Triple therapy combined with ventriculoperitoneal shunts can improve neurological function and shorten hospitalization time in non-HIV cryptococcal meningitis patients with increased intracranial pressure

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Abstract

Background: Raised intracranial pressure (ICP) and insufficient antifungal regimens are the two main factors result to unsatisfactory outcomes in non-HIV cryptococcal meningitis (CM) patients. In this study, we try to discuss that whether triple therapy of amphotericin B (AmB), fluconazole, 5-flucytosine (5-FC) plus ventriculoperitoneal shunts (VPS) is superior to AmB, 5-FC, fluconazole plus intermittent lumbar puncture in induction therapy in non-HIV CM patients with increased ICP.

Methods: We reviewed 66 clinical records from non-HIV CM patients with increased ICP. The demographic and clinical characteristics, BMRC staging, cerebrospinal fluid profiles (CSF), brain magnetic resonance imaging, treatment, and outcomes of these individuals were retrospectively analyzed. All non-HIV CM patients with increased ICP (≥ 25 cmH2O) were divided into two groups, including 27 patients treated with triple antifungal agents and 39 patients treated with the same triple therapy plus VPS.

Results: Triple therapy plus VPS group had more satisfactory outcomes, and more CSF sterilization at 10 weeks follow-up,lower CSF opening pressure, lower BMRC staging scores one week after VPS, less CSF C. neoformans counts and CSF culture positive. Patients in triple therapy plus VPS group got the improvement in neurological function circumstances evaluated by comparing the BMRC staging before and after VPS. These patients had shorter hospital stay.

Conclusions: Triple antifungal agents combined with VPS can effectively reduce ICP, have faster rate of clearance of C. neoformans counts, more improved neurological function, shorten hospitalization time and better outcomes in non-HIV CM patients with increased ICP. Our study indicated that triple therapy plus early VPS is maybe the optimal treatment for non-HIV CM patients with increased ICP.

Background

Cryptococcal meningitis (CM) is one of the most common clinical presentations of cryptococcosis, which accounts for more than 223 100 cases and 181 100 deaths per year [1]. Elevated intracranial pressure (ICP) is the most common complication of CM, and can cause impaired mental status, neurological deterioration, and severe disability [2-3].

The Infectious Diseases Society of America (IDSA) recommended the induction therapy of amphotericin B deoxycholate (AmB) (0.7-1.0 mg/kg per day) combining with 5-flucytosine (5-FC) (100 mg/kg per day) for at least 4 weeks as the preferred regimen for non-HIV-infected and non-transplant patients with CM [4]. However, AmB and 5-FC may often cause severe toxic effects so that CM patients can't endure the recommended dosages. In addition, increased ICP (≥ 25 cm H_2O) is frequent in CM patients, is associated with reduced short-term survival and impaired treatment response [5]. Raised ICP and only moderately effective antifungal regimens, which frequently take more than 4-6 weeks to sterilize cerebrospinal fluid (CSF), are two main factors result to unsatisfactory outcomes in CM patients with elevated ICP [6]. Despite therapy, mortality rates in HIV-seronegative individuals with CM are high [7]. Our previous clinical observations and retrospective study showed that non-HIV patients with triple therapy of AmB, 5-FC plus Fluconazole at sub-therapeutic doses seemed to have a better prognosis than therapy of AmB and Fluconazole [8], and early placement of ventriculoperitoneal shunts (VPS) is helpful in decreasing ICP and fungal overload in non-HIV CM patients [9]. It is maybe the optimal treatment with aggressive management of ICP and induction therapy with antifungal combination [10]. Therefore, we try to discuss that whether triple therapy of AmB, 5-FC, Fluconazole plus VPS is superior to AmB, 5-FC, Fluconazole plus intermittent lumbar puncture in induction therapy in non-HIV CM patients with increased ICP.

Materials And Methods

In this study, data from all 66 patients with a first episode of non-HIV CM patients were retrospectively reviewed. These patients were admitted to The Third Affiliated Hospital of Sun Yat-Sen University in Guangzhou, China, from January 2011 to December 2018. The diagnosis was confirmed by symptoms and signs that were consistent with CM and at least one of the following factors: positive India ink staining of the CSF or a positive CSF culture for *Cryptococcus neoformans*. All patients were confirmed to be non-HIV infected by a negative serum HIV antibody test, with CSF opening pressure ≥ 25 cmH_2O. These selected CM patients were divided into two groups according to the treatment regimens. In triple therapy group, the 27 patients were treated

with a combination of AmB, Fluconazole, and 5-FC plus intermittent lumbar puncture. In triple therapy plus VPS group, the 39 patients were administered triple therapy of AmB, Fluconazole, and 5-FC plus VPS. Patients meeting one of the following criteria were excluded: (1) prior surgical intervention due to intracranial hypertension; (2) recurrent CM.

