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## ORIGINAL RESEARCH ARTICLES

### Buccal, intranasal or intravenous lorazepam for the treatment of acute convulsions in children in Malawi: An open randomized trial



#### *Le lorazépam par voie orale, intranasale ou intraveineuse pour le traitement des convulsions aiguës chez l'enfant au Malawi: étude ouverte randomisée*

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**Introduction:** Acute convulsions in children are a common emergency worldwide. Benzodiazepines are the recommended first line treatment. Intravenous lorazepam is inexpensive, long acting and the first line drug in resource-rich settings. However, comparable efficacy by other routes of administration is unknown. We wished to compare the efficacy of lorazepam by the buccal, intranasal or intravenous route in the treatment of acute seizures in Malawian children.

**Methods:** A prospective, open-label, randomised, non-inferiority trial was performed in children aged 2 months to 14 years presenting to the Queen Elizabeth Central Hospital in Blantyre, Malawi with acute seizures lasting longer than 5 min. Children were randomly assigned to receive lorazepam, 0.1 mg/kg, by the buccal, intranasal or intravenous route. The primary endpoint was seizure cessation within 10 min of drug administration.

**Results:** There were 761 seizures analysed, with 252 patients in the buccal, 245 in the intranasal and 264 in the intravenous groups. Intravenous lorazepam stopped seizures within 10 min in 83%, intranasal lorazepam in 57% (RR 2.46, CI 1.82–3.34), and the buccal route in 46% (RR 3.14, CI 2.35–4.20;  $p = 0.001$ ) of children. There were no significant cardio-respiratory events and no difference in mortality or neurological deficits. The study was halted after an interim analysis showed that the primary endpoint had exceeded the protocol-stopping rule.

**Conclusions:** Intravenous lorazepam effectively treats most childhood seizures in this setting. Intranasal and buccal routes are less effective but may be useful in pre-hospital care or when intravenous access cannot be obtained. Further studies comparing intranasal lorazepam to other benzodiazepines, or alternative doses by a non-intravenous route are warranted.

**Introduction:** dans le monde entier, les convulsions aiguës constituent une urgence fréquente. Il est recommandé d'utiliser des benzodiazépines en traitement de première intention. Le lorazépam administré par voie intraveineuse est peu coûteux, a une action prolongée, et constitue le traitement de première intention dans les régions riches en ressources. L'efficacité comparable de ce traitement par d'autres voies d'administration est cependant inconnue. Nous souhaitons comparer l'efficacité du lorazépam par voie orale, intranasale ou intraveineuse dans le traitement des attaques aiguës chez les enfants au Malawi.

**Méthodes:** Une étude prospective, ouverte, randomisée et de non infériorité a été réalisée sur des enfants âgés de deux mois à 14 ans se présentant à l'hôpital central Queen Elizabeth à Blantyre, au Malawi, souffrant d'attaques aiguës de plus de cinq minutes. Les enfants étaient répartis de manière aléatoire pour se voir administrer 0.1 mg/kg de lorazépam par voie orale, intranasale ou intraveineuse. Le point final primaire était l'interruption de l'attaque dans les 10 min suivant l'administration du médicament.

**Résultats:** 761 attaques ont été analysées, dont 252 patients dans le groupe d'administration par voie orale, 245 dans le groupe d'administration par voie intranasale et 264 dans le groupe d'administration par voie intraveineuse. Le lorazépam administré par voie intraveineuse arrêtait les attaques dans les 10 min dans 83% des cas, le lorazépam administré par voie intranasale dans 57% des cas (RR 2,46, IC 1,82–3,34), et le lorazépam administré par voie orale dans 46% des cas (RR 3,14, IC 2,35–4,20;  $p = 0,001$ ). Aucun événement cardio-respiratoire significatif n'a été enregistré, et aucune différence n'a été rapportée dans les taux de mortalité ou déficits neurologiques. L'étude a été interrompue après qu'une analyse intérimaire a indiqué que le point final primaire avait dépassé la règle d'interruption du protocole.

