PHASE II TRIAL ON THE USE OF DEXTRAN OR STARCH FOR SUPPORTIVE THERAPY IN KENYAN CHILDREN WITH SEVERE MALARIA

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Registration

ISRCTN REGISTER, registration number 35536139,

URL <http://www.controlled-trials.com/isrctn/trial/0/35536139.html>

Trial Sponsor: Oxford University

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ABSTRACT

Objective: A previous meta-analysis has shown a consistent survival benefit in children with severe malaria receiving human albumin solution (HAS) compared to other resuscitation fluids. HAS is expensive and not readily available in Africa. We examined the safety and efficacy of the fluid resuscitation with two synthetic colloids, Dextran 70 and hydroxyethyl starch to inform future trial design.

Design: An open-label randomised controlled, phase II safety and efficacy trial.

Setting: High Dependency Unit, Kilifi District Hospital, Kenya.

Patients: Children aged >6 months with severe falciparum malaria and acidosis (base deficit >8 mmol)

Interventions: 20 - 40mls/kg boluses of 6% Dextran 70 and 6% hydroxyl-ethyl starch (HES 130/0.4)

Measurements: Primary endpoint: resolution of shock over 8 hours. Secondary endpoints include resolution of acidosis, in-hospital mortality, adverse events (allergic reactions, pulmonary oedema, neurological sequelae).

Results: A total of 79 children were enrolled: 39 received Dextran and 40 received HES. No significant difference was observed in Dextran and HES groups for shock resolution at 8 hours: 23/37 (62%) and 25/39 (64%) respectively ($p=0.99$). Acidosis resolution and respiratory distress was marginally superior in HES group: 3/39 (8%) remained acidotic at 8 hours versus 10/37 (27%) in Dextran arm ($p=0.05$). There were 4 deaths (5%), two per arm; including 3 deaths in the coma subgroup (3/39, 8%). No other new adverse event was reported.

Conclusions: Correction of shock by volume expansion with either Dextran or HES in children with severe malaria acidosis is safe with low mortality, including the highest risk cases admitted in coma. Both solutions present an attractive and practical option for consideration in future volume resuscitation trials in severe malaria.

INTRODUCTION

Malaria remains a major health burden in many countries across Africa. For children developing severe and complicated *Plasmodium falciparum* malaria case fatality on current treatment remains high [1]. Amongst the physiological derangements associated with severe, life-threatening malaria, metabolic acidosis has emerged as a central feature, being widely recognised as the best independent predictor of death in both children and adults [2-5]. The highest mortality occurs in children presenting in deep coma with metabolic acidosis [6, 7]. We have previously hypothesised that acidosis in severe malaria is due in part to impaired perfusion (or hypovolaemia) [3, 8-10]. We have generated, together with others, new clear evidence indicating that volume depletion contributes to the pathophysiology of severe malaria and that volume expansion, the usual treatment of hypovolaemia, is safe and may improve outcome [3, 10]. Nevertheless, there remains considerable debate over whether volume depletion contributes to the pathophysiology in children with severe malaria; with anxieties expressed that volume expansion may result in more harm than benefit [8, 11, 12]. Current World Health Organization guidelines are unclear regarding which fluid to give, the volume and rate of administration, and clinical assessment for the need for fluid [13, 14].

In a series of trials we have established that fluid resuscitation with 5% human albumin solution (HAS) results in a lower mortality than either 0.9% saline or Gelofusine® (a gelatin polymer) [3, 10, 15, 16]. The greatest benefit was seen in the high risk group with acidosis and coma [10]. Since HAS is costly, difficult to generate locally, and potentially unsustainable in Africa, we aimed to generate clinical data that extend our experience with colloidal based resuscitation fluids in a randomised controlled trial using two other less costly synthetic colloids, 6% Dextran 70 (Dextran) and 6% hydroxyethyl starch (HES 130/0.4) (HES) in children with severe malaria. The aim was to collect data on the safety and efficacy of these two colloids for treatment of shock.

