0.149 |
| - Diabetes mellitus type II | 8 (32%) | 8 (32%) | 1 |
| - VPS | 7 (28%) | 7 (28%) | 1 |
| - Cancer colon | 0 (0%) | 2 (8%) | 0.149 |
| - Chronic kidney disease | 0 (0%) | 1 (4%) | 0.312 |
| - Ischemic heart disease | 0 (0%) | 1 (4%) | 0.312 |
| *Clinical presentation:* | | | |
| - Fever | 25 (100%) | 25 (100%) | 1 |
| - Fatigue | 10 (40%) | 8 (32%) | 0.556 |
| - Headache | 10 (40%) | 12 (48%) | 0.569 |
| - Nausea and vomiting | 8 (32%) | 5 (20%) | 0.333 |
| - Disturbed conscious level | 8 (32%) | 9 (36%) | 0.765 |
| Blood leukocytes (x $10^9$/L) | 21.50±2.92 | 20.54±3.24 | |
| CSF leukocytes (cells/$mm^3$) | 3000 (1050-9100) | 5850 (1400-10000) | 0.124 |

Table (2): Outcomes in the two groups.

| | Group I (n=25) | Group II (n=25) | $p$-value |
|---|---|---|---|
| CSF WBCs significant improvement after EVD (days) | 4 (3-5) | 12 (6-29) | <0.001 * |
| CSF protein significant improvement after EVD (days) | 12.96±2.32 | 27.22±4.44 | <0.001 * |
| Blood WBCs significant constant for 3 days improvement after EVD (days) | 41 (28-102) | 71 (40-164) | 0.001* |
| EVD placement (days) | 18 (11-24) | 60 (36-100) | <0.001* |
| Hospital stay (Days) | 59 (40-121) | 81 (50-188) | 0.007* |
| Mortality | 5 (20%) | 12 (48%) | 0.037* |

WBCs: White blood cells.

Table (3): MRS score at presentation and after the intervention.

| | Group I (n=25) | Group II (n=25) | *p*-value |
|---|---|---|---|
| MRS pre | 3 (1-5) | 3 (2-5) | 0.188 |
| MRS post | 1 (0-6) | 5 (0-6) | 0.013* |

## Discussion

CSF infections have serious consequences, including intellectual dysfunction, seizures, neurological deficits, and even death **[18,19]**. The proper management of that condition entails effective drainage of the purulent material from the ventricles via the EVD **[20]** and achieving a sufficient antibiotic level within the CSF to eradicate the incriminated microorganism **[19]**. However, the blood-brain barrier hinders the free passage of most antibiotics from circulation to the brain tissue and CSF.

A possible solution for the previous obstacle is to deliver antibiotics locally into the ventricular system of the brain. As the patients already need EVD, one could use an additional ventricular catheter for irrigation and local antibiotic delivery.

We conducted the current study to evaluate the efficacy of CSF irrigation with antibiotics, and its effect on outcomes in patients with CSF infections. On looking at our preintervention data, one could see almost no significant statistical differences between our two groups. That reflects our good randomization technique, and that should also decrease any bias skewing our findings in favor of one group over the other one.

We noted a significant shortening in the duration of EVD placement in the irrigation group (range, 11-24) compared to the other group (range, 36-100). As EVD removal is an indicator of CSF improvement and the resolution of infection, that could reflect a faster recovery in association with irrigation.

That is in accordance with Terada et al., who reported that CSF irrigation was associated with a significant shortening in the duration of external catheter drainage (19.8±10.1 vs. 70.9±36.8 in the non-irrigation group - $p<0.001$) **[14]**. One should consider that long-term placement of a ventricular drain is a common cause of ventriculitis **[7]**. Thus, decreasing the duration of EVD placement should decrease the risk for super- or recurrent infection.

In the current trial, patient disability showed a significantly better improvement in the irrigation group, as it had lower MRS compared to the conventional group. In the same context, another study reported that CSF irrigation was associated with significantly better outcomes (MRS of three or more) than the conventional drainage technique, as good outcomes were encountered in 68.8% of the irrigation cases, compared to only 23.5% of the conventional group ($p<0.05$) **[12]**.

Similar findings were reported by Terada and his colleagues, who reported that good outcomes were encountered in 66.6% of the irrigation cases, compared to only 25% of conventional cases **[14]**. The reader should also note that these good outcomes are far below those obtained by the conventional technique **[7,21,22]**.

