

Non-invasive Ventilation and levetiracetam for seizure prophylaxis In Children with Cerebral Malaria Trial (NOVICE-M): Phase I Trial

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Abstract

Background

African children hospitalised with cerebral malaria and seizures have poor outcomes. are at high risk of poor outcomes including death and neurobehavioural sequelae. Agonal events include hypoventilation and respiratory arrest post-seizures caused by 'spikes' of intracranial pressure. We hypothesised that a neuroprotective strategy of prophylactic levetiracetam (LVT) to prevent seizure and providing adequate ventilation through non-invasive biphasic Cuirass Ventilation (BCV) may improve outcome.

Methods

A Phase I trial with a sequential design examining in 3 blocks of 10 participants: i) respiratory support with BCV alone; ii) BCV plus prophylactic LVT: 40mg/kg loading dose then 30mg/kg every 12 hours and if dose-escalation warranted; iii) BCV prophylactic LVT 60mg/kg loading dose then 45mg/kg every 12 hours. LVT syrup was given via nasogastric tube for 72 hours (or until fully conscious). Children aged 3 months to 12-years hospitalised to Kilifi County Hospital, Kenya with falciparum malaria, a Blantyre Coma Score ≤ 2 and seizures in current illness were eligible for the trial. The primary outcome measure was detected cumulative time with seizures over 36 hours. Secondary outcomes include feasibility or ability to implement BCV and time spent on BCV, and recovery from coma within 36 hours. Safety endpoints included aspiration during admission; death to Day 20 and Day 180; and *de-novo* neurological impairments at 180 days.

Results

Between Jan 2020 and November 2023, 12 participants (5 and 7 in the first and second blocks) with a median age of 60 months (interquartile range (IQR) 31–78) were enrolled. 12 participants (5 in block 1; 7 in block 2), median age 60 months IQR(31–78), were enrolled. BCV was initiated and well-tolerated in 6/7 children. Block 1 was stopped prematurely after two deaths consistent with seizure-induced central apnoea. In block 1, 4(80%) children had seizures (median 90 seconds IQR(76–157) recorded by electroencephalography. In block 2 one child had a clinically observed seizures lasting 120 seconds. No drug-related respiratory depression or aspiration events were detected. The trial was stopped prematurely for feasibility.

Conclusions

BCV was feasible in this setting and LVT was well tolerated and safe and resulted in fewer witnessed seizures.

Registration:

ISRCTN76942974 (registered 5.02.2019); PACTR202112749708968 (registered 20.12.2021).

Introduction

Plasmodium falciparum malaria results in over half a million deaths each year, with African children accounting for 97% of global malaria mortality(1). Moreover, progress in malaria control has stalled(2), indicating that across malaria endemic Africa, severe malaria remains a common cause of paediatric hospital admission. Typically, the clinical presentation of severe malaria can be categorized into three non-exclusive presentations: severe anaemia (a haemoglobin less than 6 g/dl), deep breathing (a clinical manifestation/compensatory feature of metabolic acidosis) and neurological involvement (reduced level of consciousness with or without seizures). Whilst some degree of altered consciousness is common in severe malaria and has reasonable prognosis(3, 4), for the most severe form, known as cerebral malaria (defined as an unrousable coma persisting > 1 hour post-seizure), outcome is not optimal. Approximately 20% or more children affected by cerebral malaria die in hospital(3, 4), while others survive with long-term neurological impairments(5). Children dying with cerebral malaria often have clinical signs(6) compatible with trans-tentorial herniation and sonographic features of progressive intracranial hypertension(7). In addition, repeated generalised tonic-clonic seizures often precipitate an agonal event due to 'spikes' in intracranial pressure with the common terminal mode of death as respiratory arrest. Adjunctive therapies investigated to date(8) including trials of antiseizure medications(9, 10), osmotherapy(6) (11) (12) and steroids(13, 14), have failed to show any benefit and, in some children, have resulted in worse outcomes in the interventional group(15).

Since seizures are common in severe malaria, in particular, in the sub-group with cerebral malaria, and are associated with adverse outcomes including death and neurological sequelae (in children), routine administration of anti-seizure medications to prevent seizures may have potential benefits.

