Early Goal Directed Therapy for Adult Meningitis in Malawi

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Introduction

Mortality rates from bacterial meningitis in adults in Africa are 54-70%, compared to 20-30% in Europe. The cause of such high death rates remains unclear, but is likely to be multi factorial. Adjunctive interventions including dexamethasone and glycerol have been ineffective in large placebo-controlled trials in Malawi.

By combining evidence based clinical interventions into target driven treatment protocols, Early Goal Directed Therapy (EGDT) has been shown to improve outcomes from sepsis. EGDT has not been tested in sub-Saharan Africa for any condition, and has never been tested for bacterial meningitis. This study, ‘Bundles for Adult Meningitis’ (BAM) tested this concept for the management of bacterial meningitis in Malawi in a pilot feasibility study.

Trial registration: ISRCTN96218197.

Research questions

1. Is delivering EGDT for bacterial meningitis in the AETF feasible in Malawi?
2. Can this approach reduce mortality and neurological disability?

Inclusion criteria

Screening
- Age >14 years, fever >38 or <35° C plus at least one of: headache/ confusion/ convulsion or meningism
- CSF
- Culture or PCR positivity for any bacteria known to cause meningitis or CSF WCC >50 cells/mm³ (>50% neutrophils).

BAM Study design: Before/After

Control Phase 1
January 2012-October 12

Introduce bundle Phase 2a
November 12-December 12

Active Bundle Phase 2b
January 13-October 13

Analyse results

Design: Studies testing EGDT in a single site must use a before/after design. Parallel design randomising participants to evidence-based care or standard management in the same hospital is considered unethical.

Sample size: Estimated 200 participants across Phase 1 and Phase 2.

Primary endpoint: Proportion of individual and combined clinical targets achieved

Secondary endpoints: Composite death or disability (mRS ≥2) at day 10 and day 40.

BAM Goal Directed Therapy Targets Ph2

Triage

Recognition of potential study participant by BAM team

1 HOUR TARGETS

A - airway maintained GCS ≥8
B - O2 given if SpO2 < 94 %, seizures or respiratory distress
C - IV line started and fluid resuscitation started if signs of shock (pulse >100, MAP <70, SpO2 <90 CRT >3 seconds, core temp <35°C)
D - Seizure control if required with diazepam +/- phenobarbitone, Blood glucose corrected if <4mmol/L
E - Early antibiotics IV given within 1 hour of arrival, LP performed within 6 hours of presentation
F - Active bundle targets achieved: IV line sited and fluid resuscitation started if signs of shock

6 hour care bundle intervention

- Hourly observations, on going EGDT and medical review
- Referral to ICU if required

Discharged to ICU/HCU/Medical ward after 6 hours

Results

628 patients were screened, 132 were included. 51% were female, 73% were HIV co-infected. S.pneumoniae was the commonest cause of ABM (41%), N.meningitidis was rare (3%). Meningitis patients were equally matched between the study phases, using the MAMS scoring tool (abstract # 46242). The 48 hour Case Fatality Rate in excluded patients was 7.6% in Phase 1, and 8% in Phase 2; p=0.55.

Figure 1: Participant recruitment Phase 1 & Phase 2

Figure 2: Comparison of the proportions of clinical targets set and achieved by routine care in Phase 1 compared to EGDT in Phase 2

Figure 3: Kaplan-Meir curve comparing composite outcome between standard care and EGDT

Conclusions

1. EGDT, modified for resource-limited settings, is feasible.
2. Clinical endpoint data examining whether the bundle affected outcome was inconclusive.
3. Further modification of the bundle based on a better understanding of the pathophysiological basis of the poor outcome of ABM in Africa is required.
4. Assessment of a modified bundle will require a large multicentre cluster randomised trial

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