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A double blind, randomised controlled trial of glycerol adjuvant therapy in adult bacterial meningitis in a high HIV seroprevalence setting in Malawi

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Summary

Background—Southern Africa has a high incidence of bacterial meningitis in adults, often associated with HIV co-infection. Even with appropriate antibiotic therapy, mortality exceeds 50% and is not improved with corticosteroids. Glycerol adjuvant therapy reduced mortality and long-term morbidity (deafness) in bacterial meningitis in children and is being promoted. If similarly effective in adults, glycerol would provide a cheap, available adjuvant therapy in Africa.

Methods—Following a dose-finding study, we conducted a randomised double-blind placebo-controlled trial of oral glycerol in adults with bacterial meningitis. Patients with clinical and CSF findings suggestive of bacterial meningitis were randomised either to glycerol or an equivalent volume of sugar solution. The primary outcome was mortality at 40 days with secondary outcomes including disability and mortality restricted to pneumococcal disease.

Findings—75ml glycerol QDS was best tolerated and was used for the main study. 265 patients were randomised to receive glycerol or placebo. The trial was stopped early on the advice of the Data and Safety Monitoring Board (DSMB) following a planned interim analysis. Mortality by day 40 was 61/125 (49%) in the placebo and 86/136 (69%) in the glycerol arms, Adjusted Odds Ratio 2.4 (95% CI 1.3–4.2 p=0.003). There was no benefit from glycerol for death and disability by

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day 40 by intention to treat or in predefined subgroups. Two serious adverse events occurred possibly due to study drug.

Interpretation—Oral glycerol therapy did not improve mortality in adults with bacterial meningitis and cannot be recommended as a suitable adjuvant therapy in resource-poor settings with a high HIV prevalence.

Introduction

Meningitis is a common cause of adult inpatient death in Malawi. The incidence of bacterial meningitis has risen markedly in Malawi, as it has in other southern African countries since the start of the HIV epidemic.¹ Even with effective antibiotics, in-patient case-fatality exceeds 50% and up to half of survivors are left with neurological sequelae and disability.^{2,3} Measures to reduce mortality are urgently needed.¹

Corticosteroids, which are an effective adjunctive treatment in low-HIV prevalence settings,⁴ are not effective where most meningitis is HIV-related, including Malawi.^{2,5} As raised intracranial pressure (ICP) is thought to be a significant contributory factor to mortality and morbidity from all forms of meningitis, early reduction of ICP might theoretically improve outcome. Glycerol, an orally administered hyperosmolar liquid widely used as a food additive, has been suggested as a potentially promising adjuvant treatment. In bacterial meningitis in children, glycerol reduces neurological sequelae but not case fatality rate when given either alone or in combination with dexamethasone.^{6,7} Glycerol has previously been used in stroke, head injury and glaucoma to reduce elevated tissue pressure.⁸⁻¹⁶ A meta-analysis of intravenous glycerol in ischaemic stroke suggested short-term advantage but no benefit in terms of long-term survival.¹⁷

No trials of glycerol adjuvant therapy in bacterial meningitis have been reported in adults. If the paediatric findings were replicated in adults, glycerol would represent a significant advance in the treatment of bacterial meningitis, particularly in resource-poor high HIV-prevalence settings such as southern Africa where the burden of disease is high and adjuvant steroid therapy has no clinical advantage.

Glycerol has been used as a food additive and for cosmetic purposes for many years. Toxicity data for oral glycerol indicate that it is safe. Side effects are infrequent, usually mild and are mostly gastrointestinal in origin.^{18,19} There are rare reports of neurological side effects such as headache, dizziness, confusion and amnesia (in elderly patients) and one report of spontaneously reversible hemiparesis in a patient who ingested 500ml pure glycerol as a single dose.²⁰ Glycerol is stable in hot climates, widely available and inexpensive. It would therefore be ideal for use in resource-poor settings.

This study set out to test whether glycerol is an effective and safe adjuvant treatment for adults with bacterial meningitis in a setting with high HIV seroprevalence and high mortality from meningitis.

