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A phase I/II randomized controlled clinical trial to assess the feasibility, safety, and preliminary effectiveness of paracetamol in resolving acute kidney injury in children with severe malaria

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A phase I/II randomised controlled clinical trial to assess the feasibility, safety and preliminary effectiveness of paracetamol in resolving acute kidney injury in children with severe malaria.

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Abstract

Background:

Acute kidney injury (AKI) is prevalent among children with severe malaria, contributing to considerable morbidity and mortality. Oxidative stress has been implicated in the pathophysiology of malaria-induced AKI, and paracetamol, with its antioxidant properties, has been proposed as a solution. This phase I/II randomized trial evaluated paracetamol as a potential renoprotective adjunct in children with severe malaria and acute kidney injury.

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Methods:

We conducted a phase I/II open label parallel randomised controlled trial of 40 hospitalised children aged >6month to <12 years with malaria-induced AKI in eastern Uganda. Participants were randomized by a sealed envelope 1:1 to receive either oral paracetamol 20mg/kg 6-hourly for 48 hours or tepid sponging every 30 minutes until fever subsided. Only the assessors of the primary outcome were masked to the intervention. The primary outcome was renal recovery at 48 hours assessed using restricted mean survival time (RMST) in intention to treat population of children according to their randomisation groups.

Results:

Between 19 September 2021 and 25 August 2023, 250 children with haemoglobinuric severe malaria were screened and the 40 enrolled were randomly assigned paracetamol (n=20) or tepid sponging (n=20). The mean age was 6.54 (2.61) years. The mean time to renal recovery in the paracetamol group was 0.491 hours (95% CI: -9.265 to 10.248; p=0.921) longer than the control group within 48 hours, but this difference was not statistically significant even after adjusting for age and weight: 1.04 hours (95% CI: -8.61-10.70; p=0.832). The safety assessment indicated no significant differences in adverse events and hepatoxicity in either group.

Conclusions:

Although Paracetamol was safe, it did not significantly improve renal recovery in children with malaria-induced AKI. Further larger studies are needed to explore this role of paracetamol.

The trial registration: ISRCTN84974248.

Keywords: Acute kidney injury, Paracetamol, Children, Severe malaria, Blackwater fever, Restricted mean survival time, Randomised controlled trial

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Background

Malaria remains a significant cause of childhood morbidity and mortality in sub–Saharan Africa (SSA). In 2023, the region recorded 246 million cases and 569,000 deaths constituting over 94% and 95% of the global cases and deaths, respectively [1]. Notably, children under five years, are disproportionately affected by this burden [2-4]. AKI is a prevalent severe malaria presentation with reports indicating incidence rates of up to 46% among paediatric patients [2, 5-7]. Furthermore, children with malaria-induced AKI are at an increased risk of mortality [4, 6, 8, 9], often requiring renal replacement therapy, such as dialysis [10]. However, in low-resource settings, these interventions are often inaccessible, necessitating the reliance on supportive care measures, such as fluid therapy [11]. Fluid management in pediatric severe malaria requires caution, since fluid boluses in critically ill African children have been associated with higher mortality[12]. The burden of kidney complications in survivors remains substantial[13]. These considerations motivated evaluation of a kidney protective adjunct that could be delivered safely alongside standard care.

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We distinguish three evidence domains that inform this trial, malaria-associated acute kidney injury, acute kidney injury from other severe infections, and preclinical models. Evidence across conditions shows that cell-free hemoglobin and heme released during intravascular hemolysis are intrinsically nephrotoxic and drive oxidative stress-mediated tubular injury, a mechanism also implicated in severe falciparum malaria-associated AKI [14]. In malaria-associated AKI, higher circulating cell-free hemoglobin and lipid peroxidation markers correlate with AKI risk and severity, and experimental hemoglobinuria causes tubular damage through intrarenal oxidative reactions [15]. Paracetamol directly inhibits hemoprotein peroxidase chemistry by reducing

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ferryl heme and quenching globin radicals, which limits hemoprotein-catalyzed lipid and protein oxidation [16].

In adults with severe falciparum malaria, a randomized controlled trial showed that acetaminophen reduced kidney dysfunction and the risk of acute kidney injury, with the clearest effect among patients with evidence of intravascular hemolysis [17]. In adults with severe sepsis and detectable plasma cell free hemoglobin, a randomized, placebo-controlled trial found that acetaminophen reduced oxidative injury measured by plasma F2-isoprostanes, consistent with inhibition of hemoprotein mediated lipid peroxidation [16, 18]. Pediatric evidence remains limited. Published pediatric work focuses on protocols and observational signals rather than completed randomized trials.This evidence provides a biologic rationale for evaluating paracetamol as an adjunct in children with malaria-induced AKI. We therefore, conducted a phase I/II randomised controlled trial in children to assess the feasibility, safety and preliminary effectiveness of paracetamol in ameliorating AKI among children with severe malaria.

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Methods

Study setting

The trial was conducted at Mbale Regional Referral Hospital, Mbale District, Eastern Uganda, a high transmission *Plasmodium falciparum* setting with seasonal peaks. The hospital has pediatric high-dependency capacity, on-site malaria microscopy and rapid diagnostic testing, basic clinical chemistry including creatinine and urea, a blood bank for pediatric transfusion, and access to intravenous artesunate per national guidelines. Supportive services include continuous inpatient nursing, bedside glucose and lactate testing, and referral access to renal replacement therapy on a case-by-case basis.

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Study design

We conducted a phase I/II open-label, randomised controlled trial that utilised a parallel design with a 1:1 allocation ratio.

Study Population

Eligibility criteria

Inclusion criteria

Children were eligible if they met all of the following:

- Age greater than 6 months and less than 12 years.
- Severe malaria per national guidelines with laboratory confirmed *Plasmodium falciparum.*
- Acute kidney injury at screening, defined by either serum creatinine ≥ 1.5 times the age expected baseline or an increase by ≥ 26.5 µmol/L (0.3 mg/dL) within 48hours, from a documented referral laboratory result.
- Elevated BUN > 20 mmol/L at screening.
- Hemoglobinuria defined as Hillmen urine color chart grade greater than 5 and supported by urine dipstick positive for hemolyzed blood.
- Guardian or parent willing and able to provide consent

Exclusion criteria

- Acute trauma or burns
- Known allergy to paracetamol

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- Impaired liver function tests /disease with ALT beyond 40IU/l
- Treated with Paracetamol in the last 24 hours prior to admission
- Known chronic renal failure
- Known malignancy
- Vomiting everything
- Refusal to consent
- Previously enrolled

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Study Interventions

Treatment group

Participants in the intervention group received paracetamol 20mg/kg administered orally 6-hourly for 48h plus standard of care for severe malaria. Patients unable to swallow received paracetamol by nasogastric tube. Dosing commenced immediately after randomization once eligibility was verified and the first weight-based dose was prepared, typically within 60 minutes of randomization. In case the patient vomited within 30 min of paracetamol administration, a further dose was given.

Control group

Participants in the control group received standard care for severe malaria [19]. Tepid sponging and fanning were applied when axillary temperature was at least 38.0°C with reassessment every 30 minutes. If axillary temperature exceeded 39.5°C and did not respond to sponging, rescue paracetamol 10 mg/kg was be given as per national fever treatment guidelines [19], with time

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and dose recorded. Scheduled sponging was not performed in normothermic or hypothermic children.

Administration and monitoring followed the hospital pediatric formulary, the Uganda Clinical Guidelines[19], and WHO malaria treatment guidance [20], including dosing checks, contraindications, and liver safety surveillance.

