Original Article

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The use of mannitol in HIV-infected patients with symptomatic cryptococcal meningitis

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Summary **Cryptococcal meningitis (CM) is a common opportunistic infection with a high mortality rate in human immunodeficiency virus (HIV)-infected patients. It is unclear whether mannitol could be used to manage neurological symptoms in HIV-associated CM. Here, we retrospectively analyzed the clinical data of 33 patients with HIV-associated symptomatic CM at our hospital where mannitol was used to relieve neurologic symptoms. With the empirical mannitol therapy, patients had a median of 2 episodes (range, 1-6 episodes) of headaches the day at the starting of anti-cryptococcal therapy. The median score of pain intensity assessed by numerical rating scales was 7-point (range, 4-8 points). After the administration of mannitol, the score of pain intensity was reduced to 3-point or less. Three weeks after anti-cryptococcal therapy, 75.8% (25/33) of the patients did not report headaches. During the initial 3 weeks of anti-cryptococcal therapy, 13 patients had a total of 42 episodes of seizures. 97.6% (41/42) of the episodes of seizures were controlled after the administration of mannitol. Overall, 87.9% (29/33) of the patients survived more than 10 weeks without the need of therapeutic cerebrospinal fluid drainage. Mannitol was used for median of 26 days (range, 1-85 days) in these 29 patients. One patient had permanent vision loss. This study indicates that mannitol may possibly relieve neurologic symptoms in HIV-associated CM. It is worth re-revaluating the role of mannitol administration as a symptom control strategy in mild cases of HIV-associated CM.**

Keywords: HIV, cryptococcal meningitis, intracranial pressure, mannitol

1. Introduction

Cryptococcal meningitis (CM) is a common opportunistic infection with a high mortality rate in human immunodeficiency virus (HIV)-infected patients. It is estimated that about 1 million cases occur yearly and lead to more than 0.6 million deaths (*1*). Treatment of HIV-associated CM includes effective antifungal therapy and aggressive management of the elevated intracranial pressure (ICP) (*2,3*). The mechanism underlying the elevated ICP in HIV-associated CM has not been well-defined. Cerebrospinal fluid (CSF) inflammatory responses tend to be modest therefore may be a less important contributor to elevated ICP in many cases of HIV-associated CM (*4,5*). At least, in severe cases, accumulation of fungal elements in arachnoid granulations, which causes CSF outflow obstruction, leads to the raised ICP (*6,7*). Based on these findings, therapeutic lumbar puncture is recommended to control elevated ICP, although the optimal frequency of therapeutic lumbar puncture and the amount of CSF to be removed need to be further evaluated (*8-10*).

For many reasons, repeated therapeutic lumbar punctures are not performed in our clinical center. Patients with neurological symptoms (such as headache, seizures and confusion) associated with elevated ICP are routinely treated with mannitol, a hyperosmotic drug used for controlling elevated ICP caused by many other reasons (*11-13*). Here, we retrospectively analyzed the clinical and laboratory data of the patients with HIV-

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associated CM at our hospital to evaluate the prognosis of the patients and the adverse effects that may be related to mannitol administration.

2. Patients and Methods

HIV-infected patients with symptomatic CM in the Second Affiliated Hospital of the Southeast University from December 2010 to September 2014 were retrospectively analyzed. We collected the following data of the patients, such as age, sex, weight, CD4 count, clinical features, CSF parameters, biochemistry parameters, treatment, and outcome. Patients were followed with regular clinic visits and by telephone. This retrospective study was approved by the Ethics Committee of the Second Affiliated Hospital of the Southeast University.

HIV infection was documented by ELISA and confirmed with a Western blot. CM was diagnosed with at least one or more of the following: isolation of cryptococci in the CSF by staining methods(India ink preparation or alcian blue staining), a positive CSF culture for Cryptococcus spp. or a positive CSF cryptococcal antigen test(IMMY, Latex-Cryptococcus Antigen Detection System). ICP was measured with an intravenous tube attached to a metered stick, as described elsewhere (*14*).

Anti-fungal treatment of CM followed the recommended clinical practice guidelines (*9*), which included an initial induction therapy with amphotericin B (0.7 mg/kg per day intravenously) plus flucytosine (100 mg/kg per day orally) for more than 2 weeks, followed by fluconazole 400 mg/d for a minimum of 8 weeks as consolidation therapy, and then suppressive therapy with fluconazole 200 mg/d. We generally added 1-2 mg dexamethasone to amphotericin B during the first 1 to 2 weeks for the purpose of reducing infusion-related toxicities of amphotericin B. After initiation of anti-cryptococcal therapy, lumbar punctures were performed every 1 to 2 weeks to monitoring CSF parameters.