Methods

Setting

Queen Elizabeth Central Hospital (QECH) is a large hospital serving a catchment population in excess of 1 million in Blantyre, Malawi. HIV prevalence in adults aged 15 to 49 at the time of the trial in Malawi was 12% [UNAIDS 2008]. Admissions to QECH exceed 10,000 per annum and 70% are infected with HIV.²¹ Meningitis is one of the commonest causes of admission, with *Streptococcus pneumoniae* the most common form of bacterial meningitis.¹ Mortality from bacterial meningitis exceeds 50%, and adjunctive steroid therapy in adults does not reduce mortality, so it is not routinely used.² There were no facilities for invasive monitoring of patients.

Trial inclusion and exclusion criteria

Adult patients admitted to hospital with signs and symptoms of meningitis were screened by clinicians on the wards. All patients underwent a lumbar puncture and received intravenous ceftriaxone. Patients were then referred to the trial staff for assessment of eligibility. Trial inclusion criteria were clinical suspicion of meningitis (headache, neck pain or stiffness, reduced level of consciousness, photophobia, confusion, fits, rash or fever) plus cerebrospinal fluid (CSF) evidence of bacterial meningitis (>100 white cells/ μ l with predominant neutrophils or Gram-stain showing bacteria) or cloudy CSF if microscopy was delayed (e.g. at night). Exclusion criteria were age less than 16 years, cryptococcal meningitis (India ink stain or cryptococcal antigen positive on CSF), <100 white cells/ μ l or lymphocytic meningitis, pregnancy, heart failure and known type 2 diabetes. A capillary whole blood glucose (BM glucose)>12mmol/L was added as an exclusion criterion for phase 2 of the study on the advice of the DSMB.

Sample size calculation and randomisation

The calculated sample size for the trial required 216 patients per arm to detect a reduction in mortality from 56% (previous mortality in observational studies) to 40% with an $\alpha=0.05$ and $\beta=0.9$. A relative reduction in mortality of less than 30% was considered unlikely to lead to a major change in hospital practice by most clinicians in Malawi or other resource-poor African settings.

Randomisation and masking

The randomisation number list was produced by an independent statistician using Stata (STACORP) version 9.0 in blocks of 12, numbers and allocation being placed into a sealed envelope. These were opened sequentially by an independent person not involved in the clinical care or assessment of trial participants who labelled pre-prepared containers of glycerol and placebo with the unique Study number. Study drug packs were then placed in consecutive order within a secure room. If a patient fulfilled the study criteria, verbal and written informed consent was obtained from the patient or, if the patient was unconscious or confused, from the legal guardian. Those unable to read gave witnessed consent. Allocation of the next available study number constituted entering the trial and intention-to-treat analysis was based on study allocation irrespective of subsequent treatment. All envelopes

were accounted for. Clinicians and patients were blind to study allocation. Treatment with glycerol or placebo was administered by trial staff.

Dose-ranging study

The study was conducted in two distinct phases. The first was an open label study to assess the ease of administration of glycerol and the tolerability of a range of doses by patients in order to define the optimum dose of glycerol to be used in the subsequent double blind randomised controlled trial. Forty five adult patients with symptoms, signs and CSF findings compatible with bacterial meningitis who fulfilled inclusion and exclusion criteria were recruited. Following consent, fifteen patients each received 50ml, 75ml or 100ml glycerol four times a day for four days. Paediatric studies used 6ml/kg/day⁷: this corresponded to 300-360ml glycerol daily for the average Malawian weighing between 50-60kg. Glycerol was diluted with water at a ratio of 5:4 so that the consistency was indistinguishable from that of 50% sugar solution (the proposed placebo for Phase 2). Patients therefore received diluted glycerol 90ml, 135ml or 180ml QDS. Clinical details of all cases, including possible or probable adverse events due to glycerol administration, were recorded.

Clinical treatment and follow-up

All patients with probable meningitis were treated with intravenous ceftriaxone 2G twice daily for at least 10 days or until treatment was changed according to results of culture and sensitivity testing. If cryptococcal infection was diagnosed after recruitment to the study, patients were treated with oral fluconazole (following national guidelines) and the study drug was discontinued. Those not enrolled to the study received standard care following national guidelines.

