

CONSORT: May stereotactic intracavity administration of antibiotics shorten the course of systemic antibiotic therapy for brain abscesses?

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Abstract

Background: Despite advances in surgical techniques in the management of the brain abscess, continuous systemic long-term antibiotics are necessary and crucial. This study was designed to evaluate the effect of intracavity administration of high-dose antibiotics on the course of antibiotic therapy.

Methods: Between 2003 and 2013, 55 patients with bacterial brain abscesses (83 abscesses) were treated with stereotactic aspiration and intracavity injection of high-dose antibiotics combined with a short course systemic antibiotic therapy. Antibiotics of one-eighth daily systemic dosage were injected into the abscess cavity after stereotactic aspiration and intravenous antibiotics were given in all patients for 3 to 4 weeks. The results of the group treated with stereotactic aspiration and intracavity injection of antibiotic solution were compared to the results of our previous patients treated by stereotactic aspiration only.

Results: Thirty-nine males and 16 females (age ranging from 1.5 to 76 years; mean age 38.7 years) were included in this study. During the follow-up (mean 26.2 months, ranging from 6 to 72 months), all the abscesses subsided with no recurrence. No adverse effects related to topical use of antibiotics occurred. At the end of follow-up, 38 patients had good outcomes, 11 had mild neurological deficits, 3 had moderate deficits, 1 was in vegetative state, and 2 died of accidents not related to brain abscesses. Compared with conventional stereotactic aspiration and drainage, intracavity injection of antibiotics shortened the course of consecutive systemic intravenous antibiotics by average 10.8 days without an increase of the recurrence rate of abscesses.

Conclusions: Our results indicate that topical application of antibiotics into the brain abscess cavity helps to reduce the length of systemic antibiotic therapy, decreases the abscess recurrence rate, avoids the side effects of long-term high dose antibiotics, shortens the hospitalization and reduces treatment costs.

Abbreviations: AIDS = acquired immunodeficiency syndrome, CRP = C reactive protein, MCPBA = multiloculated pyogenic brain abscess, MPBA = multiple pyogenic brain abscess, PLA = People's Liberation Army.

Keywords: antibiotics, brain abscess, medication route, stereotactic aspiration

1. Introduction

Brain abscess is a potentially fatal disease. With modern imaging, improved surgical techniques and better antibiotics, great achievements have been made in diagnosis and treatment of brain abscess. However, the treatment of brain abscess still remains a major challenge for neurosurgeons.^[1-3] In recent years, more and more surgeons choose the simple and safe aspiration surgery as the first line treatment option.^[4-6] But whatever the treatment is, a long-term adjuvant systemic antibiotic therapy is

needed, which may cause adverse effects in patients during treatment and recovery.^[7,8] Local abscess recurrence is the major reason for treatment failure.^[9] Therefore, we assumed that increasing the concentration of antibiotics in the brain abscess cavity could increase the cure rate and shorten the application of systemic antibiotics. Starting from 2005, we conducted a prospective clinical study of stereotactic aspiration combined with intracavity administration of high-dose antibiotics in the treatment of brain abscess. The goal of this study was to compare the results of the combined treatment for the brain abscess during a 10 years' period and to compare with the results of our previous conventional stereotactic operations and to evaluate the possibility and feasibility of shortening the systemic antibiotic treatment course.

2. Patients and methods

2.1. Patient demographics

From January 1995 to February 2015, 106 patients with brain abscesses were admitted to the Navy General Hospital, 51 patients were treated with conventional stereotactic surgical treatment from 1995 to 2004 (conventional treatment group). From January 2005, we conducted a prospective clinical study of stereotactic aspiration combined with intracavity administration

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Table 1
The clinical features of patients with pyogenic brain abscess.