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**Conclusions:** Le lorazépam administré par voie intraveineuse traite efficacement la plupart des attaques dont les enfants sont victimes dans cet environnement. Les voies intranasale et orale sont moins efficaces mais peuvent s'avérer utiles dans les soins préhospitaliers ou lorsqu'un accès par voie intraveineuse est impossible. Des études supplémentaires comparant le lorazépam intranasal à d'autres benzodiazépines, ou à d'autres doses par voie intraveineuse, sont recommandées.

## African relevance

- Control of seizures is highly relevant to African paediatric emergency care.
- The cost and ease of delivery of medications is important in resource restricted health care settings.

## Introduction

Acute convulsions are a common medical emergency in children worldwide.<sup>1,2</sup> Rapid and effective treatment is essential; the longer a convulsion lasts the more difficult it is to terminate.<sup>3-6</sup> Prolonged convulsions (> 30 min) are associated with significant morbidity and mortality.<sup>7-9</sup> Access to emergency care in resource-constrained countries is uneven and patients often present late: health centres may have only basic facilities.<sup>10</sup> An effective, safe, inexpensive, long acting and easy to administer anti-convulsant is required.

Benzodiazepines are effective first line anti-convulsants. Therapeutic options include diazepam, lorazepam or midazolam, which have different pharmacokinetic properties. Historically, diazepam has been used; it is widely available, inexpensive and acts rapidly but it is short acting, breakthrough seizures are common and can cause respiratory depression.<sup>11-14</sup>

Midazolam can be given by buccal, intranasal and intramuscular routes. Buccal midazolam is as effective as rectal diazepam<sup>7,15-18</sup> but it is short acting<sup>19</sup> and consequently associated with seizure recurrence.<sup>16,20</sup>

Lorazepam is inexpensive,<sup>21</sup> long acting (up to 72 h)<sup>22</sup> and has less risk of seizure recurrence.<sup>23</sup> Refrigerated lorazepam has a shelf life of 3 years.<sup>21</sup> Stored at 15–30 °C, it retains 90% of its original concentration for 150 days.<sup>24,25</sup> At > 30 °C, stocks have to be replenished every 30–60 days. It can be given intravenously (IV), intramuscularly (IM), buccally or intranasally (IN). Intravenous lorazepam (100 µg/kg) is recommended as first line treatment of acute childhood seizures in resource-rich settings when IV access is available.<sup>26-29</sup> However, IV access can be problematic. Intranasal lorazepam (100 µg/kg) was effective and safe in treating children with protracted convulsions in Malawi<sup>30</sup>; it is well absorbed, with rapid action and comparable elimination profiles to IM and IV routes.<sup>31</sup> A 2 mg dose achieves concentrations above therapeutic levels in adults.<sup>32</sup> Sublingual/oral lorazepam is absorbed more slowly but has successfully controlled seizures in children.<sup>33</sup>

We compared the efficacy of lorazepam when given by the buccal, intranasal or intravenous route in the treatment of acute seizures in Malawian children.

## Methods

This was an open-label, randomised, non-inferiority trial with the hypothesis that buccal and/or IN lorazepam were non-inferior in efficacy to IV lorazepam. The study was carried

out at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi, a tertiary government hospital for southern Malawi and district hospital for Blantyre district. The paediatric emergency centre (EC) reviews 80–90,000 children annually of whom 25,000 are admitted. During the rainy season the number of admissions is high with mainly infectious diseases such as malaria, gastroenteritis and pneumonia. Children are stabilised in the EC. Acutely ill children are admitted to high dependency areas in the acute care wards. Seizures are managed in all these sites. Children (2 months to 14 years) with acute generalised seizures  $\geq 5$  min were eligible for inclusion. Seizures were defined as rhythmic twitching of the arms, legs, trunk or facial muscles, tonic eye deviation, or nystagmoid eye jerking in a comatose child. Patients were eligible for re-recruitment if they had further seizures and had not received anti-convulsants within the previous hour.