Glycerol/placebo was given immediately after enrolment orally or via naso-gastric tube at a dose of 135ml (75mg glycerol mixed with water or 135ml 50% sugar solution) four times a day for four days (16 doses). This was the optimum tolerated dose in the dose-ranging study. The dose was repeated after antiemetics if vomiting occurred within 30 minutes of administration. A naso-gastric tube (NG tube) was inserted in those with a Glasgow coma score of less than 8/15, or unable to swallow for any other reason. Position of the tube was checked daily by auscultating over the epigastrium while injecting air via the naso-gastric tube and by ensuring NG tube aspirate was acidic (turned blue litmus paper pink).

After 48 hours or at least 8 doses of glycerol therapy, a second lumbar puncture was performed. After 10 days of antibiotic therapy a full neurological examination including hearing assessment was carried out. Hearing tests were performed using a Kamplex Diagnostic Audiometer AD12. All patients were treated in hospital for at least 10 days with daily clinical assessment. Patients alive at discharge were requested to return at day 40 for review; those who failed to attend were traced at home. At day 40 patients underwent a full neurological examination including hearing assessment using audiometry, and a Glasgow Outcome Score was assigned as a measure of neurological disability.

All patients underwent testing for HIV. Consent with appropriate counselling was sought at recruitment to the study, or retrospectively after recovery for those initially unconscious or confused. Patients' guardians were aware that HIV testing would be carried out but they

were not informed of results. Relatives and guardians were encouraged to attend for voluntary HIV testing, regardless of the patient's results. Patients were counselled regarding their results before discharge from hospital. Those found to be HIV positive were commenced on cotrimoxazole prophylaxis and referred to the antiretroviral therapy clinic.

Laboratory investigations

CSF and blood for culture were analysed by the Malawi-Liverpool-Wellcome Trust (MLW) laboratory. CSF was processed using standard laboratory techniques for cell count, differential white cell count (when >20 cells/mm³ present) and Gram stain. CSF was cultured on sheep blood and chocolate agar for 48 hours and subcultured for identification as appropriate. Blood was cultured using the BacT alert system. Organisms were identified using conventional culture-based microbiological techniques. CSF cryptococcal antigen agglutination tests (Pastorex Crypto Plus Biorad) were performed by MLW on a subset of patients. Blood for malaria film, full blood count and biochemistry was analysed by the QECH laboratory. HIV serological testing was carried out in duplicate in every patient using Uni-Gold Recombigen® HIV Rapid test [Trinity Biotech plc, Ireland] and Determine® HIV-1/2 [Abbott]. BM glucose was measured using Glucostix® (Bayer Diagnostics) at least twice a day while taking study drug.

Endpoints and analysis

The primary endpoint was death by day 40. Secondary endpoints were death or disability by day 40 (Glasgow Outcome Score 1 or 2);²² death by day 10; hearing loss in those not dead or disabled by day 40; time to death; CSF opening pressure 2 days after treatment; and serious adverse events. A priori subgroup analyses included patients with proven or probable bacterial meningitis alone and proven pneumococcal meningitis.

Adverse events and serious adverse events (SAEs) were recorded. SAEs were classified as definitely, possibly or probably related to study drugs as defined by ICH Harmonised Tripartite Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1994).

Data were double entered into Access (Microsoft) and verified before being analysed with STATA 8.0 (Statacorp). The analytical plan was finalised prior to unblinding.

The primary analysis was conducted on an intention to treat basis. A per protocol analysis (restricted to those not withdrawn from glycerol/placebo for reasons other than death) was also planned for the mortality-defined end-points. Logistic regression was used to construct a model to estimate the primary and secondary outcomes (with the exception of hearing loss and CSF opening pressure at 2 days), and Odds Ratios calculated unadjusted, and adjusted for prespecified potential confounding factors. These were: HIV serostatus, antiretroviral use, prior AIDS defining illness (modified WHO grades 3 or 4),²³ age, sex, prior antibiotic use, Glasgow Coma Score on admission, fits prior to admission, duration of symptoms, pre-treatment with antibiotics and organism isolated from CSF or blood. The secondary analysis of time to death was analysed using Cox's Proportional Hazard Ratios, unstratified and stratified by the same potential confounding factors. Statistical significance for the primary outcome was defined as $p < 0.05$.