Seizure prophylaxis, with phenobarbitone, the most readily available antiseizure medication at the time, has been investigated in a placebo-controlled trial in 1995–1998(9). Children in the intervention arm received a single parenteral dose of phenobarbitone (20mg/kg) alongside of routine treatment which resulted in fewer multiple seizures than the placebo group (18 [11%] vs 46 [27%], odds ratio 0.32 [95% CI 0.18–0.58]), but mortality was more than double in the phenobarbitone group (30 [18%] compared to 14 [8%] placebo deaths; relative risk 2.39 [95% CI 1.28–4.64])(9). The main mode of death (in the phenobarbitone arm) was respiratory arrest, and the major risk factor was the receipt of 2 or more additional doses of diazepam for seizure control. Phosphenytoin for seizure prophylaxis was investigated in a double-blind controlled trial in children with non-traumatic coma, including 110 children with cerebral malaria, and showed no demonstrable effect in preventing seizures(10).

Newer formulations of anti-seizure medication, with limited respiratory depression side effects, have been developed including levetiracetam (LVT) which is increasingly the drug of choice in children with

status epilepticus(16). We proposed that prophylaxis with LVT would be safer and results in less clinical seizure events. In addition, since in resource-limited hospitals in Africa few children have access, or have been managed on mechanical ventilation, we proposed that providing LVT alongside non-invasive ventilation (NIV) as joint strategy may further improve neurological status in surviving children. The most suitable option for NIV is Biphasic Cuirass Ventilation (BCV) Heyek Medical since it applies both negative and positive pressure to the chest, covering both inspiration and expiration phases of breathing, which is more appropriate for periods of hypoventilation and apnoea (technical details covered in the Supplement).

We hypothesized that negative pressure ventilation (NPV) for preventing respiratory arrest in combination with prophylactic ASM may prevent or reduce intracranial hypertension by reducing cerebral vasodilation caused by increasing partial pressure carbon dioxide ($p\text{CO}_2$) in the blood, and is thus a promising combined strategy to avert deaths and neurological impairments from cerebral malaria.

Methods And Materials

Trial Design and participants

This Phase I trial proposed 3 intervention strategies given sequentially in blocks of 10 participants aimed at escalating the intervention and dosage of LVT (30 children in total). Children in the first block were to have respiratory support with BCV alone to test the feasibility, tolerability and safety of using NIV in cerebral malaria. The second and third block aimed to investigate BCV given alongside of LVT at two different dosages (details below). In both arms treatment of witnessed seizures followed a standard escalation protocol (see below). Eligible children aged 6 months to 12 years hospitalized with falciparum malaria (blood slide or rapid diagnostic test positive for *P. falciparum*) with a Blantyre Coma Score of ≤ 2 plus a history of seizures in this illness were enrolled. Children with cerebral palsy or significant neuro-development delay; respiratory or cardio-respiratory arrest prior to enrolment or a medical comorbidity (e.g. malignancy, end-stage renal failure, major cardiac condition), which the trial clinician believed had a significant risk of poor outcome were excluded. The trial protocol has been published(15) and the statistical analysis plan is available on the trial registry (ISRCTN76942974).

Screening and Treatment allocation

All children admitted with suspected malaria and impaired consciousness (Blantyre Coma Score (BCS) ≤ 2) were screened for study inclusion by the paediatric triage/admission team in a high dependancy ward in Kilifi County Hospital, Kenya. When prior written consent from parents or legal guardians could not be obtained, ethics committees approved verbal assent with delayed written informed consent as soon as practical(17). Otherwise, written informed consent was obtained from parents or guardians before randomisation.

The first ten participants were to receive respiratory support with BCV alone; if this was feasible, well tolerated and safe; the next ten participants were to receive a neuroprotective strategy of BCV plus oral LVT 40 mg/kg loading dose and 30mg/kg every 12 hours (via nasogastric tube) for up to 3 days or until coma resolution. If the neuroprotective strategy reduced seizures such that 80% of participants do not require additional anti-seizure medication, based on the judgement of an independent Data Monitoring Committee (DMC), then it was anticipated an additional 10 children were to be enrolled using LVT at this dosage. If the strategy failed to adequately control seizures, then anticipated a strategy of BCV plus a higher dose (150%) of LVT was to be studied, namely 60 mg/kg loading dose and 45mg/kg every 12 hours given via nasogastric tube for 3 days or until coma resolution. Levetiracetam Crescent 100mg/ml solution (Crescent Pharma Limited) was used for this trial.