Convulsing children were managed according to Advanced Paediatric Life Support guidelines (except that in Malawi IM rather than rectal paraldehyde is used) and hypoglycaemia was corrected.<sup>28</sup> Continuing seizures received one of the following: 100 µg/kg of lorazepam (Ativan, Wyeth-Ayerst, Philadelphia, USA) by slow IV injection followed by a 0.9% 2 ml saline flush, rapid intranasal delivery using a mucosal atomisation device (MAD 100, wolfetory.com) closely applied to one nostril and angled upwards with the child's head in the recovery position, or a buccal solution injected directly from a 1 ml syringe between the lower gum and cheek that was then massaged. The IV solution of lorazepam was used for all routes.

If seizures continued at 10 min, a second similar dose by the same route was given. Seizures lasting  $\geq 20$  min was managed according to local guidelines; usually IM paraldehyde (0.2 ml/kg) followed by IV phenobarbitone (10 mg/kg) then by a loading dose of IV phenytoin (18 mg/kg) as necessary, in 10-min intervals.

Consent was given in accordance with the Code of Federal Regulations (Title 21) for clinical research in emergency settings.<sup>34</sup> Convulsing children were randomised and treated and guardians were kept informed throughout. Once the child was stable and all seizures had ceased, formal consent was sought. If consent was refused no further information was collected.

The College of Medicine Ethics Committee approved the study (COMREC P03/07/499) and it was registered with Clinical Trials.gov (NCT0343096).

The primary endpoint was the number of seizures that stopped (cessation of all visible seizure activity) within ( $\leq$ ) 10 min of receiving lorazepam.<sup>28</sup> Secondary outcomes were frequency of side effects, need for additional drugs to terminate the seizure, seizure recurrence within 24 h, length of seizure, time from drug administration to seizure cessation, and outcome at discharge. Clinically significant adverse events were reported.

All clinical staff were trained six-monthly in the study protocol. Weight-dosing charts were available in every clinical area.

We anticipated that lorazepam by any route would halt seizures within 10 min in 75% of children.<sup>30</sup> Sample size calculations assumed this rate and a –10% non-inferiority limit. Thus, 293 patients were required in each group to have 80% power to accept non-inferiority using a significance level of 2.5%.

The predefined stopping criterion was an absolute difference of 30% in the number of seizures controlled within 10 min between the groups. Interim analyses were carried out after 100 and 400 recruitments, and then a year later, after which the study was stopped.

Pre-study computer-generated randomisation was in blocks of 10 within two strata – ‘IV access’ already established or ‘no IV access’. Treatment allocations were sealed in identical envelopes marked with consecutive study numbers.

Investigators were masked to treatment allocation prior to opening an envelope. Inpatients who already had IV access were randomised to receive intravenous, intranasal or buccal lorazepam in a 1:1:1 ratio. Children without IV access were randomised to receive intravenous, intranasal or buccal in a 3:1:1 ratio to allow for failure to achieve IV access. If a child was randomised to IV lorazepam, attempts to gain IV access were for a maximum of 2 min. To prevent treatment delay should access fail, children were randomised within a second stratum to receive intranasal or buccal lorazepam in a 1:1 ratio.

Intention to treat and per-protocol statistical analyses were done using STATA 9.0. Baseline characteristics were compared by one-way ANOVA or Wilcoxon tests. Categorical variables were compared by Pearson Chi-square or Fisher’s exact tests. The Binomial regression model was used to obtain risk ratios and 95% confidence intervals. Analyses were considered significant at the  $\alpha$ -level of 0.05, decided *a priori*. When multiple testing was involved, the Bonferroni correction was used.