Rationale for interventions

Paracetamol 20 mg/kg was administered orally every 6 hours for 48 hours to sustain target engagement during the early hemolysis window. This schedule is supported by mechanistic work showing that acetaminophen reduces ferryl heme to ferric heme and attenuates hemoprotein-mediated lipid peroxidation, a pathway implicated in hemolysis-related tubular injury [16]. Regular q6-hour dosing has shown biologic and renal signals in hemolysis-enriched critical illness, including reduced oxidative injury in severe sepsis with detectable cell-free hemoglobin [18] and reduced kidney dysfunction and AKI risk in severe falciparum malaria [17]. This regimen exceeds conservative antipyretic caps used for routine outpatient care, 60 to 75 mg/kg per day [21], so delivery was time-limited and monitored in hospital, consistent with precedent in critical illness trials and with paediatric dosing summaries that show short-term higher totals can be safe under supervision [22]. Tepid sponging and fanning were included for non-pharmacologic fever control in line with malaria case-management guidelines [23]. Dosing was protocolized for 48 hours in the inpatient setting with recorded administration times, clinical monitoring, and liver safety assessments.

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Outcomes

Primary outcome

Primary renal recovery was defined per the protocol as serum creatinine less than 80 µmol/L and blood urea nitrogen less than 20 mmol/L (≈ 56 mg/dL) within 48 hours of randomization. KDIGO criteria for acute kidney injury diagnosis and recovery are based on changes in serum creatinine and urine output rather than BUN thresholds, and we follow KDIGO for staging while using the BUN threshold as a prespecified operational criterion for this trial [24, 25].

Secondary outcomes

Secondary outcomes of this trial included:

Renal recovery at day 28 defined as sustained normalisation of serum creatinine and BUN levels at day 28.

Safety outcomes included assessment of adverse events and monitoring for hepatoxicity.

Monitoring of hepatotoxicity using Hy's law: Safety monitoring in this trial included assessment of liver function tests (LFTs) to identify potential hepatotoxicity associated with paracetamol. Hy's law criteria were used as follows: Alanine transaminase (ALT) or aspartate transaminase (AST) levels >3x the upper limit of normal (ULN), total bilirubin >2X ULN in the absence of significant cholestasis (elevated alkaline phosphatase) and no other plausible explanation for observed liver injury.

Mortality: Mortality at 48 hours and day 28 were recorded to assess the overall safety and survival effect of the intervention.

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Sample size

Using the A'Hern table of sample size determination, (with the assumption of Po = 10% P1=25% alpha (α)= 4.19 power (d) =81.80), we arrived at the sample size n= 40 with an estimated response rate r=8. As a phase I/II trial, the sample size was chosen to evaluate feasibility and safety and to generate preliminary effect estimates rather than to detect small efficacy differences.

Procedure

The PARIST study protocol was published and it gives a detailed description of the various study procedures [26].

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Screening

Eligible participants were identified by trained nurses and clinicians and registered in the eligibility screening log. A study team member performed a rapid structured assessment; of conscious level, vital signs (heart rate, oxygen saturation, respiratory rate, axillary temperature, and blood pressure) and history of haemoglobinuria in the current illness defined by dark urine with Hillmen urine colour chart grade >5 (Supplementary figure S1). Children who were potentially eligible had a rapid test using iSTAT® system (Abbott Point of Care, Princeton, NJ, USA) to measure creatinine and blood urea nitrogen (BUN) on a whole-blood sample to confirm eligibility prior to randomization. Testing was performed by trained study staff according to the manufacturer's operating procedures. Eligibility did not require waiting 48 hours. A rise in creatinine of above the protocol threshold, was established using a documented referral laboratory results given the fact that the recruiting site is the regional referral tertiary hospital.

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Details of those fulfilling the entry criteria were entered onto a screening form, while reasons for non-eligibility were added to the eligibility screening log.

Randomization and masking

After screening, the patients who qualified were assigned study numbers which correspond to those assigned in envelopes which were arranged consecutively in sealed opaque envelopes, each assigned across the seal. These numbers were randomly assigned prior to the start of the study by an independent statistician using the "randomizeR" package of the statistical software R, which allows simple randomization and adaptive assignment through a minimization procedure. Minimization allocated patients to best maintain balance in the treatment group by calculating an imbalance score at each randomization. It then assigned with higher probability each patient to the treatment that would reduce the imbalance. The allocation was on a 1:1 ratio to Paracetamol (A) and no Paracetamol (B). During enrolment, the study staff picked the cards consecutively and opened it. Each envelope had a card that showed which group the participant was in (A or B). Because of the nature of the intervention, participants and treating staff were not blinded to allocation. Before enrollment began, the clinical team completed protocol training that included competency checklists and case-based simulations on eligibility screening, dosing, temperature management, and strict non-disclosure of allocation during follow up contacts, with refresher sessions every two weeks during enrollment. Outcome assessors and statisticians were blinded to allocation to minimize bias in outcome measurement and analysis.

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Delivery of the intervention

The intervention was initiated as soon as possible following randomization. The study investigational product. Paracetamol tablets 500mg (Kamadol, Kampala Pharmaceutical Industries (KPI) Limited)) was sourced locally from a certified pharmaceutical supplier and

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stored according to the manufacturer's recommendations. Treatment protocols and guidelines for paracetamol administration and monitoring were provided to the trial clinical team. The intervention was administered by trained clinicians and nurses. All the staff involved in the trial received prior training on the study protocol, including paracetamol administration, safety monitoring and adverse event reporting. Clinical staff were trained to follow strict procedures to ensure correct dosing and adherence to the study protocol. Every staff member qualification and training were captured in the trial 's personnel log.

Concomitant care

All participants received guideline based antimalarial therapy, with intravenous artesunate as first line treatment and step down to an oral artemisinin-based combination once enteral intake was reliable, per national guidance. Empiric or targeted antibiotics were given when bacterial co infection was suspected. Packed red cell transfusion was provided for severe anemia (hemoglobin less than 5 g/dL or 5-7 g/dL with signs of decompensation), per national guidance. Intravenous fluid support used isotonic crystalloids and was titrated to clinical perfusion, mental status, capillary refill, urine output, and lactate, with close monitoring to avoid fluid overload. Potential nephrotoxins such as NSAIDS like Ibuprofen were avoided. Intake and output, vital signs, and bedside glucose were recorded on standardized charts, and electrolyte abnormalities were corrected according to local protocols. All medications and supportive care were administered under the supervision of trained clinical staff to ensure adherence to the study protocol.

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Laboratory investigations

After consent and randomization, admission blood samples were obtained for capillary glucose, whole blood lactate, malaria microscopy, hemoglobin, creatinine and blood urea nitrogen.