MATERIALS AND METHODS

Participants

The study was conducted at the high dependency unit (HDU) of Kilifi District Hospital, Kenya. Children > 6 months of age fulfilling our *clinical* definition of severe malaria [17], that is, either impaired consciousness (prostration or coma, Blantyre Coma Score (BCS) ≤ 2 [18]) or

respiratory distress (increased work of breathing) [7], were screened for inclusion in the study. Children were eligible for inclusion if they had all of the following criteria: *Plasmodium falciparum* parasitaemia, clinical features of severe malaria, and metabolic acidosis (a base deficit >8). Children with any of the following at admission were excluded: haemoglobin of <5 g/dl, pulmonary oedema (defined as clinical evidence of the presence of fine crepitations in both lungs plus oxygen saturations < 90%); any condition that may contraindicate the use of volume replacement, for example, established renal failure, known congenital heart disease, clinical evidence of severe malnutrition (severe wasting and/or kwashiorkor); and children with decompensated shock (systolic blood pressure <70mmHg for children less than 1 year old or <80mmHg if aged > 1 year). The participants in the trial were therefore comparable to study cohorts enrolled in our previous fluid resuscitation trials [3, 15, 19], with one exception [16]. Children were only recruited to the trial if prior consent was obtained from parents or guardians since ethical approval was not granted to defer consent in critically ill cases with decompensated shock.

Children eligible for the current trial were also eligible for an on-going multi-centre trial comparing intravenous Artesunate versus quinine (AQUAMAT; ISRCTN: 50258054) so were co-enrolled into both the current trial and AQUAMAT trial. Children whose parents refused consent were not enrolled into either trial. The trial, including co-enrolment, was approved by the Kenya Medical Research Institute (KEMRI) National ethics committee, Nairobi in December 2005 and Oxford Research Committee OXTREC. Prospective informed consent was obtained from all parents/guardians prior to enrolment. This trial was registered in September 2005 (ISRCTN: 35536139: URL <http://www.controlled-trials.com/isrctn/trial/0/35536139.html>).

Interventions

Children received an initial bolus of the intervention fluid; Dextran or HES of 20 ml/kg over 1 hour. At one hour after assessment a further bolus of 20mls/kg was given if features of shock persisted. Shock was defined as non-attainment of all the following resuscitation endpoints: heart rate within appropriate ranges for age, capillary refill time less than 3 seconds, systolic blood pressure within threshold range for age (using a pragmatic cut off of ≥ 70 mmHg for children less than 1 year old or ≥ 80 mmHg if aged > 1 year), and oxygen saturations > 95% in room air. Beyond 2 hours, further boluses were given only for the development of

decompensated shock (hypotension and any of the above clinical features of shock). Children were continuously monitored for blood pressure, electrocardiography, respiratory rate, oxygen saturation and core temperature using a Siemens® multi-channel recorder. Children received anti-malarial medication as specified in the AQUAMAT trial protocol. Otherwise all other aspects of treatment were identical between the two groups (reported previously [19]). Whole blood transfusion (20mls/kg) infused over the course of admission was reserved for cases whose haemoglobin fell below 4g/dl (or to < 5g/dl if associated with deep 'acidotic' breathing). Ventilation facilities are not available, but children with short term apnoea following convulsions were resuscitated with mask and bag manual ventilation.

Adverse events, serious adverse events and serious unexpected events were reported to the local safety monitor and national ethics board on a case by case basis. Annual summaries of events were prepared for the data safety and monitoring committee. The trial was monitored twice by independent clinical trial monitors. The trial continued until completion when 80 children had been recruited.

Objectives

To establish whether hypovolaemic shock manifesting as acidosis in severe malaria can be safely corrected by volume replacement with Dextran (Gentran® 70, Baxter Healthcare Pty Ltd, UK: batch numbers 0SJ14BM and 07G03BX) or HES (Voluven®, Fresenius Kabi Ltd, UK: batch numbers TIL196 00:31 and WDL18313:28). The other main objective was to assess the frequency of serious side effects, namely pulmonary oedema, suspected raised intracranial pressure and allergic reaction. The null hypothesis was that there is no difference in the safety profile or effect on physiological parameters of shock using starch or dextran-based colloids for fluid resuscitation.