Analyses were in pre-specified subgroups: those with malaria parasitaemia, cerebral malaria (malaria parasitaemia and Blantyre Coma Score  $\leq 2$ ), meningitis (cerebrospinal fluid or clinical diagnosis) and fever ( $> 38^\circ\text{C}$ , with or without malaria).

Children were observed until clinically stable. Oxygen and bag-mask ventilation was given if there were noticeable changes in colour, respiratory effort, or airway compromise. All patients had axillary temperature measurement, blood test for malaria, blood glucose level, and a full clinical assessment with further investigations as appropriate. Demographic information included past history and estimated seizure duration prior to hospital arrival.

## Results

Recruitment was from June 2006 to January 2009 and stopped when an interim analysis showed a difference in primary endpoint of  $> 30\%$  between the groups.

Figs. 1a and 1b show patient stratification by intravenous access prior to randomisation.

There were 454 seizures randomised in children without intravenous access and 434 episodes in children with pre-existing intravenous access. Overall 888 seizures were randomised in 733 patients: 88 patients stopped convulsing without treatment and were excluded from analysis. In 41 patients lorazepam was given by a route to which they were not randomised; 20 in the buccal, 17 in the intranasal and four in the intravenous group. Analyses were by intention to treat and per protocol. Thirty-seven patients were lost to follow

up or had incomplete data. The primary analysis included 761 seizure episodes; 252 in the buccal, 245 in the intranasal and 264 in the intravenous group. Of these, 606 patients were recruited once and 69 were recruited two to four times. Recruits were shared equally between the treatment groups. They were randomised as new cases. Follow-up was until discharge or death.

Baseline characteristics are shown in Table 1. Seizures were due to cerebral malaria or meningitis in 113/252 (45%) in the buccal group, 95/245 (39%) in the intranasal group and 127/264 (48%) in the intravenous group. Time from start of seizure to drug administration was similar in all groups.

Outcomes are shown in Table 2. Seizures stopped within 10 min of receiving lorazepam in 115/252 (46%) of the buccal, 139/245 (57%) of the intranasal, and 218/264 (83%) of the intravenous group ( $p \leq 0.01$ ).

Similar outcomes were seen with protocol analyses. In the buccal group, 130 (50%) seizures required a second dose of lorazepam and a further 80 (30%) required additional drugs to terminate the seizure. In the intranasal group, 99 (40%) seizures required a second lorazepam dose and 56 (20%) required additional drugs. In the intravenous group 46 (17.5%) seizures required a second lorazepam dose and 23 (9%) required additional drugs. Meningitis, history of seizures and prior neurological deficit predicted the need for a second dose of lorazepam (Table 3).

A planned, secondary analysis of the remaining 129 episodes without these children and adjusted for age, weight, and gender, showed no difference in the primary outcome (presenting seizure stopped within 10 min). There was no significant difference in seizure recurrence at 24 h between the groups.