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Capillary glucose was measured at bedside using a calibrated point of care glucometer per manufacturer quality control procedures. Lactate was measured by point of care whole blood assay in the emergency unit. Thick and thin blood films were examined by two trained microscopists to confirm malaria infection and identify *Plasmodium falciparum*. Parasite density was not quantified as part of the study procedures. Slides were prepared and stained with Giemsa and read according to local laboratory standard operating procedures. For quality assurance, a third microscopist performed an adjudication reread of all slides; discordant findings between the first two reads (for example, positive versus negative, or disagreement in species identification) were resolved by the third read. Hemoglobin was measured on an automated hematology analyzer in the hospital laboratory. Serum creatinine and BUN used for study outcome assessment were measured in the clinical chemistry laboratory using enzymatic methods traceable to international reference materials. Creatinine was measured using an enzymatic creatinine method (IDMS-traceable calibration) on the (Abbott Architect c4000). BUN was measured using an enzymatic urea/BUN method (urease-based) on the same analyzer. In accordance with national guidelines, HIV testing was performed after admission procedures were complete and with parental or guardian consent. Hemoglobin and lactate were reassessed at 8 hours, 12 hours, 24 hours, and 48 hours, and serum creatinine and blood urea nitrogen were repeated at 12 hours, 24 hours, and daily through 48 hours, then as clinically indicated to day 5 or until normalization. At the day 28 follow up visit, an additional 2 to 3 mL blood sample was collected for hematological and parasitological recovery. All assays followed internal quality control procedures with daily controls

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Clinical Monitoring and further assessments

All children were reassessed clinically at 1, 4, 8, 24 and 48 hours. At each review consciousness level, urine output and fluid intake, daily body weight measurement, vital signs (heart rate, oxygen saturation, respiratory rate, axillary temperature, blood pressure). Creatinine and BUN were measured at 0, 12, 24 hours and thereafter daily till 5 days of admission or until normal. In addition, serum electrolytes assessment was monitored. Jaundice severity was graded at the bedside using a standardized 3-level clinical scale adapted from pediatric guidance: mild, scleral icterus only; moderate, scleral icterus plus cutaneous icterus of the face or upper trunk; severe, generalized cutaneous icterus beyond the trunk and/or deep mucosal icterus. Examinations were performed in natural daylight when feasible or under bright white indoor lighting, with the child's skin exposed and cleaned of topical agents. Assessors were trained with a photo atlas and case vignettes before enrollment and completed competency checklists; uncertain grades were discussed with a senior clinician, and disagreements were resolved by consensus at the same visit. Grading was clinical only and did not incorporate laboratory bilirubin values; serum total and conjugated bilirubin were analyzed separately and reported as laboratory outcomes.

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Follow up schedule

Participants were reviewed at 48 hours for the primary outcome and again at day 28 to assess renal recovery. Only participants who had not achieved renal recovery at day 28 were scheduled for additional follow up at day 90 and day 180, with safety contact maintained for all participants.

Safety monitoring

Safety monitoring was an integral component of this trial to ensure participant well-being. The adverse events and severe adverse events were monitored continuously during the study period,

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including emesis, right upper quadrant pain, tachycardia, hypoglycaemia, hypotension and impaired liver function documenting and categorising them based on the Common Terminology Criteria for Adverse Events (CTCAE), and timely reporting them to the principal investigator.

Independent study oversight and monitoring

An independent Data and Safety Monitoring Board (DSMB) reviewed unblinded safety data at predefined intervals and had authority to recommend protocol modification or temporary suspension for safety, feasibility, or scientific concerns. Stopping rules and review schedules were prespecified in the DSMB charter.

Data management

All clinical and laboratory data was recorded using a standardised case report form (CRF) by a trained study team. Data was entered into a secure, password-protected Redcap database at the Mbale Clinical Research Institute (MCRI), with routine audits for completeness and accuracy. Consistency checks were conducted to resolve any discrepancies. Participant confidentiality was secured by de-identifying records, and access to the database was restricted to authorised study staff. Furthermore, all data was anonymised before the presentation or publication of any results.

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Statistical analysis

All trial analyses were conducted on an intention-to-treat (ITT) basis, including all randomised participants in their allocated groups and the level of statistical significance set at $p<0.05$. The primary outcome (renal recovery at 48 hours) was analysed using the restricted mean survival time (RMST) approach. Although traditional survival analysis methods were prespecified for analysis of survival outcomes, these methods were not used due to the violation of the proportional hazard's assumption. In particular, the Shoenfelds residual test (supplementary

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figure 2) showed that the hazard ratio for treatment was not constant over time. Consequently we adopted the restricted mean survival time (RMST) approach, which estimates the mean survival time within a restricted time window allowing for the direct comparison between groups without the limitations imposed by the proportional hazards assumption [27]. The cumulative recovery time was compared between the paracetamol and no paracetamol group at a truncation time (τ=48 hours) and results were reported as differences in the RMST together with the 95% confidence interval. RMST was also used to compare renal recovery between the two groups at day 28 (τ=672 hours). Adjusted RMST analyses were performed to control for potential confounding effects of baseline covariates including age and weight in both the primary and secondary outcome analyses. Age was selected because renal function and recovery may vary with developmental stage [28] while the selection of weight was to account for differences in the distribution and dosing, which may influence treatment efficacy [29]. These models provided adjusted estimates of group differences in renal recovery time. Secondary outcomes including the frequency of participants with adverse events and those meeting the Hy's law criteria for hepatotoxicity were compared between the two treatment groups using Fisher's exact test. Further descriptive statistics were used to summarise changes in LFTs over the time points of assessment for each of the groups. Owing to the small sample size, no subgroup analysis was done. All statistical analyses were performed using R statistical software (version 4.3.2).

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Trial registration

PARIST study was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry under the identifier ISRCTN 84974248.

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Results

Participant Characteristics and Study Flow

A total of 250 children diagnosed with haemoglobinuric severe malaria were initially screened for eligibility into the study. Forty participants met eligibility criteria and were randomized 1 to 1 to paracetamol or no paracetamol. The screening and randomisation process were carried out in strict accordance with the trial protocol. All participants who were randomised completed the primary outcome assessment at 48 hours. By day 28 post discharge evaluations, there were 3/40 mortality events; two in hospital deaths (one in the Paracetamol group and one in the no paracetamol group) and one community death in the control group. This trial was conducted between 19 September 2021 and 25 August 2023. The CONSORT diagram (Figure 1) provides a summary of the study participant's flow.

Figure 1. CONSORT diagram, illustrating the screening, randomization, and follow-up processes

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Baseline Characteristics

The baseline characteristics including demographic, clinical, and laboratory characteristic of study participants in the paracetamol and no paracetamol group are shown in Table 1.

Table 1. Baseline demographic, clinical, and laboratory characteristics of study participants in the two intervention groups.

Characteristic	**Overall** (n = 40)	**No Paracetamol** (n = 20)	**Paracetamol** (n = 20)
Sex			

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Female	17 (41%)	8 (40%)	9 (42%)
Male	23 (59%)	12 (60%)	11 (58%)
Age	6.54 (2.61)	6.66 (2.82)	6.43 (2.44)
Axillary Temperature (^{o}C)	37.03 (0.75)	37.15 (0.88)	36.90 (0.58)
Weight (Kg)	18.3 (3.6)	18.5 (3.9)	18.1 (3.4)
Lactate	2.07 (1.36)	1.98 (1.34)	2.15 (1.42)
Yellow eyes			
Yes	39/40 (98%)	20/20 (100%)	19/20 (95%)
Capillary refill (sec)			
<2 sec	21 (54%)	11 (55%)	10 (53%)
2-3 sec	18 (46%)	9 (45%)	9 (47%)
Temperature gradient	1 (2.6%)	1 (5.0%)	0 (0%)
Pallor			
Mild	2 (5.1%)	2 (10%)	0 (0%)
Moderate	14 (36%)	4 (20%)	10 (53%)
Severe	23 (59%)	14 (70%)	9 (47%)