For patients with neurological symptoms such as headache, seizures and confusion, they were treated with 20% mannitol intravenously infused over 15-30 minutes. As a general rule, symptomatic patients were usually started with 125ml or 250 mL 20% mannitol every eight to six hours. The dosage of mannitol was adjusted according to the frequencies of headache or seizures at the discretion of treating physicians. If symptoms persisted, the daily dosage of mannitol was increased. If patients' clinical condition was improved, and there was no new episode of headache or seizures, the daily dosage of mannitol was gradually reduced. Patients were hospitalized until they did not need intravenous therapy. The pain intensity was assessed by numerical rating scales that 0 represent no pain and 10 represent the worst pain imaginable (*15*).

3. Results

3.1. *Patient characteristics*

During December 2010 to September 2014, 39 cases of HIV-associated CM were identified in the Second Affiliated Hospital of Nanjing. Two patients early gave up therapy (within 2 days of admission) due to economic reasons, therefore were excluded from analysis. Four cases of CM with good prognosis were early diagnosed before the onset of any neurologic symptoms. The patients were screened for cryptococcus infection because of the presence of pulmonary cavitary nodules, which were regarded as common lesions of HIV-associated pulmonary cryptococcosis (*16*). As mannitol was not used, these four patients were excluded from analysis. The remaining 33 symptomatic patients with headaches who had received at least one dosage of mannitol were included in the case-referent analysis, including one patient with coexisting tuberculosis meningitis. At admission, 69.7% (23/33) of the patients also had fever and 30.3% (10/33) of the patients had seizures or confusion.

Of the 33 studied patients, 26 were men; median age was 34 years (range, 12-71 years); median body weight was 54.5 kg (range, 30-71 kg); median CD4 cell count was 16 cells/μL (range, 2-280 cells/μL), and 87.9% (29/33) of the patients had CD4 count less than 100 cells/μL. Eight patients were on anti-retroviral therapy (ART) for a median of 2.3 months (range, 25 days to 25 months) at the time of CM confirmation. Virologic failure was confirmed in two patients who had received ART for 12 months and 25 months, respectively. Short courses of corticosteroids (about 2 weeks) were used in 4 patients that newly initiated ART. One patient on ART with suppressed HIV viral load received corticosteroids due to coexisting tuberculosis meningitis and CM.

For the baseline CSF parameters, the median CSF opening pressure was 230 mm H2O (range, 60-900 mmH2O); median white cell count was 6 cells/μL (range, 1-56 cells/μL); median sugar level was 2.6 mmol/L (range, 0.4-4.3 mmol/L); median protein level was 418.7mg/L (range, 171.2-993 mg/L).

3.2. *Patients' outcome and mannitol administration*

After initiation of anti-cryptococcal therapy, the survival rates at 2 weeks and 10 weeks were 93.9% (31/33) and 90.9% (30/33), respectively. One patient had permanent vision loss. Of the 3 patients that died within 10 weeks, 1 patient died of respiratory failure 4 days after the diagnosis of CM, 1 patient gave up therapy after 10 days' anti-cryptococcal therapy and the other patient developed brain herniation after a lumbar puncture when she had received anti-cryptococcal therapy for about 2 weeks. That patient with brain herniation survived another 2 weeks with her respiration controlled by a

ventilator. Of the 30 patients that survived more than 10 weeks, one patient received closed continuous lumbar drainage of CSF after 52 days' anti-cryptococcal therapy, and he died 86 days later due to neurological damages. Taken together, 87.9% (29/33) patients recovered from acute stage of CM without the need of therapeutic serial lumber punctures or surgical interventions such as ventriculoperitoneal shunt. Mannitol was used for median of 26 days (range, 1-85 days) in these 29 patients.

The median daily dosage of mannitol at the starting of anti-cryptococcal therapy was 4 times (range, 1-12 times). To maximally limit the frequency of headache or seizure, varying dosages of mannitol were added (Figure 1). Overall, 54.5% (18/33) of the patients had at least once received more than 4 times of mannitol administration in a day during hospitalization. Two weeks after the initiation of anti-cryptococcal therapy, 66.7% (22/33) of the patients' condition was stabilized that no more than 4 times of mannitol was administered every day and there was no increase of mannitol dosage thereafter (Figure 1). Nevertheless, 18.2% (6/33) of the patients still need 7 times or more mannitol administration, of whom 33% (2/6) finally died of CM.