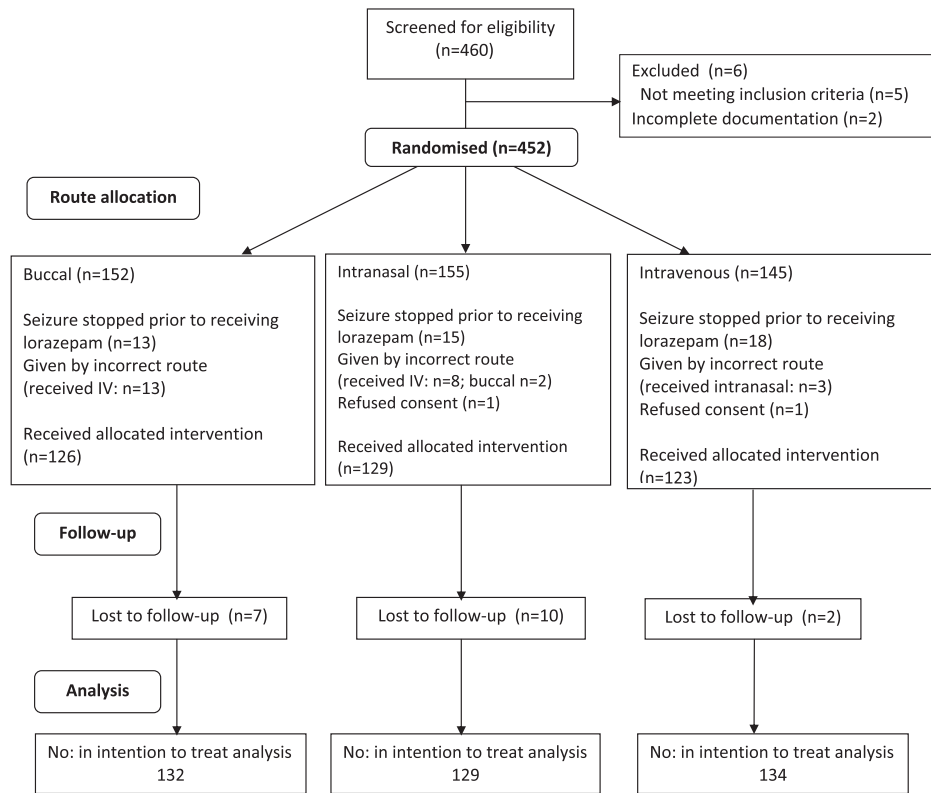
Median seizure duration was longer in the buccal and intranasal groups (buccal: median 20, min IQR 15–35, intranasal: median 19, min IQR 10–31) than in the intravenous group (median 12, min IQR 8–20) (Fig. 2), though time from seizure identification to drug administration was similar for all groups.

No child was reported to require bag-mask ventilation after lorazepam administration.

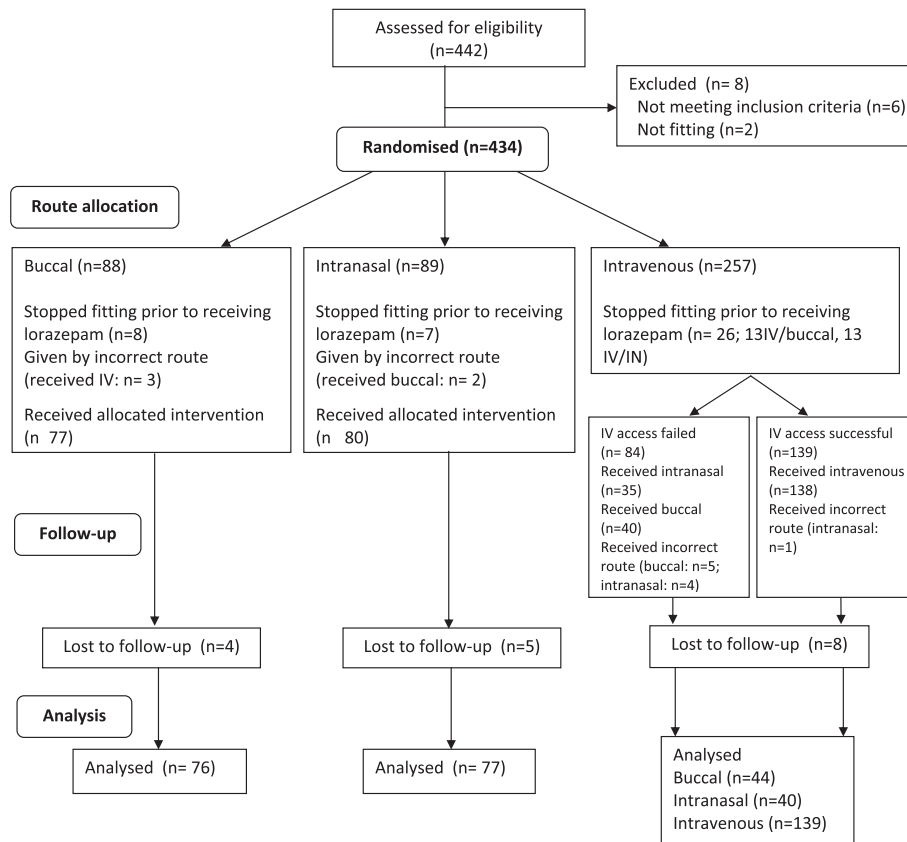
On discharge, 10.6% ( $n = 78$ ) of survivors had neurological deficits (10 were pre-existing) with no difference between the treatment groups; there was no difference in mortality (Table 2,  $p = 0.6$ ). Mean total seizure duration was similar for children who died or had neurological deficit and the general cohort.