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Sunken eyes	2 (5.1%)	1 (5.0%)	1 (5.3%)
Dry mucus	6 (15%)	4 (20%)	2 (11%)
Level of consciousness			
Alert	37 (95%)	18 (90%)	19 (100%)
Verbal	2 (5.1%)	2 (10%)	0 (0%)
Prostration	19 (49%)	11 (55%)	8 (42%)
Jaundice			
Mild	20 (51%)	11 (55%)	9 (47%)
Moderate	17 (44%)	9 (45%)	8 (42%)
Severe	2 (5.1%)	0 (0%)	2 (11%)
Na^+ (mmol/L)	134.9 (3.5)	134.8 (3.0)	135.1 (4.2)
K^+ (mmol/L)	4.25 (0.71)	4.36 (0.67)	4.13 (0.75)
Cl^- (mmol/L)	102.6 (5.2)	102.3 (6.0)	102.9 (4.2)
iCa (mmol/L)	1.10 (0.09)	1.10 (0.08)	1.10 (0.10)
TCO_2 (mmol/L)	18.73 (3.03)	18.65 (3.27)	18.82 (2.83)
Glucose (mmol/L), median (Q1-Q3)	4.7 (4.0 to 5.5)	4.6 (3.9 to 5.4)	4.8 (4.1 to 5.7)

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BUN (mmol/L)	24.6 (15.7)	23.6 (15.4)	26.1 (16.8)
Creatinine (μmol/L)	214 (269)	232 (310)	193 (221)
Anion Gap (mmol/L)	18.95 (2.34)	19.25 (2.65)	18.59 (1.94)
WBC (10^3/uL)	11 (8)	12 (7)	10 (9)
NEU (%)	63 (20)	66 (18)	59 (23)
Hb (g/dL)	5.91 (1.99)	5.58 (2.33)	6.25 (1.56)
PLT (10^3/uL)	198 (156)	202 (153)	194 (163)
Dark urine grade (Hillmen urine colour chart scored ≥5)			
5	7 (20%)	4 (24%)	3 (17%)
6	8 (23%)	4 (24%)	4 (22%)
7	14 (40%)	5 (29%)	9 (50%)
8	2 (5.7%)	2 (12%)	0 (0%)
9	2 (5.7%)	1 (5.9%)	1 (5.6%)
10	2 (5.7%)	1 (5.9%)	1 (5.6%)
Urine bilirubin			
Negative	27 (84%)	15 (94%)	12 (75%)

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Small (+)	4 (13%)	1 (6.3%)	3 (19%)
Moderate (++)	1 (3.1%)	0 (0%)	1 (6.3%)
Urine ketone (mg/dL)			
Negative	24 (75%)	10 (63%)	14 (88%)
Trace	4 (13%)	3 (19%)	1 (6.3%)
Small	3 (9.4%)	3 (19%)	0 (0%)
Moderate	1 (3.1%)	0 (0%)	1 (6.3%)
Urine blood (Dipstick)			
Negative	5 (16%)	4 (25%)	1 (6.3%)
Trace	3 (9.4%)	2 (13%)	1 (6.3%)
Small	1 (3.1%)	0 (0%)	1 (6.3%)
Moderate	5 (16%)	1 (6.3%)	4 (25%)
Large	18 (56%)	9 (56%)	9 (56%)
Urine protein			
Negative	11 (34%)	5 (31%)	6 (38%)
Trace	5 (16%)	2 (13%)	3 (19%)
30 (+)	10 (31%)	5 (31%)	5 (31%)

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100 (++)	6 (19%)	4 (25%)	2 (13%)
Urine leukocytes			
Negative	20 (63%)	11 (69%)	9 (56%)
Trace	4 (13%)	2 (13%)	2 (13%)
Small (+)	5 (16%)	1 (6.3%)	4 (25%)
Moderate (++)	2 (6.3%)	1 (6.3%)	1 (6.3%)
Large (+++)	1 (3.1%)	1 (6.3%)	0 (0%)
ALT/SGPT (IU/L)	17 (12)	15 (11)	19 (13)
AST/SGOT (IU/L)	135 (126)	140 (133)	130 (122)
LDH (IU/L)	1,277 (827)	1,325 (888)	1,224 (775)
Total bilirubin (mmol/L)	26.2 (52.0)	21.2 (30.1)	31.5 (68.4)
Conjugated Bilirubin (mmol/L)	10 (33)	4 (6)	16 (48)

Data are mean (SD) if approximately normal or median (IQR) otherwise. Normality was assessed by visual inspection and the Shapiro-Wilk test. Abbreviations. BUN, blood urea nitrogen; WBC, white blood cell count; NEU, neutrophils; Hb, hemoglobin; PLT, platelets; LDH, lactate dehydrogenase; AST/ALT, aspartate/alanine aminotransferase; TCO_2, total carbon dioxide. Units: serum creatinine µmol/L; BUN mmol/L; glucose mmol/L; lactate mmol/L; Na, K, Cl, iCa, TCO_2 mmol/L; hemoglobin g/dL; WBC and platelets 10^3/µL; AST/ALT/LDH IU/L; total bilirubin mg/dL; conjugated bilirubin µmol/L. Urine dipstick categories are semi-quantitative as shown; Hillmen urine color grades 5-10 indicate dark urine.

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Feasibility outcomes.

Feasibility targets were achieved, with 40 of 40 randomized children, 100 %, receiving their allocated initial treatment, 40 of 40, 100 %, completing the 48-hour primary outcome assessment, and 37 of 40, 92.5 %, completing day 28 follow up. These prespecified process indicators support the feasibility of protocol implementation in this setting. However, scheduled PK sampling was completed in 2 of 20 children, 10 %, yielding 3 samples in total, median 1 per child. Samples were obtained outside the prespecified windows, median 6.5 hours post dose, IQR 5.0 to 8.0, which was insufficient for formal pharmacokinetic modeling or assessment of target exposure.

Renal recovery at 48 hours

By 48 hours after randomization, renal recovery (serum creatinine <80 µmol/L and BUN <20 mmol/L) was observed in 5/20 (25%) children in the paracetamol group and 6/20 (30%) children in the no-paracetamol group. Children in the Paracetamol group achieved an average renal recovery time of 39.16 hours (95% CI: 32.41 to 45.90) while children in the no Paracetamol group achieved an average renal recovery time of 38.67 hours (95% CI: 31.62 to 45.72) within 48 hours (Figure 2).

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Figure 2. Time to renal recovery within 48 hours. Kaplan-Meier curves show the proportion with renal recovery over time in the paracetamol group and the no paracetamol group, with corresponding restricted mean survival time (RMST) estimates for τ=48 hours. Numbers at risk are shown below the x axis. Y axis: Proportion with renal recovery.

The average time to renal recovery in the Paracetamol group was 0.49 hours longer than the no paracetamol group, but this difference was not statistically significant as indicated by RMST

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difference of 0.49 hours (95% CI: -9.27 to 10.25; p=0.921). The time to renal recovery in the Paracetamol group was 1.3% longer than the no Paracetamol group, but this ratio was also not statistically significant as indicated by the RMST ratio of 1.01 (95% CI: 0.79 to 1.30; p=0.921) as shown in Table 2.

Table 2. Between-group comparisons for renal recovery at 48 hours.

Paracetamol vs no paracetamol	**Estimate**	**95% Confidence Interval**	**p-value**
Difference in RMST	0.49 hours	(-9.27, 10.25)	0.921
Ratio of RMST (1 / 0)	1.01	(0.79, 1.30)	0.921

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After adjusting for Age and weight, the average time to renal recovery in the paracetamol group was 1.04 hours longer than in the no-paracetamol group, however, this difference was not statistically significant as indicated by the adjusted difference in RMST between the groups of 1.04 (95% CI: -8.61, 10.70; p=0.832).

Table 3. Adjusted RMST treatment effect for renal recovery within 48 hours (model adjusted for age and weight).