In the current study, CSF irrigation with antibiotics led to a significant shortening of the hospitalization period. That could be explained by the faster recovery achieved in the irrigation patients, which manifested in rapid improvement of CSF and CBC parameters as well as the shortening of EVD placement days.

Our findings coincide with those of Al Menabbawy et al., who also reported a significant decline in the hospitalization period when CSF irrigation was used (20.5±14.2 vs. 39.7±16.9 in the conventional group - $p<0.05$) **[12]**. Moreover, Terada et al., also noted a significant shortening of the hospitalization period when CSF irrigation was performed (76.8 ± 37.1 vs. 76.8±37.1 in the conventional group). Nonetheless, that difference turned out to be insignificant in the statistical analysis ($p>0.05$) **[14]**.

Our findings revealed that CSF irrigation also has a positive impact on patient survival, as 12 patients died in the non-irrigation group (48%), compared to only 20% of the irrigation patients ($p=0.037$).

Although Al Menabbawy and his colleagues reported a higher mortality rate in the conventional group (52.9% vs. 25% in the irrigation group), that difference was not significant in statistical analysis ($p>0.05$) **[12]**.

All in all, we see that CSF irrigation is associated with significantly better outcomes in patients with CSF infections. That technique should be encouraged to improve patients' disabilities and enhance their survival.

This trial has some limitations. The small sample size and the lack of long-term follow-up are the main limitations. These should be addressed in the upcoming studies.

*Conclusion:*

CSF irrigation with antibiotics has great benefits for patients with CSF infections. It is associated with significantly better outcomes, manifested in a better disability score, a shorter hospitalization period, a more rapid time to CSF normalization, and lower mortality rates.

*Conflicts of interest:* Nil.

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# دور رى السائل النخاعى فى العدوى البكتيرية للسائل النخاعى : تجربة عشوائية منضبطة

يعتبر إعطاء المضادات الحيوية عن طريق الوريد مكوناً أساسياً فى تدبير المرضى المصابين بعدوى السائل النخاعى. ومع ذلك، تصل التركيزات المنخفضة جداً إلى السائل الدماغى بسبب الحاجز الدموى الدماغى. يمكن أن يكون الرى المحلى بالمضادات الحيوية خياراً واعداً لتعزيز النتائج لمثل هؤلاء المرضى.

فى هذه التجربة العشوائية المرتقبة، قمنا بتقييم ما إذا كان الرى البطينى بالمضادات الحيوية المحلية له فائدة كبيرة فى هذه الحالات.

تم تشخيص خمسين مريضاً مصاباً بعدوى السائل الدماغى تم تقسيمهم إلى مجموعتين. تضمنت المجموعة الأولى ٢٥ مريضاً تم ريهم فى السائل الدماغى النخاعى بالمضادات الحيوية المحلية، وشملت المجموعة الثانية المرضى الباقين الذين لديهم تصريف بطينى خارجى فقط. كانت النتائج الرئيسية هى مقياس رانكين المعدل، وفترة الاستشفاء، والوفيات.

كانت معايير ما قبل التدخل الديموغرافية والسريرية والمخبرية قابلة للمقارنة إحصائياً بين المجموعتين. ومع ذلك، أظهر المرضى فى مجموعة الرى تحسناً مبكراً فى كريات الدم البيضاء (٤١ مقابل ٧١ يوماً)، والكريات البيض فى السائل الشوكى (٤ مقابل ١٢ يوماً)، وبروتينات السائل النخاعى (١٢.٩ مقابل ٢٧.٢٢ يوماً) مقارنة بالمجموعة الأخرى. كان هناك تقصير كبير فى مدة وضع أنبوبة التصريف الخارجية فى مجموعة الرى (١٨ يوماً مقابل ٦٠ يوماً فى المجموعة الأخرى). علاوة على ذلك، كان لدى المرضى فى مجموعة الرى مقياس إعاقة أقل. توفى أثنا عشر مريضاً فى المجموعة غير المروية (٤٨٪)، والتى كانت أعلى بكثير من معدل الوفيات فى مجموعة الرى (٢٠٪).

إن رى السائل الدماغى النخاعى بالمضادات الحيوية الموضعية يرتبط بنتائج أفضل بشكل ملحوظ فى المرضى المصابين بعدوى السائل النخاعى.