Outcomes

Primary endpoint was the resolution of shock in either arm as determined by proportions attaining locally-adapted American College of Critical Care Medicine/Paediatric Advanced Life Support (ACCM/PALS) therapeutic (resuscitation) end points (here called resuscitation targets) at 8 hours [20, 21]. Attainment of resuscitation targets was defined as the absence of all of the following features: severe tachycardia (>180 beats/minute if aged <12months, > 160 beats/minute if aged 1-5years or >140 beats/minute if aged ≥ 5 years); hypoxia (oxygen

saturation <95%); hypotension: systolic blood pressure (SBP) (<70mmHg for <12 months and <80mmHg for > 1 year) or delayed capillary refill time (CRT) (≥3seconds).

Secondary endpoints included in-hospital mortality, resolution of acidosis (percentage reduction of base deficit by 8 hours), potential complications of volume resuscitation (pulmonary oedema, raised intracranial pressure (systolic blood pressure of >90th centile for age in association with a falling heart rate, or papilloedema, or brain stem features of transtentorial herniation [22])), allergic reaction, and neurological sequelae determined at discharge and one month following discharge by standardised neurological assessment.

Sample size

Our aim was to generate safety data regarding the use of these two colloids in children with severe malaria and therefore the numbers required to address the trial objectives were balanced against minimizing the exposure of children to a therapeutic intervention for which there is no available data for severe malaria. Formal sample sizes were therefore not calculated. We aimed to recruit 80 children: 40 to receive Dextran and 40 to receive HES which would give sufficient data on the frequency of serious adverse events and clinical data on correction of hypovolaemic shock. Our previous experience suggested that this number was sufficient to provide information on these key endpoints [3, 10, 15, 16]. Additional new data generated by the study included bolus volumes required of Dextran and HES to achieve satisfactory improvements in haemodynamic features of shock (primary endpoint). The trial had a similar design to previously published trials [3, 10, 15, 16] but differed since children with decompensated shock (low systolic blood pressure) were excluded in the current trial since ethical approval to defer consent for these cases, permitted in the previous studies, was declined. The ethics committee raised concerns over the safety of the Dextrans – which in a previous trial had resulted in acute febrile reactions [23].

Randomisation procedure

Fluid interventions were randomly assigned using cards in pre-sealed opaque envelopes indicating either Dextran or HES by the admitting clinician. A separate randomisation was used for AQUAMAT trial. The randomisation lists and envelopes for each trial were prepared separately and in advance of the each trial by an independent person not involved in

recruitment, and the lists were not available to the investigators. Randomisation cards were numbered consecutively and opened in numerical order. The intervention arms were not masked in both trials.

Statistical analysis

The analyses conducted were by intention to treat (ITT). Primary and secondary outcome measures were compared between intervention arms. The primary endpoint (achievement of resuscitation targets) and secondary endpoints (death and adverse events) were compared using chi-square tests or Fisher's exact tests as appropriate. Base deficit reduction was examined at 8 hours post-admission to determine the extent of resolution of acidosis.

We also compared the area under curve (AUC) and maximum value (MV) for repeated measures such as heart rate, base excess, systolic blood pressure and respiratory rate between the two interventions according to the method of summary measures proposed by Matthews et al [24, 25]. We used these two summary measures to avoid any potential biases from missing observations at any time point.

RESULTS

The trial ran from June 2006 to December 2008. In total 133 children were screened for trial eligibility and 101 were eligible, 16 (16%) refused consent, and 6 children were excluded for other reasons (see Trial flow: Figure 1). Eight emergencies did not qualify for the trial; seven were managed on 0.9% saline and mortality was (2/7, 28.5%), while one child died before 0.9% saline infusion could be started. Seventy nine children were enrolled; 39 to Dextran arm and 40 to with HES arm. The final envelope was inadvertently opened prematurely, since parental consent was withdrawn prior to enrolment. The median age of the trial participants was 40 months [inter-quartile range (IQR); (28-53)] with no statistically significant differences in the age or weight for the two intervention groups. Data from all the patients enrolled were analysed.

Baseline Variables

Admission baseline clinical and laboratory features of the trial participants are shown in Table 1. As an index of imbalance inherent within study groups in a small trial we compared *a priori* risk factors by treatment arm and found very few differences. The exception was hypoglycaemia, being slightly more common in children randomised to HES 12(30) compared to

5 (13) receiving Dextran ($P = 0.09$). At admission 39 (50%) of cases were complicated by deep coma, 52 (65%) had deep breathing (a clinical sign of metabolic acidosis), and 50 (63%) had one or more signs of impaired perfusion, with no differences between the allocation arms. A total of 20/79 (25%) children received blood transfusion per protocol after admission, 11 (28%) in the Dextran arm and 9 (23%) in the HES arm ($p=0.71$).