Difference of RMST					
Variable	Coefficient	Standard Error	z-value	p-value	95% CI
Intercept	48.09	17.26	2.79	0.005	(14.27, 81.92)

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Treatment (Paracetamol – No paracetamol)	1.04	4.93	0.21	0.832	(-8.61, 10.70)
Age	3.76	2.39	1.57	0.116	(-0.93, 8.46)
Weight	-1.89	1.67	-1.13	0.259	(-5.17, 1.39)

Ratio of RMST

Variable	Coefficient	Standard Error	z-value	p-value	Exp (Coefficient)	95% CI
Intercept	3.87	0.45	8.63	0.000	48.13	(19.96, 116.04)
Treatment (Paracetamol – No paracetamol)	0.03	0.13	0.21	0.834	1.03	(0.80, 1.32)
Age	0.09	0.06	1.55	0.120	1.10	(0.98, 1.24)
Weight	-0.05	0.04	-1.09	0.276	0.96	(0.88, 1.04)

Renal recovery at day 28

By day 28 after randomization, renal recovery (serum creatinine <80 µmol/L and BUN <20 mmol/L) was observed in 13/20 (65%) children in the paracetamol group and 16/20 (80%) children in the no-paracetamol group. Children treated with paracetamol group achieved renal

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recovery in an average of 279.16 hours (95% CI: 143.57–414.75), while children in the no paracetamol group achieved recovery in an average of 308.78 hours (95% CI: 161.28–456.28) within 28 days (Figure 3).

Figure 3. Time to renal recovery within 28 days. Kaplan-Meier curves show the proportion with renal recovery over time in the paracetamol group and the no paracetamol group, with corresponding restricted mean survival time (RMST) estimates for τ=672 hour (day 28). Numbers at risk are shown below the x axis. Y axis: Proportion with renal recovery.

On average, children in the paracetamol group had a 29.62-hour (95% CI: -229.97 to 170.73; p=0.772) shorter renal recovery time compared to the no paracetamol group, but this difference was not statistically significant. The recovery time in the paracetamol group was approximately 90.4% of the recovery time in the no paracetamol group, but this result was not statistically significant as indicated by the RMST ratio of 0.90 (95% CI: 0.46–1.79; p=0.772) (supplementary table 1).

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After adjusting for age and weight, the average time to renal recovery in the paracetamol group was 9.1 hours shorter than in the no-paracetamol group, but this difference was not statistically significant as indicated by adjusted RMST between the groups of -9.10 hours (95% CI: -192.23 to 174.02; p=0.922) (supplementary table 2).

Eventual recovery at different follow up time points

All randomized participants completed the 48-hour primary outcome assessment. By 48 hours, renal recovery (serum creatinine <80 μmol/L and BUN <20 mmol/L) was observed in 5/20 (25%) participants in the paracetamol group and 6/20 (30%) participants in the control group.

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Post-discharge assessments were scheduled at day 28 for all participants, and at day 90 and day 180 only for those without renal recovery at day 28.

At day 28, assessments were completed for 19/20 participants in the paracetamol group and 18/20 in the control group (37/40 overall). By day 28, renal recovery was observed in 13/20 (65%) participants in the paracetamol group and 16/20 (80%) participants in the control group.

Among those without renal recovery at day 28, assessments at day 90 were completed for 5/19 participants in the paracetamol group and 2/18 in the control group (7/37 overall). At day 180, assessments were completed for 1/19 participants in the paracetamol group, and recovery status was confirmed at all visits using the protocol definition. No participant initiated renal replacement therapy after discharge.

Rescue paracetamol in the control group

Rescue paracetamol use in the control group was rare. Two of 20 control participants, 10 %, received a single 10 mg/kg rescue dose for refractory fever after exceeding the 39.5°C trigger despite tepid sponging. No control participant received more than one rescue dose within the first 48 hours.

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Safety outcomes

Adverse events and serious adverse events were summarized by randomized group. The most frequent events were fever persistence and vomiting with similar distributions between treatment groups. Three deaths occurred (one in Paracetamol group and two in the no paracetamol group). No participants in either group fulfilled the Hy's law criteria for drug-induced hepatotoxicity (Table 4).

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Table 4. Safety assessment between the groups

Outcome	**No Paracetamol (n = 20)**	**Paracetamol (n = 20)**	**Test Statistic**
ALT $_{0hours,}$ IU/L	10.9 (5.4 to 18.9)	17.9 (11.5 to 25.9)	$F_{1,39}$=2.29, P=0.14[3]
ALT $_{48hours,}$ IU/L	8.0 (3.7 to 15.1)	8.3 (5.7 to 15.9)	$F_{1,39}$=0.34, P=0.56[3]
Δ ALT $_{0\text{-}48\ hours,}$ IU/L	−1.8 (−7.1 to −0.5)	−8.8 (−12.2 to −2.2)	$F_{1,39}$=2.43, P=0.13[3]
AST $_{0hours,}$ IU/L	69.2 (20.7 to 243.9)	89.4 (43.0 to 229.2)	$F_{1,39}$=0.39, P=0.54[3]
AST $_{48hours,}$ IU/L	17.9 (9.3 to 38.8)	26.3 (19.3 to 34.1)	$F_{1,39}$=0.68, P=0.42[3]
Δ AST $_{0\text{-}48\ hours,}$ IU/L	−51.9 (−197.7 to −9.9)	−62.5 (−168.2 to −26.4)	$F_{1,39}$=0.07, P=0.79[3]
LDH $_{0hours,}$ IU/L	876.5 (565.1 to 2154.7)	887.6 (714.4 to 1520.1)	$F_{1,39}$=0.01, P=0.91[3]
LDH $_{48hours,}$ IU/L	604.8 (428.1 to 1196.2)	749.1 (529.7 to 1045.3)	$F_{1,39}$=0.04, P=0.85[3]
Δ LDH $_{0\text{-}48\ hours,}$ IU/L	−293.2 (−686.2 to 4.3)	−273.8 (−903.4 to −75.6)	$F_{1,39}$=0.02, P=0.88[3]
Total bilirubin $_{0hours,}$	4.3 (2.4 to 21.4)	10.3 (2.3 to 32.2)	$F_{1,39}$=0.62, P=0.44[3]

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mg/dL			
Total bilirubin $_{48hours,}$ mg/dL	1.7 (1.7 to 8.1)	1.7 (0.3 to 9.7)	$F_{1,39}$=0.03, P=0.86[3]
Δ Total bilirubin $_{0\text{-}48\ hours,}$ mg/dL	−1.7 (−18.5 to 1.0)	−3.4 (−29.9 to −1.7)	$F_{1,39}$=1.34, P=0.26[3]
Direct bilirubin $_{0hours,}$ mg/dL	2.1 (0.9 to 4.1)	3.4 (0.9 to 6.9)	$F_{1,39}$=0.42, P=0.52[3]
Direct bilirubin $_{48hours,}$ mg/dL	1.0 (0.6 to 2.9)	1.6 (0.4 to 4.7)	$F_{1,39}$=0.47, P=0.50[3]
Δ Direct bilirubin $_{0\text{-}48\ hours,}$ mg/dL	−0.4 (−2.5 to 0.2)	−1.1 (−2.9 to −0.1)	$F_{1,39}$=0.42, P=0.52[3]
Indirect bilirubin $_{0hours,}$ mg/dL (Total − Direct)	2.2 (−1.7 to 20.5)	6.9 (−4.6 to 31.3)	$F_{1,39}$=0.61, P=0.72[3]
Indirect bilirubin $_{48hours,}$ mg/dL (Total − Direct)	0.7 (−1.2 to 7.5)	0.1 (−4.4 to 9.3)	$F_{1,39}$=0.03, P=0.51[3]
Δ Indirect bilirubin $_{0\text{-}48\ hours,}$ mg/dL	−1.3 (−18.7 to 3.5)	−2.3 (−29.8 to 1.2)	$F_{1,39}$=0.09, P=0.35[3]
Hy's law composites			
ALT_{48hrs}>3x ULN +	0	0	-