With the empirical mannitol therapy, patients still had a median of 2 episodes (range, 1-6 episodes) of headaches the day at the starting of anti-cryptococcal therapy. The median score of pain intensity assessed by numerical rating scales was 7-point (range, 4-8 points). Fifteen minutes after the finish of mannitol administration, the score of pain intensity was reduced to 3-point or less. After 1 week's anti-cryptococcal therapy, 36.4% (12/33) of the patients did not report headaches. After 3 weeks' anti-cryptococcal therapy, 75.8% (25/33) of the patients did not report headaches.

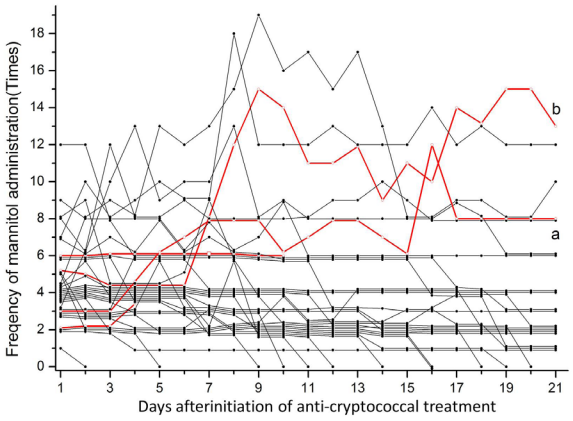

Figure 1. Dynamic of mannitol dosages after initiation of anti-cryptococcal therapy. To maximally limit the frequency of neurologic symptoms such as headache and seizures, varying dosages of mannitol were administered. Of the 4 patients (marked with red color) that were not saved by mannitol treatment, 2 patients died within 2 weeks of anti-cryptococcal therapy, 1 patient **(a)** developed cerebral herniation after having received anti-cryptococcal therapy for about 2 weeks and died 2 weeks later, and 1 patient **(b)** finally received closed continuous lumbar drainage of CSF after 52 days of anti-cryptococcal therapy and died 86 days later. In this figure, overlapped points were displayed with Y offset by manually changing the Y values.

During the initial 3 weeks of anti-cryptococcal therapy, 13 patients had a total of 42 episodes of seizures (median 3 episodes; range, 1-10 episodes), accompanied by loss of consciousness. 97.6% (41/42) of the episodes of seizures were controlled after the administration of mannitol. Sudden cardiopulmonary arrest occurred after one episode of seizure that mannitol treatment was considered unsuccessful. This patient with suspected brain herniation survived another 2 weeks with her respiration controlled by a ventilator, as above mentioned. At the time of starting anti-cryptococcal therapy, 6 patients had different degrees of confusion. The mental status gradually recovered in 5 of those 6 patients after a median of 5 days (range, 2 to 14 days), however, mental status in one patient continued to progress even though he was aggressively treated with mannitol. After 10 days' anti-cryptococcal therapy, the patient, who had become unconsciousness for 1 day, gave up therapy and was considered to be dead.

3.3. *Monitoring of laboratory parameters*

Hyponatremia, defined as serum sodium level of less than 135 mmol/L, was detected at least once in 72.7% (24/33), 43.8% (14/32) and 32.3% (10/31) of the patients during the first, second and third week, respectively. Serum sodium level of less than 130 mmol/L was detected at least once in 36.4% (12/33), 25% (8/32) and 12.9% of the patients during the first, second and third week, respectively. Serum sodium level of less than 125 mmol/L was detected at least once in 9.1% (3/33), 9.4% (3/32) and 3.2% (1/31) of the patients during the first, second and third week, respectively.

Hypokalemia, defined as serum potassium level of less than 3.5 mmol/L, was detected at least once in 18.2% (6/33), 21.9% (7/32) and 45.2% (14/31) of the patients during the first, second and third week after the initiation of anti-cryptococcal therapy, respectively. Serum potassium level of less than 3.0 mmol/L was detected at least once in 3.0% (1/33), 3.1% (1/32) and 12.9% (4/31) of the patients during the first, second and third week after the initiation of anti-cryptococcal therapy, respectively. Serum potassium level of less than 2.5 mmol/L was only seen in one patient during the third week. During the initial 3 weeks of anti-cryptococcal therapy, elevated serum blood urea nitrogen (BUN) level (more than 8.3 μmol/L) and/or elevated serum creatinine level (more than 97 μmol/L) was detected at least once in 18.2% (6/33) and 12.1% (4/33) of the patients, respectively. None of the patients had a serum creatinine level exceeding 220μmol/L during hospitalization.