An unblinded interim analysis by the DSMB had been pre-specified after 100 deaths. Indicative criteria for stopping included:

- a. Recruitment to be halted if a treatment arm has evidence of harm exceeding conventional levels of chance alone ($p < 0.01$)
- b. Recruitment to be halted if clear evidence of benefit with significance level of $p < 0.001$.

Ethical approval was granted by the College of Medicine Research Committee, Malawi and the Liverpool School of Tropical Medicine, UK. The trial was pre-registered on www.controlled-trials.com ISRCTN 70121840

Results

Dose finding study

The dose-finding study ran from March to July 2006. 45 patients were randomised to one of three doses of glycerol (Table 1). Approximately 50 % of patients in each group experienced nausea, vomiting or diarrhoea. Vomiting did not occur in any patient receiving glycerol via NG tube. There was no clear relationship between the dose of glycerol and frequency of side effects. Transiently elevated blood glucose >12.2 mmol/L was observed in 14 (31%) patients post study drug. Peak hyperglycaemia ranged from 12.2-20.4mmol/L in all. One patient had a single reading of 40mmol/L at recruitment but died prior to receiving study drug. No patients needed treatment with insulin. Five patients had hyperglycaemia (12.2-20.4mmol/L) after glycerol had been discontinued suggesting type 2 diabetes or a stress response was the cause. Patients randomised to the largest volume found it difficult to swallow. 8/15 patients in the 50ml arm, 7/15 in the 75ml arm and 10/15 in the 100ml arm died in hospital. Based on volume tolerability, the 75ml dose was used for the subsequent trial.

Randomised trial

The trial commenced September 2006 and recruitment was halted in August 2008. 380 patients were screened; 265 met the inclusion criteria and were randomised, 128 to placebo and 137 to glycerol (Figure 1). Baseline characteristics between the two arms were similar (Table 2). Follow up of survivors to day 40 was 98% and 99% in the placebo and glycerol arms respectively.

The study was stopped following the planned interim analysis after 100 deaths, with 7 months of the trial still to run and 61% of the pre-determined recruitment completed. The DSMB advised stopping recruitment on the primary grounds of futility. Patients already recruited into the trial were followed until the completion of follow-up or the primary endpoint was reached.

Overall, 61/125 (49%) in the placebo and 86/136 (69%) in the glycerol arms died by day 40 (Odds Ratio 1.8 (95%CI 1.1-3.0, p 0.02)). The OR adjusted for prespecified potential confounding factors was 2.4 (1.3-4.2, p 0.003). Glycerol did not improve death and disability by day 40, or death at day 40 in proven bacterial disease or pneumococcal disease (Table 3). Among survivors tested by audiometry, 14/41 in the placebo group and 4/31 in

the glycerol group were deaf at day 40 ($p=0.02$). Time to death is shown in Figure 2. The unadjusted Hazard Ratio for death was 1.7 (95%CI 1.2-2.4) and 2.0 (95%CI 1.4-2.9) in adjusted analysis with glycerol appearing to be detrimental.

The median opening pressure of CSF 2 days after randomisation was 15cm H₂O (IQR 9-21) in the placebo and 11.5cm H₂O (IQR 6-19) in the glycerol arm (Wilcoxon Rank Sum difference $p=0.08$). Median BM glucose on day 2 in both arms was 6mmol/L. (range 4-11mmol/L)

There were two serious adverse events considered possibly due to study drug in view of the rapid and unexpected deterioration in clinical condition. A 70 year old HIV positive female was admitted with one week's history of headache, fever and confusion and on admission had GCS 13/15. She was randomised to glycerol. Her level of consciousness improved but on Day 2 she developed seizures refractory to anticonvulsant therapy and she became hypertensive (170/90mmHg from a baseline of 120/80mmHg). *Salmonella typhimurium* was cultured from CSF. A second lumbar puncture was not performed and the study drug was discontinued on Day 3. She died on Day 12. The second case was a 35 year old HIV positive female with a one day history of illness and GCS 12/15 on admission who was randomised to placebo. She improved rapidly to GCS 15/15 by Day 2. *Streptococcus pneumoniae* was cultured from blood and CSF. Discharge was planned on Day 10 when she developed generalised weakness and vomiting without fever. She maintained a normal blood pressure and good urine output. On Day 11 her level of consciousness fell to GCS 6/15, although no focal neurological deficit was identified. She died on Day 13. The most likely diagnosis for both patients was a major cerebrovascular event secondary to meningitis. CT brain scan was not possible in either case owing to their rapid clinical deterioration.

