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 (Flu), 5-flucytosine (5-FC) plus ventriculoperitoneal shunts (VPS) is superior to AmB, 5-FC, Flu 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 a significantly higher frequency of satisfactory outcomes. More patients in triple therapy plus VPS group have CSF sterilization at 10 weeks follow-up. And patients in triple therapy plus VPS group present with lower CSF opening pressure, less CSF cryptococci count and CSF culture positive, and lower BMRC staging scores one week 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. Triple therapy plus VPS group patients had shorter hospital stay.

Conclusion: Triple antifungal agents combined with VPS can effectively reduce ICP, have faster rate of clearance of *Cryptococcus*, improve nerve function, shorten hospitalization time and get 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 1 million cases and 625 000 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 (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 of antifungal drugs. In addition, increased ICP (≥ 25 cm H₂O) is frequent with CM, and 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 the non-HIV patients with triple therapy of AmB, 5-FC plus Flu at sub-therapeutic doses seemed to have a better prognosis than therapy of AmB and Flu [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, Flu plus VPS is superior to AmB, 5-FC, Flu 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 cmH₂O. 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, Flu, and 5-FC plus intermittent lumbar puncture. In triple therapy plus VPS group, the 39 patients were administered triple therapy of AmB, Flu, and 5-FC plus VPS. Patients meeting one of the following criteria were excluded: (1) prior surgical intervention due to intracranial hypertension; and (2) recurrent CM.

The demographic and clinical characteristics, British Medical research council (BMRC) staging [11], cerebrospinal fluid profiles, brain magnetic resonance imaging, treatment, and outcomes of these individuals were retrospectively 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 cultures. 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), Flu (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. Unless contraindicated, all patients were also subjected to some measures to minimize antifungal drug toxicities, for example, the administration of nonsteroidal anti-inflammatory drugs or antihistamines to prevent chills and fever, heparin sodium injection to prevent and reduce the occurrence of phlebitis and a series of symptomatic and supportive treatments.

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 $\pm$ 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 16.0 version for Windows was used. A P-value of < 0.05 was considered statistically significant.

Results

The demographics, baseline CSF parameters, cranial computed tomography (CT)/magnetic resonance imaging (MRI) and baseline BMRC staging of the study patients are presented in Table 1. Triple therapy plus VPS group patients had higher median burdens of cryptococcal organisms in the CSF before treatment than triple therapy group patients (median 9533 vs. 1398 *Cryptococci*/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 cmH₂O).

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. Though no significant differences were

both 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 *cryptococci* count and CSF culture positive of patients in triple therapy plus VPS group decreased significantly 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 nerve 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 were 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, one case occurred shunt obstruction and one case turned up excessive shunt after operation. There was no *cryptococcal* infection spread to other organs.

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 patient in triple therapy plus VPS group died of multiple organ failure on the 18th day and 47th day respectively. One patient died in triple therapy group after the 10 weeks.

Discussion

In our study, triple antifungal agents combined with VPS can effectively reduce ICP, have faster rate of clearance of *Cryptococcus*, improve nerve function, shorten hospitalization time and get better outcomes in non-HIV CM patients with elevated ICP (≥ 25 cmH₂O). No significant difference was observed in the incidence of adverse events and sequelae between the two groups.

As stated in our previous study [8], there were 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 suggest early mycological clearance was favored with AmB deoxycholate plus Flu combination therapy [17]. Although AmB and Flu are theoretically antagonistic drugs, in vitro and clinical observations support the effectiveness of the combination [6, 18–19]. Flu in triple therapy administered at a conventional dosage may have compensated for the less power of AmB at lower dosage, particularly when Flu 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 significance was found about adverse events 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 function, assessed 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 (≥ 25 cmH₂O) 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 have 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 for those without CSF overdrainage, 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 (4–21 days) (Fig. 2).

CM patients with elevated ICP who placing a VPS attributed for several 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 in one month (4–21 days) after admission with triple therapy (Fig. 2), which decrease the CSF pressure, CSF *cryptococci* count quickly. 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 *cryptococci* count quickly, and cetainly reslut 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*, improve nerve function, shorten hospitalization time and get better outcomes in non-HIV CM patients with elevated ICP (≥ 25 cmH₂O). It is a optimal treatment with aggressive management of intracranial pressure and induction therapy with antifungal combination to non-HIV CM patients with intracranial hypertension (≥ 25 cmH₂O).

