#1439

rhei0005@umn.edu

The Effect of Therapeutic Lumbar Punctures on Acute Mortality from Cryptococcal Meningitis

Melissa A Rolfes[1], Joshua Rhein[1,2], Katherine Huppler Hullsiek[1], Henry Nabeta[2], Kabanda Taseera[3], Charlotte Schutz[4], Radha Rajasingham[2], Darlisha A Williams[2], David Meya[2], Conrad Muzoora[3], Graeme Meintjes[4] and David Boulware[1]

[1] University of Minnesota, Minneapolis, MN; [2] Infectious Disease Institute, Kampala, Uganda; [3] Mbarara University, Uganda; [4] University of Cape Town, South Africa

Abstract

Background: Individuals with cryptococcal meningitis (CM) typically have elevated intracranial pressure (ICP). Prior studies suggest an association between uncontrolled ICP and mortality, yet few studies of interventions have been conducted. We evaluated the effect of therapeutic lumbar punctures (LPs) on acute mortality after CM diagnosis.

Methods: 248 individuals in Uganda and South Africa diagnosed with CM and screened for entry into the Cryptococcal Optimal ART Timing (COAT) trial were included. All individuals received: diagnostic LP, two weeks of amphotericin B (0.7-1.0mg/kg/day) plus 800mg/day fluconazole, and therapeutic LPs as needed. Observation began one day after CM diagnosis. Therapeutic LPs were any LP occurring after diagnostic LP. A marginal structural model, pooled Poisson regression with inverse-probability weights, was used to assess the effect of therapeutic LPs on 11-day mortality. Multiple imputation accounted for missing baseline parameters.

Results: 75 individuals (30%) had at least one therapeutic LP. Those who received therapeutic LPs were more likely to have lower heart rates and mental status, and higher ICP and fungal burden at baseline. Death occurred among 5 of 75 (7%) with a therapeutic LP and among 31 of 173 (18%) without a therapeutic LP. Mortality was associated with greater age, heart rate, and respiratory rate; but not fungal burden or raised ICP. With adjustment for heart rate, mental status, and fungal burden, the relative risk of mortality was 0.31 (0.12, 0.82) in those with compared to without therapeutic LP. This effect did not differ by baseline ICP.

Conclusion: Current CM treatment guidelines support therapeutic LPs to reduce ICP. This analysis suggests a possible survival benefit (69% reduction in mortality risk) to undergoing at least one therapeutic LP, regardless of baseline ICP. Further investigation is warranted to evaluate the benefits of therapeutic LPs and optimal ICP control in larger groups of patients.

Study Population

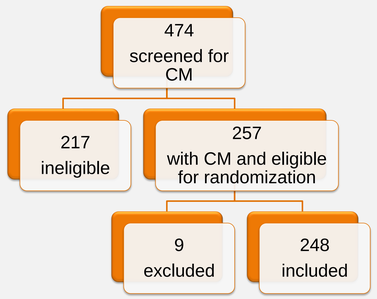


Figure 1: Analysis Cohort:

- 474 individuals screened for CM in Kampala & Mbarara, UG & Cape Town, SA.
  - Screened for enrollment into Cryptococcal Optimal ART Timing (COAT) trial & a subsequent observational cohort.
- 257 had HIV and CM and were eligible.
  - ≥ 18 years old, ART naïve, no prior CM, not on immunosuppressive therapy
- 9 subjects excluded - died or had therapeutic LP same day CM was diagnosed.
- 204 subjects from COAT and 44 from observational cohort were included in analysis.

Methods

- Observation began one day after CM diagnosis and extended to death, COAT randomization, or 11 days of observation.
  - COAT randomization occurred 7-11 days after starting CM therapy.
- All subjects had diagnostic LP for CM diagnosis.
- Therapeutic LPs defined as any LP occurring after diagnostic LP during observation.. These occurred by physician discretion until COAT randomization.
- Discrete-time hazard model, using Poisson distribution, compared mortality risk between therapeutic LP groups. Exposure to LPs was modeled as time-varying.
- Confounding adjusted for using inverse probability weights, using stabilized exposure and censoring weights.