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Total bilirubin >2X ULN*			
ALT_{48hrs}>3x ULN + Indirect bilirubin ≥2X ULN*	0	0	-
AST_{48hrs}>3x ULN + Total bilirubin >2X ULN*	0	0	-
AST_{48hrs}>3x ULN + Indirect bilirubin >2X ULN*	0	0	-
Mortality	2/20 (10.0%)	1/20 (5.0%)	$\chi^2_1 = 0.66$, P=0.25[2]
Vomiting	7/20 (35.0%)	5/20 (25.0%)	$\chi^2_1 = 0.48$, P=0.49[2]
Right upper quadrant abdominal pain	3/20 (15.0%)	4/20 (20.0%)	$\chi^2_1 = 0.17$, P=0.68[2]
Allergic rash	0	0	-
Diarrhea	1/20 (5.0%)	2/20 (10.0%)	$\chi^2_1 = 0.36$, P=0.55[2]

[1]Kruskal-Wallis, [2]Pearson, [3]Wilcoxon. Data are presented as number (%) or median (IQR), unless otherwise specified as mean (95% CI). Fisher's exact test and Mann-Whitney U test were used to assess differences between

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categorical and continuous variables. T-tests were employed for comparing differences in log-normal transformed data. The upper limit of normal (ULN) for ALT and AST were 50 U/L and 35 U/L for males and females, respectively. Indirect bilirubin was calculated as total bilirubin minus direct bilirubin. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, Lactate Dehydrogenase. Hy's Law stipulates that: (i) A drug must cause hepatocellular injury, indicated by a 3-fold or greater elevation above the ULN of ALT or AST compared to control or placebo: (ii) In patients with ALT or AST > 3×ULN, there must be an elevation in serum total bilirubin >2×ULN, without evidence of cholestasis; (iii) No other explanation accounts for the combination of elevated ALT/AST and bilirubin levels. Indirect (unconjugated) bilirubin was calculated as total bilirubin minus direct (conjugated) bilirubin at the participant level prior to summarisation and hypothesis testing.

Discussion

This study evaluated the treatment feasibility, safety and preliminary effectiveness of paracetamol as a renoprotective adjunctive treatment for malaria-induced AKI in children. Despite promising findings in adult studies indicating paracetamol's potential renoprotective effects, our phase I/II trial found no significant difference in renal recovery at 48 hours and day 28 between the paracetamol-treated group compared to the control group. This trial was designed to evaluate delivery and safety and to generate preliminary effect estimates rather than to detect clinically important efficacy differences. The estimated treatment effects therefore have limited precision, and the absence of a statistically significant difference should be interpreted as preliminary, not as definitive evidence of no benefit. We used 20 mg/kg every 6 hours for 48 hours to maintain steady antipyretic exposure and sustain inhibition of hemoprotein peroxidase activity during the early hemolysis window. Acetaminophen directly reduces ferryl heme to the ferric state and attenuates hemoprotein-catalyzed lipid peroxidation, a mechanism implicated in hemolysis-mediated kidney injury [16]. Adult randomized trials that enriched for intravascular hemolysis signals have used regular q6h dosing and demonstrated reduced oxidative injury in

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severe sepsis with detectable cell-free hemoglobin and a renoprotective signal in severe falciparum malaria [18]. Although, this regimen exceeds conservative antipyretic caps used for routine outpatient care, 60 to 75 mg/kg per day [21], so delivery was time-limited and monitored in hospital, consistent with precedent in critical illness trials and with paediatric dosing summaries that show short-term higher totals can be safe under supervision [22].

Our findings contrasts with from studies in adult populations with AKI [30-33] however, given the pilot sample size and resulting imprecision, these differences between our findings and adult studies should be interpreted cautiously, since both a clinically meaningful benefit and no effect remain compatible with our estimates. For instance, Plewes et al. (2018) reported that regular paracetamol administration protected kidney function in adult patients with moderate and severe falciparum malaria [33]. While in adult patients with sepsis, paracetamol was associated with a reductions in markers of renal injury, such as serum creatinine, and an improvement in renal function [30-32]. Several factors may explain the discrepancy between our findings: firstly, there is a difference in the pathophysiology of AKI across age groups. In paediatric populations, AKI often has multiple causes, including renal tubular damage, vasoconstriction, and inflammation, which may differ from the pathophysiology in adults with severe infections and hemolysis [34]. Additionally, the therapeutic efficacy and safety profile of paracetamol, may be significantly affected by the maturation of renal function and differences in drug metabolism between children and adults. In children, renal clearance and metabolic pathways are not fully developed, resulting in differing drug pharmacokinetics. For instance, the glucuronidation capacity, essential for paracetamol metabolism, matures over time, affecting drug clearance rates in neonates and infants [35]. Moreover, drug absorption, distribution, metabolism, and excretion may be affected

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by age-related physiological differences, such as gastric pH, intestinal transit time, and enzyme activity [36].

In this phase I/II feasibility trial, we did not observe a clear signal of improved renal recovery with paracetamol, and the effect estimates were imprecise. Malaria-associated AKI is biologically multifactorial, so any benefit from targeting oxidative stress with paracetamol may be limited in magnitude or restricted to specific subgroups, but this remains hypothesis-generating and requires evaluation in adequately powered trials. Consistent with the published protocol, this study was designed to assess feasibility and safety and to generate preliminary effect estimates, not to draw definitive conclusions about efficacy or mechanism. The multifactorial pathogenesis of malaria-associated AKI involves hemodynamic disturbances, immune-mediated damage, and metabolic dysregulation [37, 38]. For example, the cytoadherence of parasitized red blood cells to the microvascular endothelium leads to impaired renal perfusion and ischemic injury [39], a mechanism that is distinct from oxidative stress alone. In addition, immune-mediated injury through excessive release of cytokines, including TNF-α and IL-6, contributes to inflammation and endothelial dysfunction, which further exacerbates the renal injury [40, 41]. While the role of oxidative stress in malaria-induced AKI is significant, its is interlinked with these broader mechanisms. For example, cell-free haemoglobin released during hemolysis contributes to oxidative stress [42] but also interacts with nitric oxide pathways, impairing vasodilation and exacerbating renal hypoperfusion [43]. Moreover, the metabolic derangements including, lactic acidosis and disrupted renal autoregulation, further complicate the clinical course [44]. These observations underscore the complexity of the underlying mechanisms in malaria-induced AKI in children and demonstrate that therapeutic interventions targeting a single pathway may fail to achieve substantial benefits of renal recovery

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in this group. Regarding safety, our findings did not show significant liver injury associated with paracetamol use, implying that short-term administration is safe in this context. However, caution is warranted with higher doses or prolonged use, as paracetamol has been associated with nephrotoxicity [45]. Additionally, nephrotoxicity following paracetamol ingestion can occur even in the absence of hepatotoxicity, emphasizing the need for careful dosing [46, 47].