Abbreviations

ICP: Intracranial Pressure; CM: Cryptococcal Meningitis; AmB: Amphotericin B, Flu: Fluconazole, 5-FC: 5-flucytosine; CSF: Cerebrospinal Fluid Profiles; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; BMRC: British Medical Research Council; IDSA: Infectious Diseases Society of America; med: Median; SD: Standard Deviation; VPS: Ventriculoperitoneal Shunts; WBC: White Blood Cell.

Declarations

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Authors' contributions

FP mainly contributed to the conception and design. ML, JL and XD has 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. All authors read and approved the final manuscript for publication.

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Availability of data and materials

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

Ethical standard

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 informed consent. Identifiable data involving the individuals in this study was encrypted.

Consent for publication

All authors has reviewed the final version of the manuscript and approve it for publication.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Baseline patient characteristics

Variables	Triple therapy (n = 27)	Triple therapy plus VPS (n =39)	p-value
Age, years (mean±SD)	44.1±14.0	47.9±14.7	0.287
Gender, male (n,%)	20 (74.1%)	28 (71.8%)	0.839
Predisposing Factors			
Chronic hepatitis B	5 (18.5%)	4 (10.3%)	0.340
Pulmonary tuberculosis	3 (11.1%)	2 (5.1%)	0.370
Type 2 diabetes mellitus	2 (7.4%)	5 (12.8%)	0.486
Autoimmune diseases	1 (3.7%)	4 (10.3%)	0.326
Solid tumor	1 (3.7%)	4 (10.3%)	0.326
Symptoms duration, days, (med, range)	30 (6-120)	30 (8-90)	0.331
Length of hospital stay days, (med, range)	77 (12-308)	35 (18-73)	<0.001
CSF parameters			
opening pressure			
≥25 cmH ₂ O(n, %)	27 (100%)	39 (100%)	1.000
CSF WBC count×10 ⁶ /l (med, range)	92 (10-649)	82 (4-840)	0.744
≥20 (n,%)	23 (85.2%)	32 (82.1%)	0.871
CSF protein g/l (med, range)	0.78 (0.08-2.58)	0.71 (0.22-5.10)	0.579
CSF glucose mmol/l (med, range)	1.19(0.00-3.79)	0.83 (0.01-3.09)	0.273
CSF cryptococci count/ml (med, range)	1398 (0-57500)	9533 (0-263000)	0.002
CSF culture positive (+)	15 (55.69%)	19 (48.7%)	0.114
Brain images (CT or MRI)			

Meningeal enhancement	18 (66.7%)	18 (46.2%)	0.182
Cryptococcosis-related lesions in brain	13 (48.1%)	17 (43.6%)	0.717
Hydrocephalus	3 (11.1%)	3 (7.7%)	0.637
BMRC staging (n, %)			0.443
1	2 (7.4%)	8 (20.5%)	
2	16 (59.3%)	10 (25.6%)	
3	9 (33.3%)	21 (53.8%)	

Data are presented as the mean±SD, median (range) or n (%). Continuous variables were analyzed by t-test or Wilcoxon rank sum test; categorical variables were analyzed by Chi-square test or Fisher's exact test.

A *p*-value < 0.05 indicates statistical significance.

BMRC British Medical research council, *med* median, *SD* standard deviation, *VPS* ventriculoperitoneal shunts, *WBC* white blood cell.

Table 2 Clinical characteristics of patients in triple therapy plus VPS group before VPS and 10 weeks follow-up.

Patient	Before VPS	one week after VPS	<i>p</i> -value
CSF parameters			
opening pressure			
≥25 mH ₂ O(n, %)	33 (84.6%)	12 (30.8%)	<0.001
CSF WBC count×10 ⁶ /l	66 (4-620)	77 (0-993)	0.220
(med, range)			
≥20 (n,%)	36 (80.0%)	41(91.1%)	0.136
CSF protein g/l(med, range)	0.67 (0.22-4.08)	2.29 (0.08-729)	<0.001
CSF glucose mmol/l(med, range)	1.16 (0.01-3.47)	0.91 (0.01-4.86)	0.380
CSF cryptococci count/ml	9533 (0-263000)	2066 (0-235000)	0.019
(med, range)			
CSF culture positive (+) (n, %)	19 (48.7%)	6 (15.4%)	0.002
BMRC staging (n=39)			0.026
1	8 (20.5%)	14(35.9%)	
2	10 (25.6%)	14(35.9%)	
3	21 (53.8%)	11(28.2%)	

Data are presented as median (range) or n (%). Categorical variables were analyzed by Chi-square test or Fisher's exact test.