Study Procedures

Admission blood was tested for haemoglobin, lactate, clinical chemistry, blood gases (including pCO₂ and base excess)(18), and blood cultures. Daily management and outcome data were collected on dedicated case report forms (including clinical parameters and recovery, developmental assessment, number of transfusions, use of BCV, and use of all drugs during admission (specifically anti-seizure medications, paracetamol and antibiotics). Children were clinically assessed at day 28, day 90 and day 180 post-enrolment. Study staff were unblinded throughout; laboratory tests were assayed blinded.

Clinical Management

Vital signs were obtained from bedside patient monitors (temperature, heart rate, respiratory rate, blood pressure, oxygen saturation; conscious level) and recorded on case reports forms. Children developing seizures warranting intervention were managed per the current treatment algorithm(19). The initial medication is a weight-adjusted dose of intravenous or intramuscular diazepam (0.15-0.2mg/kg) to treat a prolonged seizure (> 5 minutes); which can be repeated once if seizures persist. Failure to control the initial seizure (or further seizures after 2 doses of diazepam) is managed with intravenous loading of phenobarbitone (15mg/kg) (or phenytoin) as second-line followed by a maintenance dosage (10mg/kg/day) until the child is seizure free.

For the first block of participants, seizures were monitored with an electroencephalography (EEG), (EEG32U™ Natus Medical, Canada) subsequently, following a protocol amendment, this was monitored through clinical observation including length of witness seizure. Clinical stopping rules were in place if a child could not tolerate the device or developed a complication including aspiration (secondary safety endpoint). The risk of aspiration was reduced through training on correct placement of the nasogastric tube (part of standard of care for children with cerebral malaria). If a child developed hypercarbia (pCO₂>45mmHg) then AirVO₂ (donated by Fisher & Paykel) would be implemented, providing continuous high-flow of humidified air and oxygen mixture to flush out excess carbon dioxide.

The trial was registered on the ISRCTN registry protocol number ISRCTN76942974 on the 5th February 2019 and on the Pan African Clinical Trials PACTR number PACTR202112749708968 20th December 2021. The protocol and statistical analysis plan have been published/uploaded to ISRCTN(20)

End Points

The primary endpoint was cumulative time with clinically observed epileptogenic seizure activity over 36 hours. Secondary endpoints assessed included feasibility, ability to implement/operationalise the BCV and time on BCV. Safety endpoints (adverse events) included aspiration (defined as a sudden decrease in oxygen saturations, and/or *de novo* presence of coarse chest crepitations, with evidence of gastric reflux/aspirate in the oropharynx); episodes of hypercarbia ($p\text{CO}_2 > 45$ mmHg); use of additional antiseizure medications; episodes of bradypnoea (defined as < 10 , 15 or 20 breaths/minute over 3 minutes for those aged $< 6\text{m}$, $6\text{--}36\text{m}$ and $> 36\text{m}$ respectively) plus hypoxaemia (oxygen saturation $< 92\%$) in a child with unrousable coma ($\text{BCS} \leq 2$); development of hypotension (defined as systolic blood pressure < 50 mm Hg in children younger than 12 months; < 60 mm Hg in children $1\text{--}5$ years and < 70 mm Hg in children older than 5 years of age); mortality by day 28 and day 180; re-admission to hospital through day 180; neurological sequelae at day 180; serious adverse events through day 180 and grade 3/4 adverse events through day 180. *De-novo* evidence of neurodevelopmental sequelae was ascertained using a modified Kilifi Developmental Index(21) (which we have adapted to use from the COAST trial)(22). The study was independently monitored by a Data Monitoring Committee (DMC) who reviewed accumulating data on the safety endpoints. According to a derived Bayesian decision rule, enrolment would be stopped if the posterior probability of the number of clinically important adverse events being above the target threshold (20%) is higher than 0.95.