Characteristics	Number of patients	
	Treatment group	Control group
Gender		
Male	39 (70.91%)	31 (60.78%)
Female	16 (29.09%)	20 (39.22%)
Age, y		
Average (range)	38.7 (1.5–76)	35.6 (3.0–66)
<14	9 (16.40%)	10 (19.61%)
History course, d		
Average (range)	13.8 d (9–25 d)	9.2 d (1–21 d)
Presenting symptoms and signs		
Fever	27	22
Headache	42	35
Nausea and vomiting	33	27
Stiff neck	15	10
Seizure	4	2
Number of brain abscess		
Single	40 (multiloculated 4)	37
Multiple		
2	6	10
3	5	2
4	4	2
Total	83	71
Abscess location		
Supratentorial	76	67
Subcortical	23	15
Deep white matter	38	40
Basal ganglia	15	12
Infratentorial	7	4
Cerebellar	5	2
Brain stem	2	2
Pretreatment neurological state*		
Grade 0	9	5
Grade I	16	12
Grade II	24	27
Grade III	6	7

We noted no statistical difference between treatment group and control group ($\chi^2=1.210$, $P=0.271$) regarding gender and pretreatment neurological state, and it does not have statistical difference between treatment group and control group in gender in pretreatment neurological state ($\chi^2=1.819$, $P=0.611$).

* Grade 0 alert, no deficits; Grade I alert, with mild neurological deficits; Grade II lethargic, moderate deficits; Grade III obtunded, marked deficits.

of high-dose antibiotics to evaluate the feasibility of shortening the systemic antibiotic treatment course. The study was approved by Ethical committee of Navy General Hospital of PLA and all included patients had signed a general informed consent form. Till February 2015 a total of 55 patients with brain abscess were treated (intracavity treatment group). The brain abscess was diagnosed based on typical clinical manifestations and imaging (CT and/or MRI) findings combined with the surgical and pathological findings as well as the etiological results. Two or more abscesses surrounded by brain parenchyma were defined as multiple pyogenic brain abscesses (MPBA). Multiple abscesses with no parenchyma between them were defined as multiloculated pyogenic brain abscess (MCPBA). Abscesses caused by fungi, parasites, and tuberculosis were excluded. After admission, tests were obtained and routine blood tests included blood clotting test, blood biochemistry test, systemic immune function, erythrocyte sedimentation rate, serum C-reactive protein, and stool and urine routine tests. All patients underwent additional examinations (including chest X-ray, dental, and skin examinations) to track the source of infection. Patients with systemic

immunodeficiency disease, such as AIDS, were excluded. Before treatment, neurological status was classified into 4 grades: Grade 0 (awake without any neurological deficits), Grade I (alert with mild neurological deficits), Grade II (sleepy or drowsy with moderate neurological deficits), and Grade III (coma with significant neurological dysfunction). The clinical features of the two groups of patients with brain abscess are shown in Table 1.

2.2. Surgical techniques

All patients received surgeries within 2 days after the brain abscess diagnosis was confirmed. For most patients we performed frame-based stereotactic surgeries. Under local anesthesia, the Leksell frame G (patients could opt for general anesthesia if they were uncomfortable with local anesthesia) was fixed to the patients' heads. The axial and coronal contrast enhanced MRI scanning was performed with a slice thickness of 3 mm. Images were sent to the stereotactic operating workstation to determine the surgical target, puncture point, and path through the stereotactic surgery planning system. A 3 mm incision was cut under local anesthesia. A skull drill with a diameter of 3.2 mm was used to drill through the skull. After the dura was pierced, a 12-size needle was used to puncture the brain abscess. For abscesses with diameters less than 4 cm, all pus was aspirated and antibiotics of high concentration were injected into the cavity after repeated flushing the cavity with normal saline. For abscesses with diameters greater than 4 cm, a latex drainage tube with a diameter of 2.5 mm was placed to gradually drain the pus. Antibiotics and physiologic saline solution was used to rinse the cavity twice a day till the drained fluid became clear. Then high-dose antibiotics were injected into the cavity in the intracavity treatment group. After each flushing treatment and injection, the puncture point was kept elevated for at least 8 hours to prevent drug infiltration into the subarachnoid space. After CT scans confirmed the disappearance of abscess cavity, the drainage tube was removed. For multiple pyogenic brain abscess and multiloculated pyogenic brain abscess, each abscess cavity was aspirated, rinsed, and injected with antibiotics of high concentration. The aspirate smears were conducted immediately and aerobic, anaerobic bacteria, fungal culture, and pathological examinations were carried out.