Glycerol was well tolerated compared to placebo. There were 79/121 (65%) gastrointestinal adverse events (nausea, vomiting, diarrhoea) in the placebo arm and 85/129 (66%) in the glycerol arm. Seizure during the initial 10 days after randomisation occurred in 37/121 (31%) in the placebo arm and 64/129 (50%) in the glycerol arm ($p=0.002$); almost half of these occurred while taking study drug. No other symptoms or signs differed between the two arms after randomisation.

Discussion

Mortality from meningitis remains very high in this high HIV prevalence setting, and glycerol has been proposed as a simple, cheap and locally appropriate adjuvant treatment. Studies in children in Latin America and Finland suggest benefit.^{6,7} In our study in adults, which was stopped early by the DSMB, glycerol was associated with significantly increased mortality within 40 days, and worse outcomes in all major secondary analyses except deafness at day 40. This trial therefore does not support the use of glycerol as adjunctive treatment for bacterial meningitis in adults in Malawi.

These findings from the first adult study of glycerol are markedly different from studies in children. Oral glycerol has been found to reduce severe or profound hearing loss in children in a small study of infants and children in Finland⁶ and this was supported by findings in a

larger multi-centre paediatric study in Latin America.⁷ A small randomised double blind study in India by Sankar et al²⁵ comparing dexamethasone and oral glycerol adjuvant therapies in children with acute bacterial meningitis, did not find any significant difference in hearing loss and neurological sequelae between the groups.²⁶ Our findings suggest glycerol confers no benefit and appears harmful. However, there are two major differences in our study population; our patients were adults and 84% of them were HIV positive. In contrast, HIV serostatus was not reported in the paediatric studies although it is highly likely that the great majority were HIV negative. In addition, access to healthcare is often delayed in sub-Saharan Africa compared with other settings; most of our patients had symptoms for 5 days compared with over 85% presenting within 48 hours of the onset of symptoms in previous studies. Despite these population differences, it is still difficult to explain why glycerol appeared to be harmful. Hyperglycaemia – which adversely affects outcome compared with normoglycaemia following stroke, acute myocardial infarct, and pneumonia and in those acutely ill on intensive care²⁷⁻³¹ – is not a plausible explanation because hyperglycaemia, although carefully looked for, was rarely detected in either of the patient groups in our study. The placebo group received sugar solution for blinding and it is possible that this was beneficial, although we did not find evidence of hypoglycaemia in any patient prior to administration of study drug.

The observation of an increased rate of convulsion in the glycerol arm is of concern. This may be a coincidental finding associated with the severely ill population in this study, or could be directly related to an effect of glycerol. This has not been previously documented in the literature. Rebound phenomena can occur with osmotherapy, particularly mannitol³² but evidence for its occurrence with glycerol therapy is mixed. Some studies do not show rebound elevation in intracranial pressure with either oral or intravenous glycerol (compared with mannitol),^{13,32,33} others demonstrate marked rises in ICP with continuous intravenous and intermittent oral administration.^{34,35} Rebound elevation of intracranial pressure is thought to be attributable to a reversal of the concentration gradient of the osmotic agent between blood and CSF (or brain interstitial fluid) as the drug is eliminated.³⁴ Although this generally is not thought to be clinically significant, its relevance is unclear in the context of bacterial meningitis.