Statistical Analysis

Baseline characteristics were summarised separately for each block with frequencies, medians and interquartile ranges (IQRs). BCV use was described by timepoint and mode. Safety and primary and secondary outcomes were described with frequencies for each event, and cumulative time in seizures were calculated from EEG monitoring and clinical observations for the primary outcome. Proportion of time in seizures will also be presented to account for when death occurred prior to 36 hours.

Results

The trial commenced recruitment on 22nd January 2020, with the first participant enrolled on 3rd February 2020. However, due to the COVID-19 pandemic, study activities were suspended on 20th March 2020, after enrolment of 5 participants into the first block (BCV alone). Two participants in this first block died with the agonal event consistent with seizure-induced terminal central apnoea, that is not amenable to BCV support. Following review of the data, the recommended enrolling directly into the next block (BCV plus LVT) when the trial restarted on 3rd January 2022. Between October 2022 and November

2023, 7 children were enrolled into this second block. The study was stopped due to low recruitment, since most children screened for eligibility had a BCS > 2 (28/75) and/or were negative on a slide or RDT for *P. falciparum* (18/75) (Fig. 1).

Baseline characteristics for the two strategies are summarised in Table 1. Median age of the cohort was 60 months (IQR 31–78). The children enrolled were predominately male (92%) with 3/12 (25%) with a BCS of 1 and 8/12 (67%) with seizures lasting more than 30 minutes in this illness. Five children (42%) had received an antiseizure medication prior to admission. Although few children had severe lactic acidosis (> 5mmol/l) or hypoglycaemia (< 3mmols/l), low platelet counts (< 150 x 10³ /μL), a marker of severity in severe malaria(23) were present in all but 1 child.

Table 1
Baseline characteristics

Number enrolled	BCV only	BCV + LVT	Total
	5	7	12
Sex – male: n (%)	4 (80%)	7 (100%)	11 (92%)
Age at admission (months): median (IQR)	67 (35, 67)	52 (26, 81)	60 (31, 78)
Weight (kg): median (IQR)	12.9 (11.0, 18.0)	13.9 (10.1, 20.7)	13.7 (10.6, 19.9)
Heart rate (bpm): median (IQR)	158 (147, 167)	151 (122, 155)	153 (135, 162)
Axillary temperature (°C): median (IQR)	38.3 (37.5, 39.4)	37.8 (35.7, 38.0)	37.9 (35.9, 38.4)
Systolic blood pressure (mmHg): median (IQR)	102 (93, 103)	97 (91, 106)	99 (92, 105)
Diastolic blood pressure (mmHg): median (IQR)	66 (56, 74)	60 (53, 77)	63 (54, 76)
Oxygen saturation: median (IQR)	98 (92, 99)	98 (97, 99)	98 (95, 99)
Respiratory rate (breaths per minute): median (IQR)	46 (45, 66)	36 (35, 43)	42 (35, 54)
Capillary refill time (s): median (IQR)	2 (2, 2)	2 (2, 2)	2 (2, 2)
Blantyre Coma Score (BCS): n (%)			
1	2 (40%)	1 (14%)	3 (25%)
2	3 (60%)	6 (86%)	9 (75%)
Temperature gradient: n (%)	0 (0%)	4 (57%)	4 (33%)
Weak pulse: n (%)	0 (0%)	0 (0%)	0 (0%)
Seizures in this illness: n (%)	5 (100%)	7 (100%)	12 (100%)
Seizures lasting more than 30 minutes: n (%)			
Yes	2 (40%)	6 (86%)	8 (67%)
No	3 (60%)	1 (14%)	4 (33%)
Number of doses of IV or IM quinine/artesunate received before enrolment: median (IQR)	2 (2, 2)	1 (1, 2)	2 (1, 2)
Received an antiseizure medication prior to admission: n (%)			
Yes	1 (20%)	4 (57%)	5 (42%)
No	4 (80%)	3 (43%)	7 (58%)