In children with protracted febrile seizures (fever  $\geq 38^\circ\text{C}$  without cerebral malaria or meningitis), buccal lorazepam was as effective as intranasal lorazepam (41/69; 60% vs. 40/66; 60%). Both routes were less effective than intravenous, which stopped seizures in 10 min in 83% (52/63) of children ( $p \leq 0.01$ ). In children with malaria parasitaemia (including cerebral malaria), buccal lorazepam was as effective as intranasal lorazepam (65/125; 52% vs. 63/104; 60%  $p = 0.24$ ), however both these routes were less effective than intravenous lorazepam (110/128; 86%). There was no difference in mean length of hospital stay among the three groups (4.1–4.5 days).

There were 392 patients with existing intravenous access. They were more likely to have previously known idiopathic epilepsy (11% vs. 18.2%;  $p < 0.01$ ), previous neurological deficit (7.6% vs. 3.3%;  $p = 0.01$ ), or meningitis (19.7% vs. 12.8%;  $p = 0.01$ ). They had more prolonged pre-treatment seizures [50 min (5–170) vs. 10 min (3–85)  $p < 0.01$ ]. There



**Figure 1a** Flowchart of participants with existing intravenous access  $n =$  seizure episode.



**Figure 1b** Flowchart of participants with no existing intravenous access  $n =$  seizure episode.

**Table 1** Baseline characteristics of trial participants.

	Buccal	Intranasal	Intravenous
Total	252	245	264
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
<i>Demographic characteristics</i>			
Age (months, median IQR)	22 (10.0–38.0)	24 (11.0–38.0)	26 (12.0–41.0)
Sex male	123 (49)	141 (57.5)	142 (54)
Sex female	125 (50)	101 (41)	119 (45)
Weight (kilograms, median IQR)	9.8 (7.4–12.0)	10 (8.0–12.2)	10.4 (8.0–12.1)
HIV positive	31 (12)	23 (9)	23 (9)
HIV status not known	148 (59)	165 (67)	183 (69)
Malaria parasite screen positive	125 (50)	104 (42)	128 (48)
Fever at presentation ( $\geq 38$ °C)	122 (48)	104 (42)	129 (49)
Seizure duration before treatment (minutes, median IQR)	10.0 (7.0–40.0)	10.0 (6.0–62.0)	15.0 (6.0–128.5)
Time from seizure identification to drug administration (minutes, median IQR)	6.0 (5.0–10.0)	6.5 (5.0–10.0)	5.5 (5.0–10.0)
<i>Underlying diagnosis</i>			
Previously known idiopathic epilepsy	30 (12)	34 (14)	45 (17)
Previously known neurological abnormality	12 (5)	12 (5)	17 (6.5)
Febrile seizure §	69 (27)	66 (27)	73 (28)
Malaria $\Delta$	125 (50)	104 (42)	128 (48.5)
Cerebral malaria $\gamma$	64 (25)	59 (24)	90 (34)
Acute bacterial meningitis $\beta$	49 (19)	36 (15)	37 (14)
Head injury	0 (0)	4 (2)	4 (1.5)
Ingestion local traditional medicine	5 (2)	14 (6)	8 (3)

Note: §, Patients who were febrile  $\geq 38$  °C at time of seizure but did not have cerebral malaria or bacterial meningitis;  $\Delta$ , Malaria parasitemia on thick blood film;  $\gamma$ , Positive malaria blood slide, persistent Blantyre Coma Scale < 2;  $\beta$ , CSF suggestive of meningitis, with or without positive culture. Clinical diagnosis *n* = 5, too unwell for lumbar puncture.