The demographic and clinical characteristics, British Medical research council (BMRC) staging [11], CSFprofiles, brain magnetic resonance imaging（MRI）, treatment, and outcomes of these individuals were analyzed. The BMRC staging system was used to assess central nervous system symptom severity in this study. The evaluation method was reassessed and compared at baseline, discharge and follow-up at 10 weeks. The outcomes mainly depended on the laboratory results. The enrolled patients underwent lumbar punctures at least once a week in accordance with guidelines during the implementation of the two study regimens [5,12]. CSF specimens were routinely evaluated for white blood cell (WBC) count, glucose, protein, India ink stain, and culture. In addition to CSF parameters, other conventional blood tests and images were also assessed during treatment.

The antifungal therapy was initiated as soon as the diagnosis was confirmed by the microscopic identification of *Cryptococcus neoformans*. In triple therapy group, the patients were treated with intravenous AmB (30-40 mg/d), Fluconazole (600-800 mg/d) plus oral 5-FC (4-6 g/d) daily for at least 2 weeks. In triple therapy plus VPS group, the patients received the same triple therapy for at least 2 weeks, and received the VPS. The 'gold standard' of the CM treatment response was as defined by clinical and mycological criteria [13], particularly the documented clearance of the CSF, which has been assigned greater importance than the clinical criteria [14]. Therefore, treatment response as the primary outcome was evaluated at 10 weeks after the initiation of antifungal therapy. The therapeutic outcomes were first identified as 'successful response' or 'failure' based on the CSF *cryptococcal* clearance and were further classified into five levels: (1) complete response: survival and resolution of all attributable symptoms and signs of disease with CSF clearance; (2) partial response: survival and CSF clearance with persistence of attributable symptoms and signs of the disease; (3) stable response: survival and minor or no improvement in attributable symptoms and signs of disease and persistently positive CSF culture results; (4) disease progression: worsening clinical disease symptoms or signs and persistently positive CSF culture results; and (5) death: death during the prespecified evaluation period, regardless of attribution [15]. Secondary clinical end points included the incidence of CSF culture sterility at 2 weeks (termed early fungicidal activity), culture-positive relapse and the end point of induction therapy.

The baseline characteristics between two groups were compared with a t-test or Wilcoxon rank sum test for continuous variables (presented as the mean ± standard deviation (SD) or median with ranges) and Chi-square test, Fisher's exact test or Wilcoxon rank sum test for categorical variables. All statistical analyses were two-tailed and SPSS (version 16.0, Chicago, IL, USA) for Windows was used. P-value < 0.05 was considered statistically significant.

Results

The demographics, baseline CSF parameters, cranial computed tomography (CT)/MRI and baseline BMRC staging of the study patients are presented in **Table 1**. Triple therapy plus VPS group patients had higher burdens of cryptococcal organisms in the CSF before treatment than triple therapy group patients (median 9533 vs. 1398 *C. neoformans counts* /ml, respectively, $P = 0.002$). Triple therapy plus VPS group patients had shorter hospital stay than that of triple therapy group (77 vs. 35 , $P = 0.000$). That means triple antifungal agents combined with VPS can obviously shorten the hospitalization time in non-HIV CM patients with increased ICP (≥ 25 cmH^2O).

The results of CSF sterilization within 10 weeks between the two groups were detailed in **Table 2**. Compared to triple therapy group, there were more patients in triple therapy plus VPS group to clear *cryptococcus* from the CSF ($P = 0.033$). So triple antifungal agents combined with VPS can more effectively clear cryptococcus from CSF. no significant differences were observed in the early fungicidal activity (CSF sterility within 2 weeks) and persistent infection (CSF sterility beyond 4 weeks [4]) between the two groups.

The CSF opening pressure, CSF C. neoformans counts and CSF culture positive of patients in triple therapy plus VPS group significantly decreased after VPS ($P = 0.000$, $P = 0.019$ and $P = 0.002$). CSF protein increased significantly after VPS. Patients in triple therapy plus VPS group got the improvement in neurological function circumstances evaluated by comparing the BMRC

staging before and after VPS (P = 0.026) (**Table 3**), which suggest that triple antifungal agents combined with VPS can significantly improve neurological function.