2.3. Systemic antibiotic treatment group

The abscess cavity was treated with saline only and without antibiotic injection in the conventional treatment group. In the intracavity treatment group, intraoperative and postoperative antibiotics lavage was carried out using 50% of a daily dose of the systemic third-generation cephalosporin plus physiologic saline 100 mL. Intracavity antibiotics dosage was 1/8 of the systemic third-generation cephalosporin dosage plus physiologic saline 2 to 5 mL (based on the volume of the abscess). After the surgery, antibiotic therapy was initiated. The initial antibiotic therapy consisted of cefotaxime in combination with metronidazole and antibiotics were adjusted according to the bacterial culture and sensitivity test results. If the result turned out negative, we continued the antibiotics prescribed previously. Other antibiotics used were ceftriaxone, norvancomycin, ceftriaxone, meropenem, and ciprofloxacin. Clinical symptoms were recorded after the surgical intervention day by day. CRP levels were obtained every 3 to 5 days. Brain CT examinations were obtained once a week. Brain MRI was performed in the

fourth week after the intervention. The indications for cessation of antibiotics were improvement of clinical manifestations, normal CRP, and disappearance of brain abscesses confirmed by brain CT scanning. Based on the degree of brain edema and mass size, glucocorticoid dosages were reduced after 3 to 5 days. Antiepileptic therapies were continued for at least 6 months for patients with epileptic seizures preoperatively or postoperatively.

2.4. Statistics

A 2-tailed un-paired Student *t* test was used for continuous data when applicable and Wilcoxon rank-sum test was used for discrete variables. Due to nonnormal distribution of the biomarker levels natural logarithmic transformation was applied before Student *t* test was used. χ^2 test was used for proportions. The statistical software used was JMP 10.0.0 (Statistical Analysis System [SAS] Institute, Cary, NC). A *P*-value <0.05 was regarded as statistically significant. Values are given as mean \pm standard deviation or median (range).

3. Results

In intracavity treatment group, total number of abscesses was 83 including 40 patients with single abscesses (4 multilocular abscesses) and 15 multiple abscesses (43 abscesses). Sixty surgeries were performed (once in 51 cases, twice in 3 cases, and three times in 1 case). In the conventional treatment group (*n*=71), there were 37 patients with single abscess, 14 patients with multiple abscesses, and 71 of the total number of abscess. Fifty-four surgical interventions were performed (1 intervention in 48 patients and 2 interventions in 3 patients). All the abscesses were aspirated. No complications related to stereotactic operations occurred. Aspiration and drainage were performed in 61 and 22, 44 and 27 abscesses in the intracavity treatment group and in conventional treatment group, respectively. In the intracavity treatment, microbial identifications from pus aspirated from 33 patients were facultative anaerobic bacteria (*Staphylococcus aureus* in 11 cases, β -hemolytic streptococcus in 7 cases, *Streptococcus viridans* in 4 cases, *Staphylococcus epidermidis* in 3 cases, *Staphylococcus constellatus* in 3 cases, *Streptococcus pneumoniae*, *Enterococcus faecium* in 2 case, and *Rhodococcus equi* in 1 case). Microbial identification from pus aspirated was positive in 26 patients in the conventional treatment group and cultured bacterial strains were similar to the treatment group. On average systemic antibiotics were continued for 25.5 days (21–28 days) in the intracavity treatment group and 36.3 days (28–47 days) in the conventional treatment group. No treatment-related seizures or other severe complications occurred during follow-up.

Brain CT scans obtained on the second day after surgery revealed that abscess size shrunk significantly after aspiration and drainage. CT scans obtained after 1 week showed no significant enlargement of brain abscess cavity. CT after 2 weeks showed that abscess volume reduced. All abscess cavities disappeared after 3 weeks. In the intracavity treatment group, patients were followed up for 6 to 72 months (mean 26.2 months). Brain MRI obtained after 1 month showed no abscess recurrence. Clinical results showed that 38 patients recovered well without any complications, 11 patients had mild neurological deficits, 2 had moderate hemiplegia, 1 had antiepileptic treatment due to preoperative seizures and 1 was in vegetative state for 15 months. A brain herniation occurred in the vegetative patient before the

Table 2

The infectious characteristics and treatment outcomes of patients with bacterial brain abscess.