Number enrolled	BCV only	BCV + LVT	Total
	5	7	12
Type of antiseizure medication: n (%)			
Phenobarbitone	0 (0%)	2 (50%)	2 (40%)
Diazepam	1 (100%)	2 (50%)	3 (60%)
Route of administration of phenobarbitone or diazepam: n (%)			
Oral	1 (100%)	0 (0%)	1 (20%)
IV	0 (0%)	4 (100%)	4 (80%)
Lactate (mmol/L): median (IQR)	1.5 (1.4, 1.9)	1.7 (1.2, 2.8)	1.7 (1.3, 2.5)
Lactate>5mmol/L: n (%)	1 (20%)	1 (14%)	2 (17%)
Glucose (mmol/L): median (IQR)	7.1 (6.7, 8.4)	6.0 (5.1, 8.1)	6.7 (5.6, 8.2)
Glucose correction given: n (%)	0 (0%)	0 (0%)	0 (0%)
Haemoglobin (mg/L): median (IQR)	5.6 (5.5, 6.5)	6.3 (4.7, 8.8)	6.1 (5.2, 8.4)
Haemoglobin<5mg/L: n (%)	1 (20%)	2 (29%)	3 (25%)
WBC ($\times 10^3$ / μ L): median (IQR)	8.1 (7.8, 15.1)	12.6 (4.9, 19.9)	10.3 (7.1, 17.5)
Platelets ($\times 10^3$ / μ L): median (IQR)	112 (111, 124)	50 (41, 75)	63 (45, 118)
Platelets > 150×10^3 / μ L: n (%)	0 (0%)	1 (14%)	1 (8%)
pH: median (IQR)	7.40 (7.39, 7.43)	7.34 (7.32, 7.57)	7.40 (7.33, 7.46)
Bicarbonate (mmol/L): median (IQR)	20.9 (11.9, 22.5)	19.6 (17.7, 21.1)	20.2 (14.8, 21.8)
pCO2 (kPa): median (IQR)	4.5 (4.4, 4.8)	4.5 (3.1, 5.1)	4.5 (3.8, 5.0)
Base deficit (b) (mmol/L): median (IQR)	-3.0 (-10.0, -2.3)	-2.8 (-6.0, 0.5)	-3 (-10, 0.5)
Base deficit (ecf) (mmol/L): median (IQR)	-3.7 (-12.4, -2.6)	-6.5 (-8.0, -0.9)	-5.1 (-10.2, -1.8)
Malaria RDT test: n (%)			

Number enrolled	BCV only	BCV + LVT	Total
	5	7	12
Positive	5 (100%)	5 (71%)	10 (83%)
Negative	0 (0%)	1 (14%)	1 (8%)
Not done	0 (0%)	1 (14%)	1 (8%)
Malaria blood film: n (%)			
Positive	5 (100%)	6 (86%)	11 (92%)
Negative	0 (0%)	1 (14%)	1 (8%)

Five children in the first block and two in the second were started on BCV (Table 2). BCV was administered for median 8 hrs (IQR 8–12 hrs) in the first block and median 0 hrs (IQR 0-0.5) in the second block. One child in the first block was unable to tolerate the BCV. BCV was not administered in the second block due to rapid recovery not necessitating BCV (n = 3) or to unstable power or a prolonged power cut (n = 1) and machine malfunction (n = 1). No child in any group was started on high-flow oxygen support. Delivery mode was in control for 5/7 children, and in triggered for 2 children with 1 started on synchronized prior to moving to triggered (**Supplementary Table S1**). All seven children in the second block received LVT with all receiving the loading dose correctly and 6/7 receiving a further 6 doses of 30mg/kg (Table 2). One child died prior to receiving additional doses.

Table 2
Treatment given

Number started BCV	BCV only (N = 5)	BCV + LVT (N = 7)	Total (N = 12)
	5 (100%)	2 (29%)	7 (58%)
Time on BCV (hours) - median (IQR)	8.0 (8.0, 12.0)	0.0 (0.0, 0.5)	0.8 (0.0, 8.0)
Non-adherence with BCV administration during treatment:			
Child unable to tolerate	1	0	1
Power cut**	0	2	2
Coma recovery prior to initiation		2	2
Childs ventilatory function not impaired		1	1
Malfunction of BCV machine#	0	1	1
Number given LVT	0	7	7
Number given LVT loading dose of 40mg/kg		7 (100%)	7 (100%)
Number of 30mg/kg LVT doses given in admission median (IQR)		6 (6, 6)	6 (6, 6)
*None of the children was started on high flow or low flow oxygen			
# BCV malfunction discovered after enrolment. Reported as a protocol deviation.			