Adverse events were common. Antifungal drugs are associated with toxic effects, particularly AmB and 5-FC. At the end of the 10th week, there were no significant differences in the two treatment groups in objective blood tests (**Table 4**). Sequelae was mainly headache and cranial nerve deficit (Optic and auditory nerves). No significant differences about sequelae in two groups were found.

In triple therapy plus VPS group, after the VPS, thirteen cases had low to moderate fever, and the temperature recovered to normal in a week by using antibiotics. One case occured shunt obstruction and he was taken second operation on the other side. One case turned up excessive shunt after operation, and his CSF open pressure was normal by adjust the drainage tube. There was no *cryptococcal* infection spread to other organs (**Table 2**).

The primary outcome of treatment response was evaluated at the 10th week after the initial therapy. The total 'successful response' rate (including complete and partial responses) in triple therapy plus VPS group reached 57.9% (22/38), whereas the rate was 29.6% (8/27) in triple therapy group (P = 0.025) (**Table 5 and Fig 1**). Two patients in triple therapy plus VPS group died of multiple organ failure on the 18st day and 47st day respectively. One patient died in triple therapy group after the 10 weeks. Triple therapy plus VPS group patients have shorter the first hospitalization stays than triple therapy group (**Fig 2**, log Rank p 0.000). In the multivariate analysis, we did not find meaningful predictors of an satisfactory outcome in the triple therapy group. The multivariate analysis showed high red blood cells levels (OR 3.210, 95% CI 1.097–9.396; p=0.033) to be a good prognosis factor for the patients with triple therapy plus VPS (**Table 6**).

Discussion

In our study, triple antifungal agents combined with VPS can effectively reduce ICP, have faster rate of clearance of *Cryptococcus*, more improved neurological function, shorten hospitalization time and better outcomes in non-HIV CM patients with elevated ICP ($\geq$ 25 cmH_2O). No significant differences were observed in the incidence of adverse events and sequelae between the two groups.

As stated in our previous study [8], there were several reasons for patients treating with triple therapy. Patients cannot bear AmB and 5-FC at the recommended doses from the beginning and (or) cannot be maintained at the effective dose during induction therapy because of drug toxic effects [16, 4]. Previous research had suggested early mycological clearance was favored with AmB deoxycholate plus Fluconazole combination therapy [17]. Although AmB and Fluconazole are theoretically antagonistic drugs, in vitro and clinical observations support the effectiveness of the combination [6, 18-19]. Fluconazole in triple therapy administered at a conventional dosage may have compensated for the less role of AmB at lower dosage, particularly when Fluconazole is combined with 5-FC [20]. Patients enrolled in this study were treated with triple therapy at conventional or sub-therapeutic doses for the induction treatment. And no significant adverse events were found in objective blood tests during the treatment between two groups.

Elevated ICP is an important risk factor for high mortality and poor outcomes in CM patients [21-22]. Among patients with uncontrollable increased ICP, the best way to decrease the pressure is to implant a permanent shunt [23]. VPS can effectively reduce ICP. The complications after VPS were controllable. Nerve functionassessed by BMRC stage, was significantly improved after VPS. But the sequelae of the triple therapy plus VPS group wasn't significantly less than the triple therapy group. We proposed that VPS placed in some patients after the time when it can prevent irreversible neurological complications. Increased ICP ($\geq$ 25 cmH_2O) is a severe complication in patients with CM, and is generally considered to relate to high fungal burden in the CSF [24]. High fungal burden at baseline is related to mortality in CM [6, 25]. A negative CSF culture at the end of the induction phase is an important predictor of fungal clearance at 10th week [26]. The goal of CM with ICH treatment is to reduce fungal burden quickly and to prevent long-term neurological deficits. In this study, triple therapy plus VPS group has faster rate of clearance of *Cryptococcus* than triple therapy group. Hung CW et al. reported that the mean hospitalization duration was 74.7 days and 70.6 days and interval between meningitis onset to shunting procedure was 68.7 days and 38.7 days for CM patients placed VPS with and without CSF over drainage, respectively [27]. Triple therapy group in our study had the similar result of