Characteristics and results	No. of patients	
	Treatment group	Control group
Predisposing factors		
Upper respiratory tract infection	7	5
Endocarditis/congenital heart disease	4	6
Lung infection	4	4
Chronic otitis media	3	4
Hormone therapy	3	2
Immunosuppressants	3	2
Skin abscess	3	3
Bacteremia	2	3
Tooth abscess	2	2
Neurological interventions	2	2
Unknown	22	18
Infectious approach		
Hematogenous spread	24	26
Contiguous infection	7	8
Neurological interventions	2	2
Unknown	22	15
Isolated microorganisms		
Aerobic gram-negative bacilli	33	16
Treatment		
Aspiration	61	46
Average abscess volume, mL	6.5 (2–12)	7.3 (3–15)
Drainage catheter (catheter time, d)	22	25
Average abscess volume, mL	(2–5, Mean 3.4)	(2–6, Mean 3.6)
Drainage	33 (15–75)	39 (20–68)
Antibiotic treatments		
Cefotaxime + metronidazole	18	17
Norvancomycin + ceftriaxone	12	6
Ceftriaxone + metronidazole	11	23
Norvancomycin + metronidazole	10	5
Ceftriaxone + ciprofloxacin	3	0
Meropenem	1	0
Antibiotic course, d	21–28 (Mean 25.5)	28–47 (Mean 36.3)
Follow up, mo	6–72 (Mean 26.2)	6–96 (Mean 31.1)
Outcome*		
Recurrence	0	3
Reoperation	0	3
Grade 0	38	33
Grade I	11	10
Grade II	3	3
Grade III	1	2
Death	2	1

We noted no significant difference between the outcome of the treatment group when compared to the outcome of the control group ($\chi^2=5.154$, *P*=0.397).

* Grade 0 alert, no deficits; Grade I alert, with mild neurological deficits; Grade II lethargic, moderate deficits; Grade III obtunded, marked deficits.

surgery and CT showed widespread cortical and brainstem alterations. Two patients died of cerebral hemorrhage and car accidents 7 and 36 months after discharge respectively. In the conventional treatment group, the period of follow up ranged from 6 to 96 months with an average of 31.3 months. During the follow-up period, we noted 3 abscess recurrences, which were treated by repeated stereotactic surgery. Clinical results showed that 33 patients recovered well, 10 recovered with mild neurological deficits, 3 with moderate neurologic deficits, and 2 showed marked neurologic impairment. One patient died of heart disease 96 months after surgery (Table 2).

4. Discussion

Different from other reports, we injected high-dose antibiotics into the abscess cavity, which increased local intracavity antibiotic concentration and shortened the course of antibiotic treatment without increasing the recurrence rate of abscess.

Treatments for brain abscess include surgical resection, stereotactic abscess drainage, and medications only.^[10] Although the complete removal of an abscess is theoretically the best way, removal of the abscess wall will inevitably damage the surrounding normal brain tissue, which leads to long hospital stay, high cost, and increased surgical trauma, especially for those abscesses located in the bilateral, deep, and functional areas. Stereotactic aspiration and drainage is now a widely accepted neurosurgical treatment option. It will not only rapidly relieve the pressure by the abscess formation but also achieve high cure rate. However, to prevent the recurrence, antibiotic treatment is required. However, the reported recurrence rate is as high as 5% to 50% and most abscess recurrences occur within 8 weeks after the surgery.^[9–15]

The course of the antibiotic therapy is not defined exactly and pharmacological regimens remain controversial. Generally, it is recommended that 4 to 6 weeks of antibiotic treatment is followed by a 2 to 6 weeks course of oral antibiotics.^[14] Intravenous antibiotics should be used for at least 6 weeks. Some authors proposed that this treatment period should be extended to 8 to 12 weeks.^[16–20] American textbooks^[21] suggest large doses of intravenous antibiotics for 6 to 8 weeks followed by oral antibiotics for 2 to 3 weeks mainly based on the study reported by Mamelak et al.^[22] The British guideline^[23] recommends that systemic antibiotics should be used for at least 4 to 6 weeks after abscess resection or aspiration. For patients with conservative treatment, the therapy interval should be extended to 6 to 8 weeks. Due to the high recurrence rate in multiple brain abscesses, some researchers argued that systemic antibiotic treatment should be continued for at least 3 months. After the phase of treatment with high dose antibiotics the antibiotic treatment should be gradually reduced to a maintenance dose.^[24]