Co- Morbidity

None of the children had microbiological evidence of sepsis, meningitis or urinary tract infection with the exception of one child, enrolled to the HES arm. The child had *Streptococcus pneumoniae* bacteraemia and concurrent streptococcal meningitis. We found no evidence of neurological sequelae arising from this admission at discharge or at follow up.

Primary endpoints

No differences were found in the proportions attaining resuscitation targets between the two intervention arms at either 4 and 8 hours (Table 2). At the 4 hour review, 25/77 (32%) patients remained tachycardic but without other features of impaired perfusion, so further boluses were not prescribed. Eighteen children who had other features of impaired perfusion (capillary refill $> \text{or } = 3\text{s}$) at this time point received extra fluid boluses. Protocol was adhered to and volume expansion was adequate including amongst those children who subsequently died.

Secondary endpoints

There were 5/35 (14%) adverse events: 4 deaths (5%) and 1 (0.01%) neurological sequelae. Two deaths occurred in each arm of the study, 3 of the 4 fatalities occurred in the subgroup of children admitted in unrousable coma. The fourth case was a child admitted with marked agitation. Overall, mortality in the high risk group (coma and metabolic acidosis) was low 8% (3/39): 2/18 (11%) respectively in Dextran arm and 1/21 (5%) in HES arm.

The proportion of patients with persistent acidosis was significantly higher in the Dextran arm compared to the HES arm at both 4 and 8 hours (Table 2). Children randomised to Dextran received a higher volume of bolus intervention as compared to HES, although this was non-significant (Table 2). Fatal cases received higher volume of fluid expansion (mean 33ml; SD 7) as compared to those who survived (mean 24ml; SD 1) ($p=0.04$). There were no other serious adverse event reported. Specifically, we did not detect evidence of pulmonary oedema, raised intracranial pressure or allergic/febrile events in any of the participants. We found no evidence

of renal impairment, as measured by urinary output and serial plasma creatinine levels. Although coagulopathy or bleeding problems were not clinically apparent, we were not able to provide laboratory evidence to support this observation. At discharge and monthly follow up all trial participants were reviewed including a detailed neurological assessment. There were no deaths between the time of discharge and one month follow-up. One child randomised to Dextran had worsening of pre-existing epilepsy at discharge and subsequent review.

Serial measurements

There was a decrease in the mean heart rate with time in both study arms with the greatest decline in the first 8-10 hours and steadier decline thereafter (Figure 2). Similarly, the mean respiratory rate decreased with time in both arms (Figure 3); however, we noted the Dextran arm had relatively higher mean respiratory rate post recruitment than the HES arm. There was some evidence, albeit weak, of a difference in the AUC and MV of the serial respiratory rates between the two intervention arms, Wilcoxon Rank Sum, $p=0.07$ and $p=0.06$, respectively (Table 2).

DISCUSSION

This trial extends our experience with colloidal resuscitation fluids in children with severe malaria. Both HES and Dextran appear to be safe in children with severe malaria complicated by acidosis, with minimal adverse events and a favourable outcome. Resolution of clinical features of shock was similar for both intervention arms. Mortality was low (5%) including children in the high risk group (coma and acidosis: 8%) with no de novo neurological complications following recovery. We noted some evidence of a better resolution of acidosis and a better resolution of respiratory distress in children receiving HES compared to Dextran but in the absence of any other superiority on outcome this finding is of uncertain significance. This is the first trial to have generated safety and efficacy of these two fluids for treating children with severe malaria complicated by metabolic acidosis. As this is part of a series of studies involving fluid resuscitation directed at correcting shock the results should be reviewed contextually with other trials involving patients randomised to colloids. In severe malaria we have previously shown although HAS and Gelofusine® (a gelatin) resulted in similar resolution of shock and acidosis, we demonstrated a superior survival benefit of children resuscitated using HAS when

analysed by intention to treat (ITT) [15]. Previous trials comparing HAS to 0.9% saline also had similar findings in the ITT analysis [3, 10, 16].