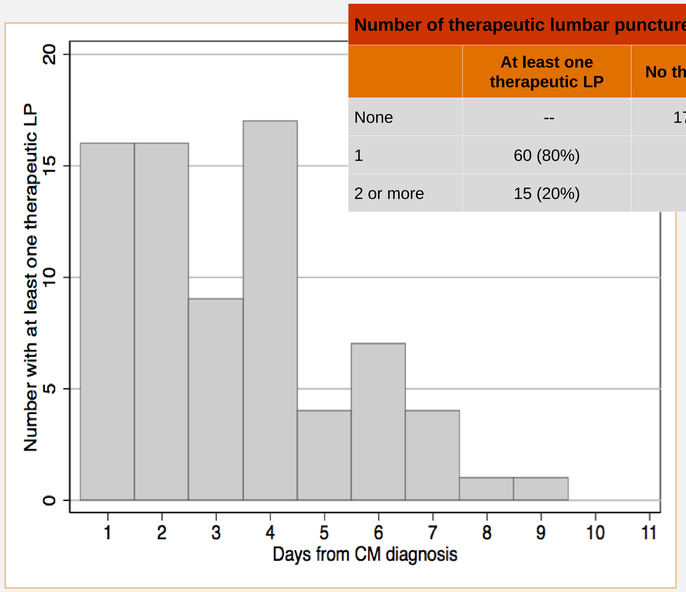
Subject Characteristics

	At least one therapeutic LP	No therapeutic LP	P-value
N per group	75 (30%)	173 (70%)	
Site			0.020
Kampala	61 (34%)	120 (66%)	
Mbarara	4 (11%)	34 (89%)	
Cape Town	10 (35%)	19 (65%)	
Clinical and Demographic Characteristics			
Age (years)	34 [29, 40]	37 [30, 42]	0.148
Males, N (%)	44 (59%)	91 (53%)	0.379
Weight (kg)	57 [46, 62]	52 [45, 57]	0.077
Papilledema, N (%)	0 (0%)	8 (5%)	0.058
Glasgow Coma Scale < 15, N (%)	26 (35%)	45 (26%)	0.148
Heart rate (beats per minute)	76 [66, 90]	81 [72, 97]	0.010
Clinical Laboratory Values			
Hemoglobin (g/dL)	11.5 [9.4, 13.0]	11.0 [8.9, 13.0]	0.412
White blood cells (x10^3 cells/μL)	3.7 [2.6, 5.3]	3.4 [2.5, 5.1]	0.407
Creatinine (mg/dL)	0.6 [0.5, 0.8]	0.7 [0.6, 0.9]	0.033
CSF Parameters			
Opening pressure (mmH_2O)	346 [220, 440]	248 [150, 338]	<0.001
Opening pressure ≥250 mmH_2O, N (%)	48 (70%)	69 (50%)	0.007
Closing pressure (mmH_2O)	100 [80, 137]	90 [60, 120]	0.040
Quant. cryptococcal culture (log_{10} CFU/mL)	5.3 [4.4, 5.6]	5.0 [3.9, 5.5]	0.028
White blood cells < 5 cells/μL	34 (46%)	66 (42%)	0.551

Table 1. Baseline Characteristics By Exposure Status. Medians (IQR) and N(%).

- 30% (75 individuals) had at least one therapeutic LP during first week of CM therapy.
- Subjects getting LPs had lower heart rate, lower creatinine, higher CSF opening pressure, and higher CSF fungal fungal burden.
- All other clinical and demographic parameters were similar between the two groups.