Four of the five (80%) children in the first block had seizures median 90 seconds with seizure activity (IQR 76–157) recorded by EEG. In the second block only 1/7 (14%) child had clinical evidence of a seizure, which lasted 120 seconds (Table 3). Children in the first block received a median of 1 anti-seizure drug (IQR 1–2), in the second block, all received LVT and 2/7 received 1 other anti-seizure drug on the day of enrolment. Three children in the first block, and 6 in the second block were discharged alive (median 5 days in hospital (IQR 3–7) and 6 days (IQR 5–6) respectively). Three fatal adverse events were reported, all deaths occurred during the initial admission 2/5 (40%) in the first block and 1/7 (14%) in the second block (See **Supplemental Table S2**). There were no aspiration events. One child in the second block had a sudden decrease of oxygen saturation, but this was in a child not receiving BCV at the time. No hypercarbia, bradypnoea, hypotension nor hypoxaemia events were reported. (Table 4).

Table 3
Recorded Seizure activity

Child	Seconds in seizure	Proportion of recording time measured in seizures	Recording quality
1	157	0.96%	Good
2	7303	4.8%	Poor/fair
3	90	0.07%	Poor/fair
4	0	0%	Poor/fair
5	76	0.78%	Good
6	0	0%	Clinically observed
7	0	0%	Clinically observed
8	0	0%	Clinically observed
9	120	0.09%	Clinically observed
10	0	0%	Clinically observed
11	0	0%	Clinically observed
12	0	0%	Clinically observed
*Seizures were recorded by EEG machine for the first 5 children			

Table 4
Primary outcome and Safety analysis

Cumulative time with epileptogenic seizure activity: median (IQR) seconds	BCV only (N = 5)	BCV + LVT (N = 7)
	90 (76, 157)	120 (120, 120)
Proportion of time measured in seizures - median (IQR) hours	33.9 (20.1, 42.3)	36 (36, 36)
Number of anti-seizure medication drugs needed: median (IQR)	1 (1, 2)	0 (0, 0)
Length of initial hospitalization if discharged alive	5 (3, 7)	6 (5, 6)
Total serious adverse events	2	1
Fatal events	2	1
Number of aspiration events in total	0	0
Number with sudden decrease in oxygen saturation	0	1
Number with de novo presence of coarse chest crepitations	0	0
Relationship of adverse event with BCV:		
Unlikely	2 (100%)	0 (0%)
N/A	0 (0%)	1 (100%)
Relationship of adverse event with LVT:		
Unrelated	0 (0%)	1 (100%)
N/A	2 (100%)	0 (0%)
During primary admission:		
Number of episodes of hypercarbia - median (IQR)	0 (0, 0)	0 (0, 0)
Number of episodes of bradypnoea - median (IQR)	0 (0, 0)	0 (0, 0)
Number of episodes of hypoxaemia - median (IQR)	0 (0, 0)	0 (0, 0)
Number of children that developed hypotension	0 (0%)	0 (0%)

Discussion

In this small Phase I trial, we examined the feasibility and safety of non-invasive respiratory support given alone or together with LVT (for seizure prophylaxis) to support and improve outcomes of children with cerebral malaria during the early part of their admission. Although the numbers are small due to stopping prior to complete trial recruitment, the data generated indicate that the use of BCV is safe and

feasible to implement in a low resource setting. No child receiving BCV developed machine-specific complications including aspiration events, episodes of hypercarbia, hypotension or hypoxaemia. Only 1 child could not tolerate BCV. The technical challenge of reliable power was experienced on two occasions in block 2. LVT was safely administered to all seven children in the second block with 6 children receiving additional doses (and one child dying early in admission). Seizures were witnessed in 1/7 (14%) children in those receiving LVT prophylaxis in block 2 and in 4/5 (80%) in those not receiving LVT prophylaxis in block 1. Additionally, children receiving LVT in block 2 did not require additional anti-seizure medication after starting LVT.