The low mortality (5%) observed in the current trial, should be cautiously interpreted and may not be strictly comparable with overall mortality in our previous trials ($\approx 10\%$), although comparable to mortality in the HAS treated groups (4%). No inference can be directly drawn over the superiority of either HES or Dextran over either saline or Gelofusine since the current trial excluded children with hypotension, included in the previous trials where consent was deferred in such children. We suggest that the cohort eligible for the current trial may have a lower *a priori* mortality. Nevertheless, the 92% intact survival of the high risk group (coma and acidosis) and the minimal neurological events (worsening of pre-existing epilepsy in one patient) is reassuring and indicate that these colloids remain an attractive option for future clinical investigation.

We have not presented data on the effect of co-enrolment into the AQUAMAT trial. The AQUAMAT trial is large, on-going multi-country trial comparing two anti-malarial drugs quinine and artesunate in over 5000 children with severe malaria. Owing to the different modes of action there is no *a priori* evidence which might suggest an interaction with these study interventions with Dextran or HES nor any rationale to indicate the existence of one.

In dengue shock syndrome, children receiving HES were found to have less requirement for a rescue colloid and faster cardiovascular recovery when compared to those randomised to Dextran during the initial stages of shock [23]. These findings are also supported by a study in adults with severe sepsis [26]. The dengue trial reported some allergic or febrile reactions in children receiving Dextran but no episodes of bleeding or laboratory evidence of worsening coagulopathy were reported in any of three arms. These findings are reassuring, especially for a condition where coagulopathy manifests in the pathophysiology, with respect to the long standing fears about the increased risk of coagulopathy in patients receiving colloids. We did not find overt bleeding problems; however, we were not able to measure micro-coagulation abnormalities but the findings in dengue suggest that this may be unlikely.

We observed a faster resolution of the metabolic acidosis and respiratory distress in children receiving HES compared to Dextran. Simultaneous improvements of respiratory distress (a clinical marker of metabolic acidosis [6, 7]) and laboratory measures of acidosis (base deficit) in HES suggest that this is unlikely to be a chance finding. Neither could the findings be explained by any differences in baseline characteristics at admission which were

similar in the two arms but we cautiously interpret these findings due the small size sample and the lack of benefit on overall outcome. The VISEP trial comparing a medium molecular weight starch (HES 200/0.5), 10% pentastarch, and modified Ringer's lactate in adults with sepsis reported an earlier normalisation of central venous pressure/oxygen concentration in the pentastarch group. Nevertheless outcome in the pentastarch group was worse due to a higher number of dose-related episodes of renal failure (doubling of creatinine levels), requirement for renal replacement therapy and poorer survival over a 90 day follow up duration [27]. Whilst concerns for safety of starches is not new [28], recent evidence suggests that newer generation of medium molecular weight starches such as HES 130/0.4 do not increase the incidence of acute renal failure [29-31]. The higher concentration (10%) starches have a higher water-binding capacity and hence reduced renal flow [32]. In addition, the higher molecular weight pentastarch, but not the medium molecular weight starches, are incompletely metabolised and thus stored in the kidney, the mechanism thought to be responsible for acute renal damage [32, 33]. A meta-analysis concluded that starches in larger doses result in an increased incidence of acute renal failure and late death [34]. Our data suggest no evidence of a renal impairment, over 24 hours of observation, as its use was associated with falling creatinine levels and good urine output. However, the volumes prescribed in the current trial were modest and less liable to result in detrimental effects on renal function. Our experience has shown that hypovolaemic shock in severe malaria is generally fluid responsive, an observation supported by recent studies examining cardiac function in children undergoing fluid resuscitation [35]. Nevertheless, further exploration of HES in future clinical trial should consider including longer term monitoring of renal function and survival.

CONCLUSIONS

Fluid resuscitation in children with severe malaria using HES or Dextran appears safe and results in similar resolution of clinical features of shock. An ongoing multicentre trial comparing HAS to saline in African children with shock secondary to severe malaria and/or severe sepsis (FEAST ISRCTN; 69856593) may lead to major policy changes. If the results concluded that HAS was superior, then the results of this study support further exploration of either colloid in future trials.