There are potential limitations to this study. Although this hospital is better staffed and supported than many in a similar setting, general medical care is sub-optimal compared to that offered in developed countries. In addition, there was limited intensive or high dependency care available for such critically ill septic patients. Overall, this is a typical southern African hospital and patient population and it is highly likely therefore that the trial is representative in a sub-Saharan African high HIV prevalence setting. The results do not exclude the possibility that glycerol might be effective in a low-HIV prevalent setting where patients present earlier and where HIV infection is less common. Residual confounding is a theoretical possibility, but the finding is highly statistically significant, no subgroup analysis suggested benefit, and adjusting for identified confounding factors only strengthened the association, making residual confounding unlikely. The mortality difference seen at interim analysis by the DSMB strengthened with follow-up of enrolled patients and the adverse effect persisted after adjusting for confounding, thus supporting the decision to stop early.

In adults in Malawi or other resource-poor regions where bacterial meningitis presents late and often occurs in those who are HIV infected, glycerol cannot be recommended as adjunctive therapy. Other ways of reducing the considerable mortality associated with this disease need to be explored.

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Figure 1. Flow through the trial

Figure 2. Survival to day 40 by study drug

Table 1
Results of the dose-finding study

	50ml glycerol QDS (90ml diluted volume)	75ml glycerol QDS (135ml diluted volume)	100ml QDS (180ml diluted volume)
Died	10/15 (67%)	8 /15 (53%)	12/15 (80%)
Gastrointestinal side effects ¹	7 (47%)	8 (53%)	8 (53%)
Number with random capillary blood glucose >12.2mmol/L ²	5 (33%)	3 (20%)	6 (40%)
Number with proven bacterial meningitis	4 (27%)	6 (40%)	7 (47%)

¹ Nausea, vomiting, diarrhoea

² World Health organisation definition for diabetes²⁴

Table 2
Baseline characteristics in main trial

	Placebo	Glycerol
Number recruited	128	137
HIV seropositive¹ (%)	104/124 (84)	111/134 (83)
Prior AIDS defining illness Stage modified WHO 3 or 4 (%)	33/128(26)	36/137 (26)
Median age (IQR)	32 (27-38)	32 (27-40)
Female (%)	67/128 (52)	72/137 (53)
Initial Glasgow Coma Score <12 (%)	48/128 (37.5)	39/137 (29.3)
Median CSF white cell count (IQR)	400 (200-1040)	395 (200-1120)
Proven bacterial (%)	54/128 (42)	64/137 (47)
Pneumococcal disease (%)	52/128 (41)	46/137 (34)
CSF opening pressure (IQR)	28 (18-34)	21.5 (12.5-34)
Fits or history of fits in last 2 weeks (%)	51/128 (40)	49/137 (36)
Prior antibiotic use (%)	59/128 (46)	53/137 (39)
On antiretrovirals (%)	16/128 (13)	23/137 (17)
Median duration of symptoms (IQR)	6(3-8)	5(3-7)

¹ HIV status not known in 3 receiving placebo and 4 receiving glycerol

Table 3
Primary and secondary outcome data

	Placebo	Glycerol	Odds ratio (95%CI)	Adjusted Odds Ratio (95%CI) *
Died before day 40	61/125 (49%)	86/136 (63%)	1.8 (1.1-3.0) p0.02	2.4 (1.3-4.2) p0.003
Died before or disability day 40 †	75/124 (60%)	93/135 (69%)	1.4 (0.87-2.4) p0.2	1.7 (0.97-3.1) p0.07
Death at day 10	53/126 (42%)	80/136 (59%)	2.0 (1.2-3.2) p0.007	2.7 (1.5-4.8) 0.001
Per protocol analysis death to day 40	57/106 (54%)	77/118 (65%)	1.6 (0.9-2.8) p0.08	2.2 (1.2-4.1) p0.01
Death at day 40 restricted to proven bacterial disease	21/53 (40%)	43/63 (68%)	3.3 (1.5-7.0) p0.002	5.5 (1.9-15.4) p0.001
Death at day 40 restricted to pneumococcal disease	20/51 (39%)	31/45 (69%)	3.4 (1.5-8.0) p0.004	8.2 (2.4-28.5) p0.001

* Prespecified factors HIV, age, organism in blood or CSF, antiretrovirals, pre-treatment antibiotics, fits prior to admission, GCS, duration symptoms, sex, prior AIDS defining events.

† No Day 40 data for 2 patients