hospital stay 77 days. Hospital stay of triple therapy plus VPS group in our study was significantly shortened (35 days), which may be result of triple antifungal agents and early VPS CM patients with elevated ICP who placing a VPS could be explained for following factors. CM patients had a typical presentation with substantially increased ICP along with severe headaches, nausea and vomiting, loss of consciousness, marked visual and auditory changes. Patients responded poorly for intermittent lumbar puncture to decrease the ICP or required continuous lumbar CSF drainage to remain neurologically asymptomatic. Progressive intracranial hypertension may lead to brain hernia or even endanger life. Patients in triple therapy plus VPS group mostly emerged aggravated symptoms or new symptoms in a short time before VPS. In addition, the timing and choice of VP shunt placement may be related to preferences of neurosurgery or physicians [28]. Recent study indicated that early shunt surgery is mandatory for the treatment of CM complicated by hydrocephalus and/or increased ICP to avoid irreversible neurological complications [27]. In our study, patients received VPS after admission with triple therapy, with lower CSF pressure, faster reduction of CSF C. neoformans counts. Baddley et al study also suggested that earlier permanent VPS placement and more aggressive treatment may potentially improve outcomes for CM patients with increased ICP [28].

Treatment in triple therapy plus VPS group decrease the CSF pressure, CSF *C. neoformans counts* quickly, and certainly result to more 'successful response' rate (including complete and partial responses) than that in triple therapy group at 10 weeks follow-up. Shoham S et al. also found that CM patients with elevated ICP treated with aggressive management of elevated ICP got better outcomes [29].

Our study was performed in a single hospital by retrospective review of the medical records. The number of patients enrolled was small, and the dosage range of the three antifungal drugs was insufficient. Large multicenter real-life studies are needed to further verify the efficiency and feasibility of this method.

Conclusions

In summary, based our previous work, triple antifungal agents combined with VPS can effectively reduce ICP, have faster rate of clearance of Cryptococcus,more improved nerve function, shorten hospitalization time and better outcomes in non-HIV CM patients with elevated ICP ($\geq$ 25 cmH_2O). It is an optimal treatment with aggressive management of intracranial pressure and induction therapy with antifungal combination in non-HIV CM patients with intracranial hypertension ($\geq$ 25 cmH_2O).

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committees of The Third Affiliated Hospital of Sun Yat-Sen University. The study was in compliance with the Declaration of Helsinki and its later amendments. All study participants provided written informed consent. Identifiable data involving the individuals in this study was encrypted.

Consent for publication

Not Applicable

Availability of data and materials

The data and materials used during the current study are available from the first author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FP mainly contributed to the conception and design. ML, JL and XD have been involved in drafting the manuscript. QG and YW have contribution to acquisition of data, give the consent to participants. XX and YJ have analyzed and interpreted data. ML, JL, FP and YJ have revised the manuscript. All authors read and approved the final manuscript for publication.

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Tables

Due to technical limitations, tables 1-6 are only available as a download in the supplemental files section.

Figures

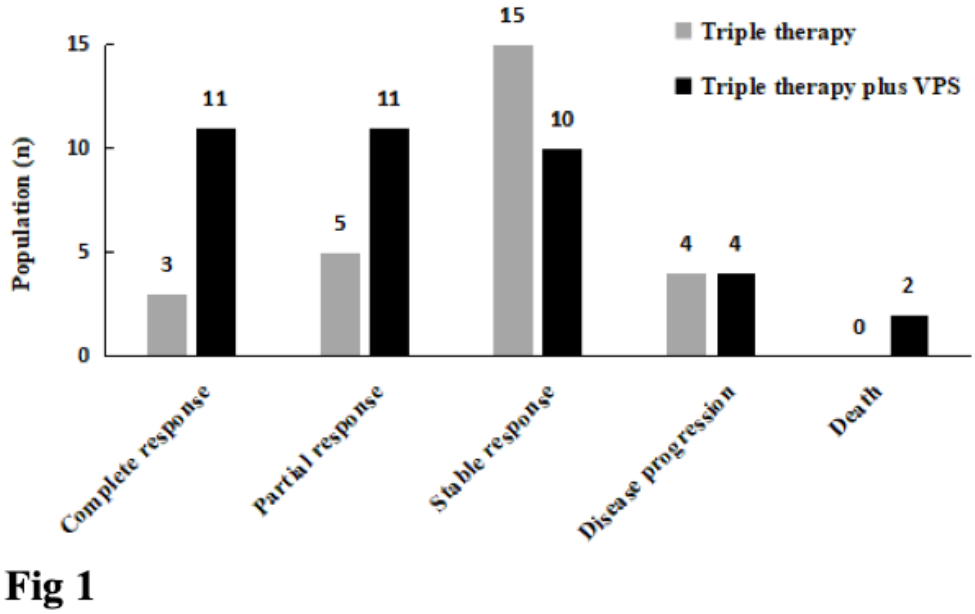

Fig 1

Figure 1

Treatment outcomes according to induction therapy at the 10th week after the initial therapy.