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DECLARATION OF COMMERCIAL INTEREST: none declared

CONFLICTS OF INTEREST: none declared

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FIGURE LEGENDS

Figure 1: Trial flow

Figure 2: Graph showing mean heart rate and 95% confidence intervals over time

Figure 3: Graph showing mean respiratory rate and 95% confidence intervals over time

Figure 4: Graph showing mean urine output and 95% confidence intervals over time

Table 1: Baseline characteristics

	6% Dextran (N=39)	HES (N=40)	P-value
Clinical features n (%)			
Coma (BCS≤2)	18(46)	21(53)	0.57
Deep breathing	26(67)	26(65)	0.88
Severe tachycardia (>160 bpm)	16(41)	19(48)	0.56
Severe tachypnoea (>40 brpm)	25(64)	27(68)	0.75
Delayed capillary refill≥3	9(23)	5(13)	0.22
Core-toe temperature gradient	14(36)	13(33)	0.75
Weak Pulse volume	4(11)	5(13)	0.68
Hypotension (SBP <80mmHg)	2(5)	1(3)	0.54
Seizures	9(23)	10(25)	0.84
Prostration	19(50)	16(40)	0.52
Posturing	4(10)	9(23)	0.14
Weight for age Z-score<3	2(8)	0	0.22
Hypoglycaemia <3	5(13)	12(30)	0.09
Creatinine>80mmol/l	12(31)	15(38)	0.74
Potassium>5mmol/l	4(10)	5(13)	0.51
Mean laboratory variable [SE]			
Haemoglobin level, mg/dl	8.18[0.3]	8.79[0.3]	0.16
pH	7.27[0.02]	7.3[0.02]	0.25
pCO ₂ ,mmol/L	3.49[0.25]	3.6[0.26]	0.70
Base Deficit, mmol/L	12.32[1]	12.12[0.6]	0.86
Sodium level, mmol/l	132.7[1.2]	133.3[0.9]	0.68
Creatinine level, mmol/l	81.9[8.2]	84.4[5.5]	0.79
Parasitaemia ^{&} (×10 ³ parasites/μL)	4.4(1.4,12.9)	4.1(1.7,10.2)	0.92

IQR = Inter quartile Range, SBP = Systolic Blood Pressure, BCS = Blantyre coma score bpm = beats per minute, brpm = breaths per minute, SE=standard error [&] Geometric mean (95% Reference Range)

Table 2: Primary and secondary endpoints

Outcome	Category	Dextran	HES	p-value
Primary outcome	Time	n/N (%)	n/N (%)	
Attained resuscitation targets	1 hr	20/39(51)	20/40(50)	0.91
	4hrs	20/39(51)	23/38(61)	0.48
	8hrs	23/37(62)	25/39(64)	0.99
Secondary outcomes				
Persistence of acidosis	4hrs	11/39(28)	3/38(8)	0.05
	8 hrs	10/36(28)	3/39(8)	0.05
Fatality	Overall	2/39(5)	2/40(5)	1.00
	8hrs	1/39 (3)	2/40(5)	1.00
Creatinine levels <80, n/N (%)	1 hr	12/39 (31)	10/40 (25)	0.89
	4 hrs	3/39 (8)	1/38 (3)	0.52
	8 hrs	2/36 (6)	1/39 (3)	0.57
Bolus Volumes, mean [95% CI]	4hrs	26[23-28]	22[20-24]	0.06
Total volume, mean [95% CI]	24hrs	49[41-57]	50[42-58]	0.85
Summary measures				
AUC for heart rate (SD)		5574 (271)	5384 (250)	0.46
Mean max heart rate [95% CI]		165 [158-172]	168[162-174]	0.47
AUC for SBP (SD)		3945(181)	3885(179)	0.58
Mean max. SBP [95% CI]		116 [108-115]	113 [108-118]	0.61
AUC for respiratory rate (SD)		1749 (101)	1498 (78)	0.07
Mean max respiratory rate [95% CI]		62 [58-67]	56[52-61]	0.06

AUC=area under curve, SD=standard deviation, CI=confidence interval, SBP=systolic blood pressure

Figure 1

Figure 2

Figure 3

Figure 4