**Table 2** Primary and secondary outcome measures analysed by intention to treat analysis.

Outcome measure	Buccal	Intranasal	Intravenous	<i>P</i> value
	<i>n</i> = 252	<i>n</i> = 245	<i>n</i> = 264	
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Presenting seizure stopped within 10 min	115 (46)	139 (57)	218 (83)	< 0.01
Risk ratio (95% CI)	3.14 (2.4–4.2)	2.46 (1.8–3.3)	1.0	
Seizure receiving a second dose of lorazepam	130 (51.5)	99 (40)	46 (17)	< 0.01
Seizure requiring phenobarbitone, paraldehyde, or phenytoin	80 (32)	56 (23)	23 (9)	< 0.01
Seizure recurrence within 24 h	48 (19)	62 (25)	47 (18)	0.09
Time from seizure identification to seizure cessation (minutes) median IQR	20 IQR 13–35	19 IQR 10–31	12 IQR 8–20	< 0.01
Time from drug administration to seizure cessation (minutes) median IQR	12 IQR 5–25	10 IQR 5–20	5 IQR 2–9	< 0.01
Died	39 (15.5)	46 (19)	47 (18)	0.6
Neurological deficit	20 (8)	33 (13.5)	25 (9.5)	0.1

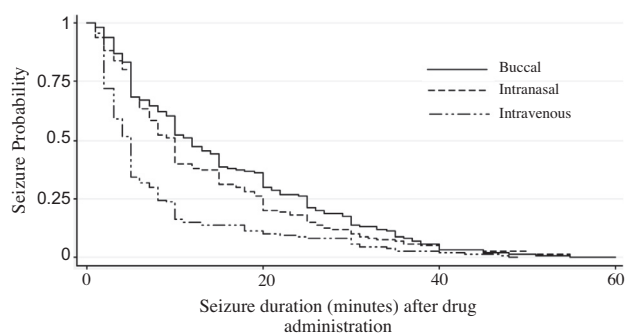
Note: *n* seizure episodes; CI confidence interval; IQR interquartile range.

**Table 3** Patient characteristics associated with requiring a second dose of lorazepam to terminate seizure activity.

Characteristic	Second dose of lorazepam		Odds ratio (95% CI)
	Yes	No	
	<i>n</i> (%)	<i>n</i> (%)	
History of epilepsy/seizures	59 (54)	50 (46)	1.81 (1.18–2.79)
History of neurological complications	25 (61)	16 (39)	2.30 (1.15–4.68)
History of meningitis	64 (52)	59 (48)	1.68 (1.11–2.52)

was no difference in time from identification to cessation of seizure when stratified by the presence of existing intravenous access.

In those without pre-treatment IV access and randomised to receive IV lorazepam, the probability of obtaining access was 0.81.



**Figure 2** Kaplan Meir curves representing seizure duration following lorazepam (excluding those who continued to seize for > 1 h after administration of lorazepam ( $n = 30$ )).

## Discussion

The study was stopped early as there was a larger than anticipated difference between the groups, with IV lorazepam successfully terminating 83% of seizures, and IN and buccal terminating 57% and 46%, respectively. We had predicted seizure termination with IV lorazepam as 60–90%<sup>14,35–38</sup> and with IN as 75%.<sup>30</sup> Although prior experience with buccal lorazepam is limited, clinical<sup>33</sup> and pharmacokinetic studies<sup>39</sup> suggest it would be efficacious. However, non-inferiority was not proven in this study.