LVT has been investigated as a safer option for seizure control in Malawian children with cerebral malaria, but not as prophylactic regimen as in our trial. In that Phase I trial children received 40 mg/kg loading dose followed by 30mg/kg every 12 hours via nasogastric tube for 3 days with a plan to escalate the dose if the primary endpoint was not achieved. The primary endpoint was defined as freedom from clinically witnessed seizure in 75% of children during the 24 hours following the initial loading dose of LVT(24). In the seven children enrolled to receive LVT in the trial all were free from seizures at 72 hours. The investigators decided not to dose-escalate, although 6 children required additional antiseizure medications drugs. The nested pharmacokinetic studies in this Malawian trial indicate the mean (and full range) of LVT concentrations was 35 (20–50) micrograms/mL which was within the therapeutic range. A follow on randomised controlled Phase II trial in the same centre implementing the same loading and follow on regime as the Phase I trial in the intervention arm and compared this to standard of care with electroencephalographic seizure control over 72 hours as the primary outcome. Seizures occurred 4/23 (17%) in the LVT arm mean 165 min duration (SD 266; IQR 26–305) versus 5/21 (24%) in the phenobarbital arm, mean 465 min (SD 639; IQR 42–734; maximum 1473)(24). All other outcomes including death and neurologic sequelae were similar. Thus, in other trials, an approach to treat seizures with other anti-seizure medication compared to preventing seizures with LVT resulted in a higher prevalence of seizures and of longer overall duration.

The major limitation of our trial is that it was stopped due to the number of cerebral malaria cases eligible for enrolment substantially decreasing over the trial period. Notably, due to the COVID pandemic resulting in a study suspension, there was 2.5 year gap between enrolment of the first block of participants and the second. We suggest that the decline in referrals of cases of severe malaria to Kilifi County Hospital was partially due to the substantial strengthening of local health centres for inpatient management prompted by COVID(25), which was sustained beyond the epidemic.

The NOVICE trial design included an oral preparation since at the time it was designed (2019) intravenous LVT formulations were too costly and largely not available across Africa. Since then, intravenous formulations have become more affordable for health services. In 2023 WHO added oral LVT for focal/generalized seizures for status epilepticus to its Model Lists of Essential Medicines recognizing it as crucial for epilepsy treatment (LVT for status epilepticus- accessed 10th Dec 2025). However, it has also been shown to be given safely intravenously to critically ill children(26) and is very commonly used in high-income countries to prevent and treat seizures(27). Given the safety data

generated from both our limited study and the Phase I and II trials conducted in Malawi we suggest that further research should focus on intravenous preparations of LVT since these are more affordable and easier to administer.

Following this trial our trial group designed a Phase II randomised controlled trial comparing LVT given for seizure prophylaxis versus standard practice (which anti-seizure medication are given when seizures are witnessed) in 150 children with clinically defined cerebral malaria. In this trial additional use of BCV was not included into the design. The trial is incorporated, as a domain, in a multi-country platform trial (SMAART MAP ISRCTN79071535). The trial is being conducted in 7 sites in 5 countries (Ghana, Democratic Republic of Congo, Uganda, Kenya and Mozambique). Trial enrolment started December 2024 and due to complete in October 2026.

Conclusions

In summary we have shown in this small study that the incidence of seizures in cerebral malaria was fewer in a group of children administered LVT, that there were no reported side-effects of LVT and that the non-invasive respiratory support with BCV was feasible. Future larger trials, alongside the one described above, to confirm prophylactic and neuroprotective effect of LVT, including IV formulations are required.

Abbreviations

BCS Blantyre Coma Scale

BCV Biphasic Cuirass Ventilation

DMC Data Monitoring Committee

EEG Electroencephalography

HFNC High Flow Nasal Cannula

KCH Kilifi County Hospital

KEMRI Kenya Medical Research Institute

KWTRP KEMRI-Wellcome Trust Research Programme

ICREC Imperial College Research Ethics Committee

IQR Interquartile range

LVT Levetiracetam

MRC CTU Medical Research Council Clinical Trials Unit

NGT Nasogastric tube

NIV Non-invasive ventilation

NPV Negative pressure ventilation

pCO₂ partial pressure Carbon Dioxide

RDT Rapid diagnostic test

SERU Scientific and Ethics Review Unit

SMAART Severe Malaria in African children: A Research and Trials consortium

Declarations

Ethical approval

Ethical approval was obtained from Kenya Scientific and Ethics Review Unit (SERU), Nairobi Kenya on 13th July 2018 (protocol number RES/7/3/1), Imperial College Research Ethics Committee (ICREC) on 19th June 2018 (protocol number 18IC4511).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors have no conflicts of interest to declare.