The long-term high-dose combination antibiotic therapy such as CSC therapy obtains good antibacterial effects.^[25] However, the incidence of side effects is high. Jansson et al^[18] studied the beta-lactam antibiotic cefotaxime combined with metronidazole in the treatment of brain abscesses and reported that the incidence of side effects was 60%. Most incidents happened in the third week of treatment or thereafter. Of 66 patients, only 12 (18%) completed the treatment and 38 (58%) stopped the therapy due to side effects. Then the antibiotic treatment was switched to other antibiotics.

Many researchers proposed to study the short course antibiotic therapy. Kutlay et al^[26] reported stereotactic aspiration combined with hyperbaric oxygen therapy in the treatment of brain abscess. Intravenous use of antibiotics was continued for 4 weeks and patients were followed up for 8 to 13 months (mean 9.5 months). In the first 2 weeks after surgery, 2 suffered abscess recurrences and underwent repeated aspiration. They hypothesize that hyperbaric oxygen could shorten the course of antibiotic therapy. Jamjoom^[27] attempted to shorten the antibiotic therapy course. They treated 26 patients with brain abscess and used C reactive protein (CRP), clinical manifestations, and CT scanning as indicators for antibiotic treatment cessation. Antibiotics were used for 11 to 30 days and no brain abscess recurrence was observed. However, the false-negative rate of CRP is 10% to 28%, which will affect the decision on further treatment.^[28–30]

And it must be kept in mind that 26% of patients had normal CRP on admission.^[31]

Intrathecal drug injection can significantly increase the drug concentration in the cerebrospinal fluid to cure severe intracranial infections. Brain abscess recurrence results from bacterial residuals in the abscess cavity or the abscess wall. Although brain abscesses can lead to an increase of permeability of the blood–brain barrier in the tissue surrounding the abscess, the amount of antibiotics entering the abscess cavity or wall is still limited compared to their concentrations in blood, which is the major reason for treatment failure and abscess recurrence. We assume that topical use of antibiotics in the abscess cavity significantly increased the local drug concentration, which would infiltrate into the cavity wall and effectively eliminate the pathogens and cure the abscess. In this study, systemic intravenous antibiotics were used for an average of 21.5 days (18–28 days). A total of 83 abscesses in 55 patients were cured and the follow-up period ranged from 6 to 72 months (mean follow-up interval: 26.2 months). Compared with 71 brain abscess in 51 patients treated with conventional stereotactic aspiration and drainage in the same hospital in the past 10 years, the course of consecutive systemic intravenous antibiotics was shortened by mean 10.8 days, and abscess recurrence rate did not increase. Of particular note is that each abscess requires aspiration and injection of antibiotics into every single cavity of multiple pyogenic brain abscesses or a multiloculated pyogenic brain abscess. Otherwise, systemic antibiotic treatment cannot be shortened.

The most likely adverse result of the highly concentrated antibiotic solution infiltrating the subarachnoid space through the puncture tract, leading to toxic irritations of the cortex and seizures, especially for lesions residing close to the cortex. Preventive measures include choosing a long puncture track, maintaining the puncture point elevated for at least 8 hours and minimizing the fluid volume. No drug leaking to the subarachnoid space causing adverse effects occurred in this study.

In this study, the mortality rate was 0. We agree that the most important factor affecting mortality and morbidity is the patient's neurological status before treatment. We hypothesize that the key to successful treatment of brain abscess is an early clinical diagnosis, timely surgical treatment and sufficient topical and systemic antibiotic therapy.

5. Conclusion

This clinical study prospectively employed intracavity injection of high-dose antibiotics combined with short course systemic antibiotics use. A total of 83 abscesses in 55 patients were treated. The cure rate was 100% and recurrence rate was 0 during the mean follow-up of 26.2 months. No topical injection related adverse effect occurred. The results show that intracavity use of antibiotics could shorten the course of systemic antibiotics therapy. This method reduced the possibility of reoperation, shortened the systemic antibiotics application, avoided the possible adverse effects of long-term systemic antibiotic use, the rate of reoperations and lowered the medical costs.

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