4. Discussion

Elevated ICP often leads to developing neurological

symptoms such as headache, altered mental status, and coma (*2*). Higher pretreatment ICP in HIV-associated CM is associated decreased short-term survival (*7*). Lumbar puncture drainage is an effective strategy to reduce the ICP and it also helps to remove fungal elements (*7*). There are accumulated evidences that therapeutic lumbar puncture in HIV associated CM is associated with improvement in survival, and non-adherence to this strategy may in part lead to neurological injury (*14,17,18*). Despite of survival benefit, therapeutic lumbar puncture is not performed in some patients, which may be due to limited awareness of the importance of ICP management (*7,17,18*).

In our clinical center, for the following reasons, mannitol is routinely used to manage neurological symptoms associated with CM in HIV-infected patients. At first, Mannitol is used to manage elevated ICP in various conditions such as bacterial meningitis, tuberculosis meningitis, and brain injury (*11,19-21*). In China, mannitol administration is still one of the recommended choices for the management of HIV-associated CM based on expert opinions (*22*). Finally, there is still lack of physicians to manage HIV-infected patients in our center. It is not possible to perform a lumbar puncture drainage whenever the patient has a headache episode, especially at night or during the weekend. Our study suggests that mannitol administration may be efficacious to relieve headaches and perhaps seizures associated with CM. With anti-cryptococcal therapy and adjunctive mannitol therapy for symptom control, 87.9% (29/33) of the patients survived more than 10 weeks without the need of therapeutic CSF drainage. The prognosis seems to be not bad as compared to a recently well-controlled clinical trial performed in Asian population (*23*). This is the most important reason why mannitol is still being used in our clinical center to managing neurological symptoms associated with CM. It should be noted that varying dosages of mannitol were needed to control neurological symptoms (Figure 1). This may reflect different extent of CSF reabsorption impairment due to accumulation of cryptococcal elements in the arachnoid granulations. 54.5% (18/33) of the patients had at least once received more than 4 times of mannitol administration in a day during hospitalization. Patients with pre-exist cardiac diseases may not tolerate frequent intravenous mannitol injection. Massive administration of mannitol warrants more frequent monitoring of renal function and electrolytes.

The findings in our study have several clinical implications. Firstly, although capable to reduce ICP, repeated lumbar punctures are not always effective to relieve headaches, and may even increase headaches in a minority of patients (*7*). In this condition, mannitol administration may be a possible choice to relieve headaches. Secondly, compared with therapeutic lumbar puncture, mannitol therapy is relatively less invasive and easier to perform. For patients not willing to receive lumbar puncture, especially those with mild neurologic symptoms, mannitol may be used to relieve headaches. Finally, mannitol may be a choice in settings where therapeutic lumbar puncture is unavailable.

This study was limited by relatively small sample size with retrospective nature and no control was included. In our study, during the first 1 to 2 weeks, 1-2 mg dexamethasone was added to amphotericin B to reduce the infusion-related toxicities of amphotericin B. A recent study showed that dexamethasone is harmful in HIV-associated CM (*24*). Nevertheless, the dose of dexamethasone in our clinical practice was very small and the duration was relatively short, therefore in our opinion, the negative effects of dexamethasone were negligible. The causes of the laboratory abnormalities in our study were multifactorial. Both mannitol and amphotericin B may induce renal damage and electrolyte disturbance. Poor appetite and vomiting associated with CM may also contribute to electrolyte disturbance. Although the prognosis of patients receiving mannitol administration as a symptom control strategy seems not to be greatly impaired in our studied patients, it should not be regarded as that mannitol is as effective as standard therapeutic lumbar puncture drainage. For the patients that need massive mannitol administration, they would better receive therapeutic lumbar puncture drainage or perhaps ventriculoperitoneal shunting (*25*), although this was not performed in our patients. Of note, adult human produces 500-600 mL CSF every day (*26*), while usually less than 30 mL CSF is removed by a lumbar puncture drainage (*14*). If one lumbar puncture is performed each day, 94-95% of the CSF still needs to be reabsorbed by meninge. It suggests that for most of the patients with CM, CSF outflow obstruction may be not severe. Perhaps, only in this condition, mannitol administration would not severely impair the outcome of HIV-associated CM.

In conclusion, although it is not known whether mannitol could reduce the ICP in HIV-associated CM, mannitol administration may be used to relieve neurologic symptoms in HIV-associated CM. Of great interesting, the prognosis of patients receiving mannitol administration as a symptom control strategy seems not to be greatly impaired. It is worth re-revaluating the role of mannitol administration as a symptom control strategy in mild cases of HIV-associated CM.

Acknowledgements

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