A *p*-value < 0.05 indicates statistical significance.

BMRC British Medical research council, *med* median, *NA* not available, *VPS* ventriculoperitoneal shunts, *WBC* white blood cell.

Table 3 Data for the CSF sterility at the 10 weeks follow-up.

	Triple therapy (n = 27)	Triple therapy plus VPS (n ^a = 38)	<i>p</i> -value
case (n, %)	8 (29.6%)	22 (56.4%)	0.033
Days ^b (mean ± SD)	29.2 ± 20.0	32.5 ± 24.8	0.909
≤ 2 weeks (n, %)	2(7.4%)	8 (20.5%)	0.662

> 2 weeks (n, %)	6 (22.2%)	14 (35.9%)	
≤ 4 weeks (n, %)	4 (14.8%)	13 (33.3%)	0.730
> 4 weeks (n, %)	4 (14.8%)	9 (23.1%)	

Continuous variables analyzed by t-test; categorical variables analyzed by chi-square test or Fisher's exact test.

A *p*-value < 0.05 indicates statistical significance.

VPS ventriculoperitoneal shunts.

^aOne patient was lost to -follow-up at the 10th week in Group II.

^b'Days' indicates the time from diagnosis to the first negative CSF india ink stain. SD = standard deviation.

Table 4 Adverse events in objective blood tests during the treatment and sequelae at the 10th week in patients between triple therapy group and triple therapy plus VPS group.

	Triple therapy	Triple therapy plus VPS	<i>p</i> -value
Adverse events (n, %)	(n = 27)	(n =39)	
Hypokalemia	13 (48.1%)	20 (51.3%)	0.804
Transaminase elevation	14 (51.9%)	15 (38.5%)	0.285
Renal impairment	5 (18.5%)	12 (30.8%)	0.267
Hematological impairment	5 (18.5%)	14 (35.9%)	0.128
Sequelae	(n=27)	(n ^a =36)	
Headache	9 (33.3%)	9 (25.0%)	0.395
Dizziness/vertigo	2 (7.4%)	5 (13.9%)	0.465
Hemiparesis	4 (14.8%)	5 (13.9%)	0.850
Visual	8 (29.6%)	6 (16.7%)	0.184
Auditory	1 (3.7%)	7 (19.4%)	0.077
Seizure	3 (11.1%)	2 (5.6%)	0.387

A *p*-value < 0.05 indicates statistical significance.

VPS ventriculoperitoneal shunts.

^aOne patient was lost to -follow-up and two patients were death at the 10th week in Group II.

Table 5 Treatment outcomes in patients between triple therapy group and triple therapy plus VPS group at 10 weeks

	Triple therapy (n = 27)	Triple therapy plus VPS (n =39)	<i>p</i> -value
Lost to follow-up	0 (0.0%)	1 (2.3%)	0.399
Successful response	8 (29.6%)	22 (57.9%)	0.025
Complete response	3 (11.1%)	11 (28.9%)	
Partial response	5 (18.5%)	11 (28.9%)	
Failure	19 (70.4%)	16 (42.1%)	0.350
Stable response	15 (55.6%)	10 (26.3%)	
Disease progression	4 (14.8%)	4 (10.5%)	
Death	0 (0.0%)	2 (5.3%)	

VPS ventriculoperitoneal shunts.

Figures

Figure 1

Treatment outcomes according to induction therapy at the 10th week after the initial therapy. In triple therapy plus VPS group, one patient was lost to follow-up at the 10th week. Comparing triple therapy to triple therapy plus VPS, the respective patient complete response rates were 11.1% (3/27) and 28.9% (11/38); the partial response rates were 18.5% (5/27) and 28.9% (11/38); the stable response rates were 55.6% (15/27) and 26.3% (10/38); the disease progression rates were 14.8% (4/27) and 10.5% (4/38) and the all-cause death rates were 0.0% (0/27) and 5.3% (2/30). The treatment ‘successful response’ rate (including complete and partial responses) in triple therapy plus VPS group (57.9%) was significantly higher than that of triple therapy group ($P = 0.025$). The data are presented as *n* (%) and were analyzed via the Kruskal-Wallis test, whereas the total ‘successful response’ rate was analyzed by the chi-square test.

Figure 2

Time to shunting from diagnosis in 39 patients in triple therapy plus VPS group, and the med (range) is 4 (0-21) days.