Efficacy of Sublingual Lorazepam Versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa

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Abstract

In Sub-Saharan Africa, intrarectal diazepam is the first-line anticonvulsant mostly used in children. We aimed to assess this standard care against sublingual lorazepam, a medication potentially as effective and safe, but easier to administer. A randomized controlled trial was conducted in the pediatric emergency departments of 9 hospitals. A total of 436 children aged 5 months to 10 years with convulsions persisting for more than 5 minutes were assigned to receive intrarectal diazepam (0.5 mg/kg, n = 202) or sublingual lorazepam (0.1 mg/kg, n = 234). Sublingual lorazepam stopped seizures within 10 minutes of administration in 56% of children compared with intrarectal diazepam in 79% (P < .001). The probability of treatment failure is higher in case of sublingual lorazepam use (OR = 2.95, 95% CI = 1.91-4.55). Sublingual lorazepam is less efficacious in stopping pediatric seizures than intrarectal diazepam, and intrarectal diazepam should thus be preferred as a first-line medication in this setting.

Keywords

convulsions, children, emergency treatment, Africa, Sublingual Lorazepam

Seizures are responsible for more than 15% of visits to pediatric emergency departments in Sub-Saharan Africa.¹⁻³ In this part of the world, seizures tend to last longer because of the difficulties of access to health facilities and the lack of appropriate treatment.⁴⁻⁷ This is of importance as it has been shown that the longer a seizure lasts, the less likely it will end spontaneously and even respond to antiepileptic drugs. Furthermore, prolonged seizures are also responsible for brain lesions and neurologic sequelae. It is therefore mandatory to achieve early intervention to avoid brain damage and reduce morbidity.⁸⁻⁹

Diazepam is the first-line medication most commonly used to treat seizures in Sub-Saharan Africa. Furthermore, in some countries (such as the Democratic Republic of Congo), there is no alternative to diazepam.⁶ However, the use of intrarectal diazepam raises some difficulties: ready-to-use intrarectal preparations are not always available⁷ and thus preparation of the solution can delay treatment. The social acceptability of the use of the intrarectal route is also low, especially for older children. The psychological stress of the convulsion could increase the risk of dosing error when the solution is prepared and administered by parents.¹⁰

Sublingually administered lorazepam has shown efficacy in the management of serial seizures in children¹⁰,¹¹ and may have some advantages. It can be easily and quickly administered by parents during the prehospital phase, even to a confused or combative child in public (eg, a school or bus), where intrarectal administration may be difficult. The potential for error is minimized by the fixed dose nature of the tablet. The dissolution of sublingual tablet is rapid (within 20 seconds), with a negligible

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risk of aspiration. Although this study was conducted on a very small sample (10 patients) and was not randomized, the use of buccal lorazepam is assuming a growing role in the prehospital treatment of seizures in some developed countries. This practice does not appear to have been preceded by any large randomized study.

Our study aimed therefore to address the efficacy of sublingual or buccal lorazepam when compared with intrarectal diazepam in a large randomized trial. Our objective was to examine if lorazepam could find a role as a valuable prehospital alternative for management of epileptic seizures in children in Sub-Saharan Africa.

Population and Methods
This study was a randomized, controlled, single-masked trial. It aimed to compare the efficacy of sublingual lorazepam against intrarectal diazepam in children with convulsions lasting more than 5 minutes admitted through the emergency departments.

Population and Study Sites
Patients included in our study were children aged from 5 months to 10 years admitted for seizures lasting more than 5 minutes between January 1, 2011, and August 15, 2012. Seizures were clinically categorized on the basis of the commonly used characteristics of seizures, that is, distribution, duration, and level of consciousness impairment. A diagnosis of status epilepticus was considered when seizures lasted for more than 30 minutes or repeated two times or more without any recovery. Those who recovered a normal level of consciousness between two seizures were classified as having serial seizures.

Four hospitals were selected to participate in the study in Kinshasa in the Democratic Republic of Congo (Kingsansi, Lisungi, “Fondation Pédiatrique,” and Makala) and 5 in the Southern Province of the Republic of Rwanda, the Butare University Teaching Hospital and 4 district hospitals (Gakoma, Kabutare, Nyanza, and Kibilizi).

Study Design
A 2-month preliminary feasibility trial was conducted at the University Pediatric Service of the University of Liege with the agreement of the Liège Regional Hospital Ethics Committee (no. 1093). This approval has been confirmed by the ethics committees of the National University of Rwanda (no. 006) and the School of Public Health of the University of Kinshasa (no. 055). Because of the need for an immediate intervention in children with convulsions, informed consent was obtained from the parents after clinical stabilization and subsequent detailed explanation of the study protocol and aims. The study was conducted according to the principles of the Helsinki Declaration.

Randomization was made by assignment to 1 of the 2 study medications on an alternate-day basis. Patients received intrarectal diazepam on even days of the month and sublingual lorazepam on odd days.

The intrarectal diazepam (Valium, Roche, France) was administered at a dose of 0.5 mg/kg of body weight of a 1 mg/mL reconstituted solution (Figure 1). Body weight was estimated by using the child’s age. Thus, 2.5 mg of diazepam was given to children between 5 and 11 months old, 5 mg between 1 and 4 years, 7.5 mg between 5 and 9 years, and 10 mg for 10-year-old children. The duration of administration of diazepam did not exceed 60 seconds. Early expulsion of the medication within 10 minutes after administration was an exclusion criterion. The sublingual lorazepam (Temesta, Expidet, Pfizer, Germany) was administered at a dose of 0.1 mg/kg of body weight. A 1 mg tablet was administered to children between 6 and 36 months old and 2.5 mg for those older than 4 years. Depending on the patient’s condition, the tablet was placed under the tongue or between the cheek and gum.