Any potential renoprotective effect is likely to be realized within a coherent care bundle. Key elements include cautious isotonic crystalloid administration with frequent reassessment of perfusion, mentation, respiratory status, and urine output, early packed red cell transfusion for severe anemia according to national thresholds, prompt recognition and treatment of possible bacterial co-infection, active avoidance or dose adjustment of nephrotoxins, bedside glucose monitoring with immediate correction of hypoglycemia, early management of electrolyte abnormalities (especially hyperkalemia and acidosis), and proactive identification of children who may benefit from renal replacement therapy where available. This practical bundled approach provides the clinical context in which any renoprotective effect of paracetamol would be most likely to translate into patient benefit while emphasizing the need for careful dosing, close monitoring, and vigilant clinical management.

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Several limitations further constrain interpretation of these preliminary findings. Firstly, the primary renal recovery endpoint followed prespecified thresholds in the protocol to support consistent bedside adjudication within the 48-hour window and to enable time to event analyses. Physiologic creatinine varies with age, so a fixed cut point can favour recovery classification in older children compared with younger ones who have lower age expected baselines. We recognize this as a design limitation of this present phase I/II study. Secondly, screening eligibility relied on iSTAT® whole-blood point-of-care creatinine and BUN, and point-of-care

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results can differ from laboratory enzymatic measurements. This may have introduced some misclassification around eligibility thresholds at enrolment. Creatinine and BUN used for outcome assessment were derived from laboratory enzymatic assays. Thirdly, as a phase I/II study, the trial was designed to assess safety and generate preliminary effect estimates rather than to detect small differences in efficacy. Lastly, although the protocol specified an exploratory PK aim, PK sampling density was insufficient, so we could not evaluate target exposure or exposure-response relationships,

Future trials should define recovery relative to age-appropriate baseline kidney function, for example KDIGO based fold changes from an age expected baseline creatinine or age adjusted eGFR percentiles, and prespecify age stratified analyses and in addition, should incorporate sparse sampling with population PK modeling to assess target attainment across ages and illness severity.

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Conclusion

Paracetamol at 20 mg/kg every 6 hours for 48 hours was safe in this cohort, with no treatment discontinuations attributable to adverse events and no excess in adverse or serious adverse events compared with control. No significant difference in renal recovery was observed between the paracetamol and control groups at the prespecified 48-hour endpoint. As a phase I/II study, these findings primarily inform safety and feasibility and provide preliminary effect estimates. The lack of preliminary efficacy observed in this trial does not preclude a potential renoprotective role of paracetamol in malaria associated acute kidney injury. Larger, adequately powered paediatric trials that incorporate age standardized kidney recovery definitions and prespecified subgroup analyses are needed to determine definitive efficacy and to identify children most likely to benefit.

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List of abbreviations

AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CFHb	Cell-Free Haemoglobin
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
Hb	Hemoglobin
iSTAT®	Point-of-Care Blood Analyzer (brand name)
ISRCTN	International Standard Randomised Controlled Trial Number
KPI	Kampala Pharmaceutical Industries
LDH	Lactate Dehydrogenase
MCRI	Mbale Clinical Research Institute
MRRH	Mbale Regional Referral Hospital
P. falciparum	Plasmodium falciparum

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RMST	Restricted Mean Survival Time
RCT	Randomised Controlled Trial
SSA	Sub-Saharan Africa
ULN	Upper Limit of Normal

Ethical approval and consent to participate

Ethical approval before starting this trial was granted by the Mbale Regional Referral Hospital Research Ethics Committee (MRRH-REC OUT 002/2019) while, regulatory approval was granted from the Uganda National Council of Science and Technology (UNCST) (HS965ES) and the National Drug Authority (NDA) (CTC 0166/2021). Written informed consent was obtained from the parents or guardians of all participating children, ensuring full compliance with ethical guidelines for research involving human subjects.

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Consent for publication

This work has been approved for publication by the Mbale Clinical Research Institute.

Availability of data and materials

The fully reproducible analysis workflow for this study including all R scripts, figure templates and the de-identified, aggregate ("derived") data that reproduce every table and figure in the manuscript is openly available on GitHub (https://github.com/gpaasi/paracetamol-for-AKI-PARIST-trial-work-flow) and permanently archived on Zenodo (https://doi.org/10.5281/zenodo.15689409).

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Competing interests

The authors declare that they have no competing of interests.

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Author contributions

All authors have made substantive intellectual contributions to the development of this manuscript. PO-O conceptualised the clinical trial and provided general guidance to the research team. All authors are involved in the implementation of this trial. GA and CN designed the database. PO, WO, DA, CN and MO are involved in data collection. RM and GM initially developed the laboratory analytical plan and schedule and did the laboratory tests. CBO oversaw the investigational product handling and storage. GP and CN did the statistical analysis, GP initiated the first draft of the manuscript, which was then followed by numerous iterations with substantial input and appraisal from all the authors. All authors approved the final version of the manuscript.

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Supplementary materials

Supplementary file 1: CONSORT 2010 checklist

Supplementary file 2: Additional methods and results.