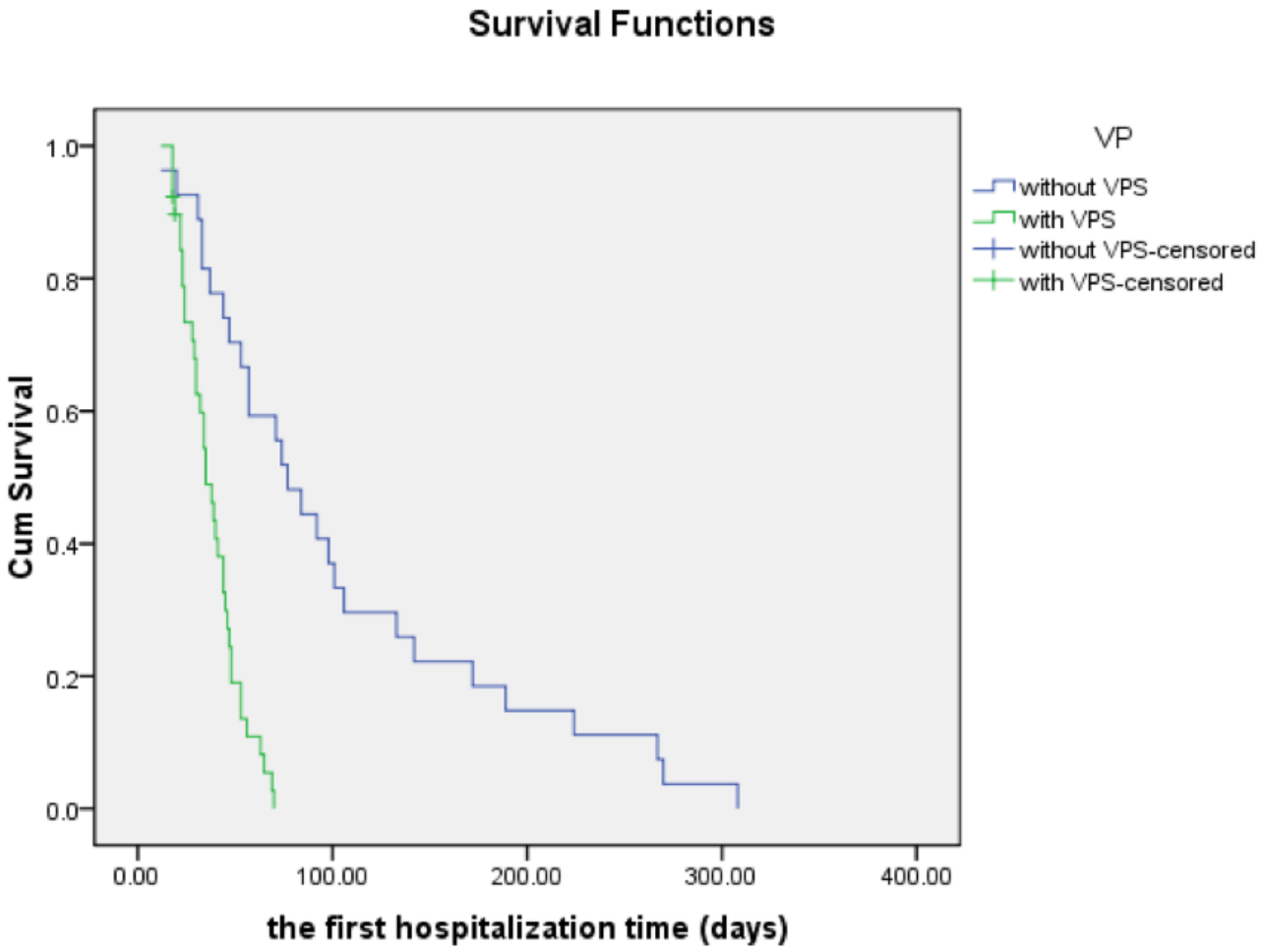

Fig 2

Figure 2

Kaplan–Meier survival curves of triple therapy plus VPS group and triple therapy group.

Supplementary Files

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