Lumbar Puncture Distribution

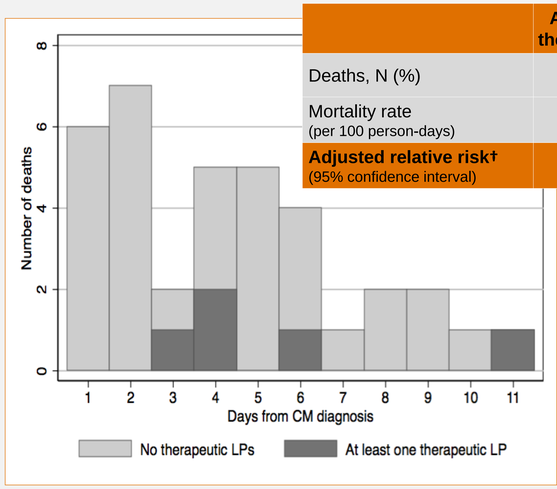


Number of therapeutic lumbar punctures, *N (%)*	At least one therapeutic LP	No therapeutic LP
None	--	173 (100%)
1	60 (80%)	--
2 or more	15 (20%)	--

Figure 2. Lumbar Puncture Timing and Distribution. Days from diagnosis of cryptococcal meningitis to the first therapeutic LP.

- Median time from diagnosis to first therapeutic LP was 3 days.
- Majority of subjects (80%) who had at least one therapeutic LP underwent only one LP during follow-up (table inlay).

Mortality by Therapeutic LP



	At least one therapeutic LP	No therapeutic LP
Deaths, N (%)	5 (7%)	31 (18%)
Mortality rate (per 100 person-days)	1.3	2.4
Adjusted relative risk† (95% confidence interval)	**0.31 (0.12, 0.82)**	

†Adjusted for heart rate, GCS <15, CFU quantitative culture

Figure 3. Distribution of days from diagnosis to death among those with and without at least one therapeutic LP

- Within 11 days of CM diagnosis,13% of the cohort had died.
- The adjusted relative risk of indicated that receiving ≥ 1 therapeutic LP was associated with a 69% reduction in the risk of death.

	At least one therapeutic LP	No therapeutic LPs	Overall
Baseline CSF Opening Pressure < 250 mmH_2O			
Number of individuals, (% of overall)	21 (23%)	70 (77%)	91 (44%)
Deaths, N(%)	0 (0%)	11 (16%)	11 (12%)
Mortality rate (per 100 person-days)	0.00	1.99	1.69
Unadjusted relative risk (95% CI)	**0.00 [0.00, 2.25]**		
Baseline CSF Opening Pressure ≥ 250 mmH_2O			
Number of individuals, (% of overall)	48 (41%)	69 (59%)	117 (56%)
Deaths, N(%)	4 (8%)	12 (17%)	16 (14%)
Mortality rate (per 100 person-days)	1.54	2.38	2.09
Unadjusted relative risk (95% CI)	**0.65 [0.15, 2.14]**		
Baseline CSF Opening Pressure Not Measured			
Number of individuals, (% of overall)	6 (15%)	34 (85%)	40
Deaths, N(%)	1 (17%)	8 (24%)	9 (23%)
Mortality rate (per 100 person-days)	3.57	3.16	3.20
Unadjusted relative risk (95% CI)	**1.13 [0.03, 8.42]**		

Table 2. Association of therapeutic lumbar puncture and acute mortality by baseline CSF opening pressure

- 56% of individuals had opening pressures ≥ 250 mmH_2O
  - Only 41% of this group received a therapeutic LP during observation.
- The mortality trend was similar among those with high pressure.
- Little evidence to suggest the effect of therapeutic LPs was differential by CSF pressure at the time of CM diagnosis.

Conclusions

- Relatively infrequent therapeutic LP within first week of CM therapy (30%).
  - More frequent when baseline OP ≥ 250 mm H_2O (41%).
- Patients undergoing ≥ 1 therapeutic LP had 69% reduced risk of mortality.
- CM patients may benefit from additional intervention to control ICP regardless of initial opening pressure.
- Future studies needed on effect of LPs in all CM patients.