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Authors' contributions

KM, NO, DMG and ASW conceived the study; KM, NO, EC, DMG ASW and ECG designed the study protocol; NO, EM, EO, MH, CN and SMK implemented the study; CM, RC and ECG verified and analysed

the data; KM wrote the first draft of the paper which all authors read and approved the final manuscript. KM and ECG are guarantors of the paper.

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Figures

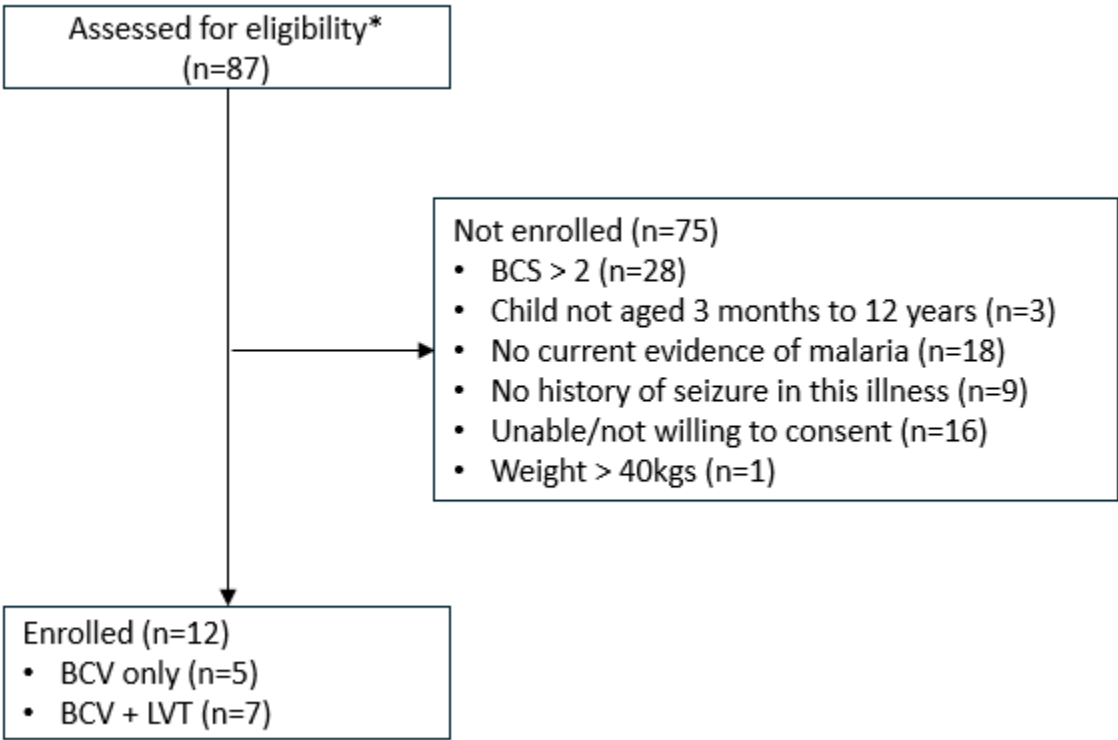


Figure 1

CONSORT Diagram

***Inclusion criteria:** Children aged 3 months–12 years admitted to paediatric wards with current or recent *P. falciparum* malaria (slide or RDT positive), Blantyre Coma Score ≤ 2 persisting after correction for hypoglycaemia (glucose < 3 mmol/L), history of seizures in the current illness, and with guardian/parent able to provide consent.

Exclusion criteria: Known cerebral palsy or significant neurodevelopmental delay affecting endpoint assessment; skin disease or burns preventing BCV use; respiratory or cardiorespiratory arrest prior to enrolment; or comorbidities judged by the clinician to carry significant risk of poor outcome (e.g. malignancy, end-stage renal failure, major cardiac disease).

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