The IN dose (100 µg/kg) was based on a previous study in a comparable population with the same primary outcome,<sup>30</sup> and pharmacokinetic data from adults.<sup>31</sup> We decided not to increase the dose due to the risk of respiratory depression and confusion between the study arms with different dosing. The efficacy of IN lorazepam was comparable to that of buccal midazolam<sup>16,17</sup> and could be a useful drug route for pre-hospital use or when IV access is difficult.

Buccal and intranasal lorazepam were equally effective for protracted febrile seizures and malaria. By 20 min, buccal lorazepam had stopped 60% of seizures and remained effective over 24 h. Oral or sublingual lorazepam are more slowly absorbed than IV but they are completely absorbed<sup>39</sup> and pharmacokinetically efficacious. In a small paediatric study, sublingual lorazepam ( $n = 10$ ) doses of 0.05–0.15 mg/kg controlled serial seizures.<sup>33</sup> We opted to give 100 µg/kg buccally for safety concerns. This may have been insufficient (compared to IV and IN) because of slower absorption and possible loss by drooling.

Additional drugs were needed to terminate seizures in 30% of the buccal, 20% of the IN and 9% of the IV groups. The IV results are comparable to other studies.<sup>35</sup> Meningitis, neurological deficit, and known idiopathic epilepsy predicted the need for a second dose of lorazepam. Seizures were longer in the buccal and intranasal groups. Intravenous drug delivery was not delayed as 80% of access attempts were successful. This supports the use of IV lorazepam as first line treatment in most settings. We had been concerned that children with existing IV access would be different (sicker), and randomised them separately. However, there was no difference in time taken to stop seizures in this group. Seizure duration was difficult to record accurately for many children from the community/local health centres.

Despite longer seizures in the buccal and IN groups, there was no increase in neurological sequelae or death.

Sequelae were diagnosed clinically and subtle deficits may have been overlooked. The incidence of neurological deficit and death (in this setting) is comparable to that of other studies.<sup>16,30</sup>

No child required assisted ventilation. In a previous study in this setting, IN lorazepam caused a temporary drop in oxygen saturations in 2/80 children and none required additional support.<sup>30</sup> Ventilation is more commonly necessitated by prolonged seizure and underlying diagnosis than by benzodiazepine associated respiratory compromise.<sup>35,40</sup>

Though additional lorazepam doses were required to control seizures in the buccal and intranasal groups there was no difference in 24-h seizure recurrence. Buccal midazolam is associated with 40% recurrence in a similar setting,<sup>16</sup> although reports suggest that the intramuscular route may reduce breakthrough seizures.<sup>35</sup>

Subgroup analysis showed that in malaria-induced seizures, buccal lorazepam was as efficacious as IN lorazepam. Around half the children had malaria, and a quarter had cerebral malaria. Cerebral malaria causes seizures in 15–50% of children in sub-Saharan Africa<sup>2,30</sup> and benzodiazepines are variably effective.<sup>16,41</sup> Lorazepam was equally effective in treating seizures with or without malaria and could be a drug of choice.

The efficacy of intravenous lorazepam has been established in several trials.<sup>14,37,38</sup> Our buccal and intranasal doses were based on previous studies,<sup>30,33</sup> and may have been too low. There were some unexplained protocol violations and bias may have occurred by re-recruiting patients who re-seized, though analysis without these patients showed no difference.

## Conclusion

Intranasal and buccal lorazepam are less effective than IV lorazepam as first line treatment for acute seizures but may be useful in children without or with difficult IV access. Studies comparing the use and dose of lorazepam with other anticonvulsants when IV access is difficult are important.

## Author contribution

S.L. coordinated data collection, analysed data and drafted the manuscript. J.K. and E.M.M. conceived and designed the study, obtained ethical approval, supervised data collection and revised the manuscript. O.J. set up the study, carried out interim analysis and data collection. T.W., G.C. and A.M. collected data. Dr. L.K. analysed the data. All authors approved the final manuscript.

## Conflicts of interest

The authors declare no conflict of interest.

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