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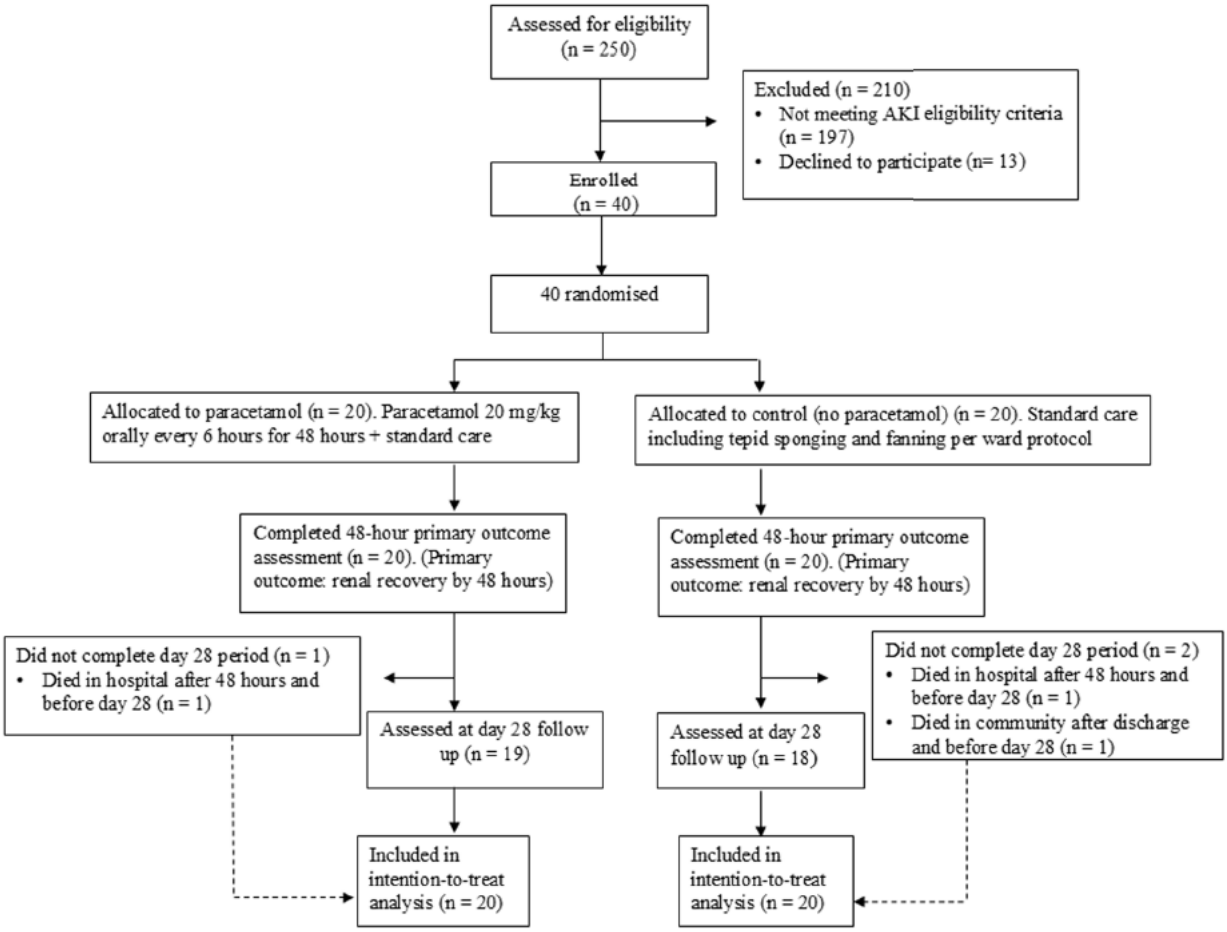
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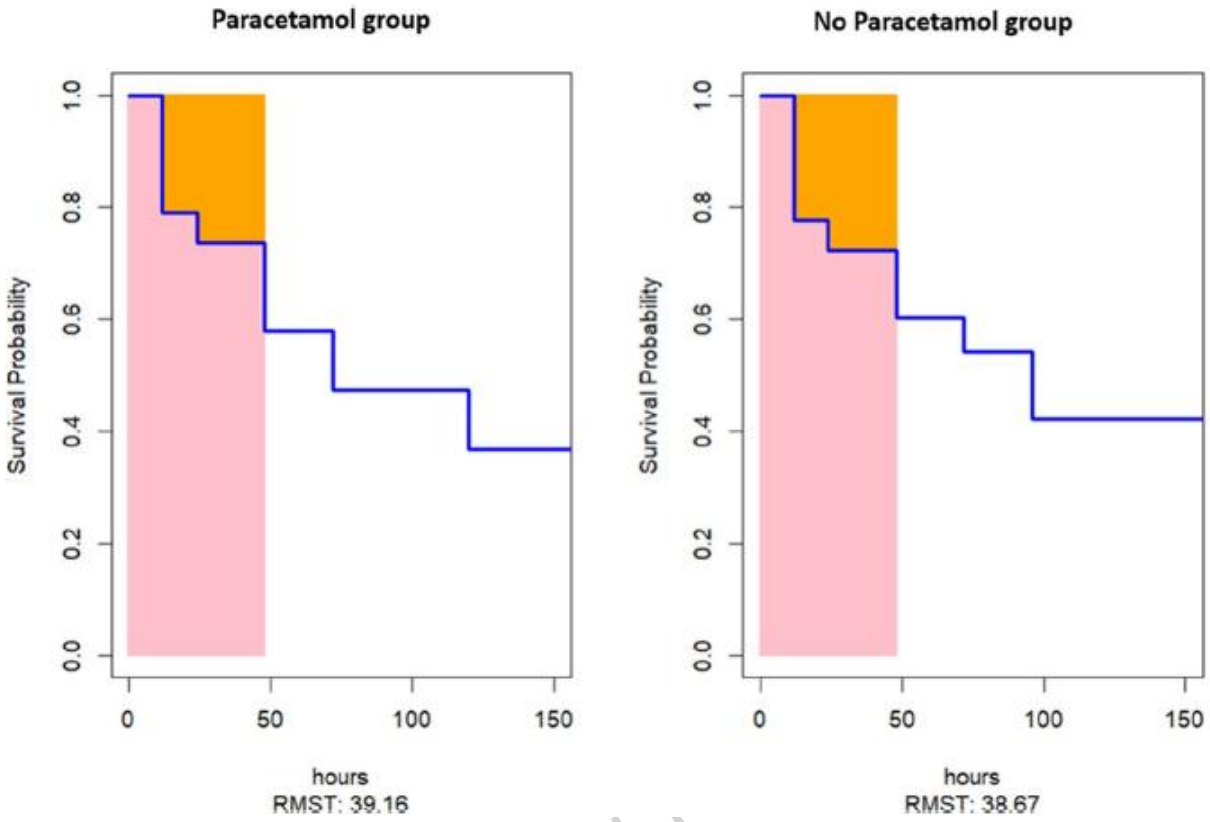
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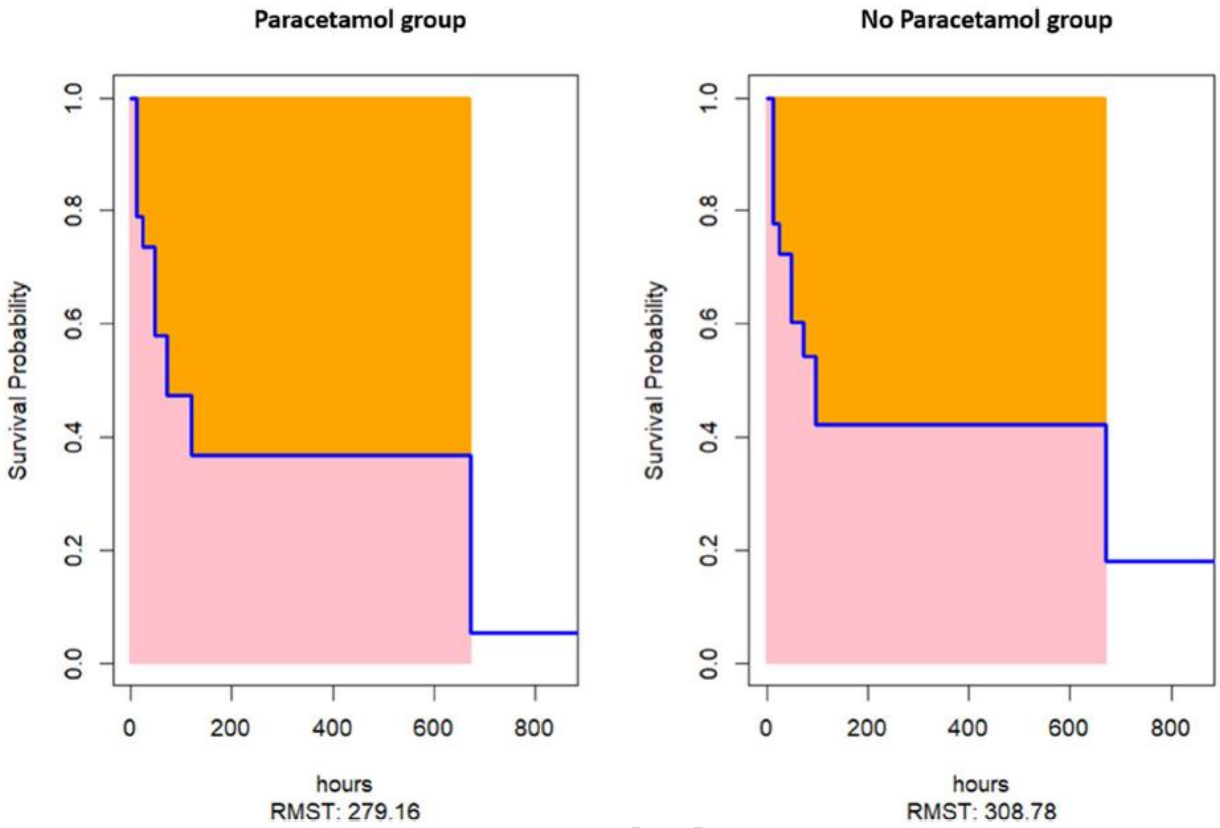
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