The end of a seizure was determined by cessation of any visible convulsive activity. Treatment was regarded as effective if one dose of the assigned treatment stopped the presenting seizure within 10 minutes of administration (primary endpoint). If seizures continued beyond 10 minutes, the treatment was considered ineffective and a rescue regimen including a second benzodiazepine administration and eventually intravenous phenobarbital was applied (Figure 1). It should be noted that the second dose of benzodiazepine was administered 10 minutes after the first, and was of the same drug and by the same route as the first administration (Figure 1).

The study also took into account as secondary endpoints the proportion of patients with seizure cessation within 10 minutes after the second dose of anticonvulsant (ie, 20 minutes after the first dose), the seizure recurrence rate at 24 hours, and the 24-hour mortality rate in each group.

Investigations
Oxygen saturation and blood pressure were monitored from the arrival up to 20 minutes. This monitoring was extended to 40 minutes in children needing two doses of benzodiazepine. Oxygen was provided via facial mask in case of oxygen saturation below 93%. Every child underwent thick smears for malaria detection and measurement of blood glucose. Cerebrospinal fluid examination was performed in cases of suspected central nervous system infection.

Sample Size and Statistical Methods
The expected seizure response rate to diazepam or lorazepam was known neither in Rwanda nor in the Democratic Republic of Congo. A minimum of 182 patients in each group was estimated as sufficient to detect a therapeutic efficacy difference of 30% between the two medications.

Data were recorded on forms designed using Epi-Data software and analyzed using SPSS 18.0 and Stata 11. We used the following summary statistics: Wilcoxon-Mann-Whitney test to compare medians, the Pearson $\chi^2$ test to compare proportions and determine the association between categorical variables, univariate analysis, and a binary logistic regression to determine the factors influencing the therapeutic failure after the administration of anticonvulsants. The significance threshold was set at $P = .05$.

Results
Population and Seizure Characteristics
Five hundred twenty-five children—308 from the Democratic Republic of Congo hospitals and 217 from Rwanda—were initially screened for this study. After taking into account exclusion criteria (administration of antiepileptic drug prior to admission, seizure duration shorter than 5 minutes, or expulsion of diazepam within 10 minutes), we ended up with 436 patients (258 in the Democratic Republic of Congo and 178 in Rwanda). According to the randomization protocol, 234
Figure 1. Study treatment algorithm.

1. Airway position, high-flow oxygen if necessary, check glucose
2. Screen for eligibility
3. Randomisation = Even/Odd days
4. Reconstituted solution: 2 mL (10 mg of diazepam) + 8 mL of physiological saline → 1 mL of solution = 1 mg of diazepam
   - Intrarectal Diazepam 0.5 mg/kg
   - Sublingual Lorazepam 0.1 mg/kg
5. If child still fitting 10 minutes after first dose of the assigned medication
6. Second dose of intrarectal Diazepam 0.5 mg/kg
   - Second dose of Sublingual Lorazepam 0.1 mg/kg
7. If child still fitting 20 minutes after first dose of the assigned medication
8. Phenobarbitalone intravenous/intraosseous (15 mg/kg) as a second-line antiepileptic agent
9. If child still fitting at 30 minutes after first dose of the assigned medication
   - Transfer to intensive care unit
children were assigned to the lorazepam regimen and 202 to diazepam (Figure 2). There was no significant difference between the groups with regard to age and previous neurologic disturbances. A slight female predominance was seen in the diazepam group (Table 1).

There were not any significant differences in seizure type and etiology between the two groups. Most children exhibited generalized seizures. About 26% of children had status epilepticus and approximately 12% already had repetitive seizures prior to admission (Table 1). Seizures were associated with fever of 38°C or more in 65% cases in the diazepam group and in 62% in the lorazepam group. Fever was mostly due to an infectious disease. Cerebral malaria and meningitis seemed to be causal in 67% cases of the diazepam group and in 73% of the lorazepam group (Table 1).

**Outcome Features**

Efficacy of the treatment was assessed at 5, 10, and 20 minutes following the first medication administration. Seizure cessation was obtained within 5 minutes in 38% (77/202) cases of the diazepam group and in 28% (65/234) of the lorazepam group ($P = .022$). Cumulative evaluation after 10 minutes revealed seizure cessation in 79% (160/202) of the diazepam group and only 56% (131/234) of the lorazepam group ($P < .001$) (Figure 3). After 20 minutes, cumulative seizure resolution was respectively 91% (184/202) and 83% (194/234) in the groups. This showed a statistically significant difference in favor of diazepam ($P = .012$).

Relapse of seizures within the 24 hours was observed in 80 patients of 202 (39%) in the diazepam group and 85 among...
Table 1. Baseline Characteristics of Children With Seizures.

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Diazepam, n (%)</th>
<th>Lorazepam, n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>91 (45.0)</td>
<td>130 (55.6)</td>
<td>.029</td>
</tr>
<tr>
<td>Female</td>
<td>111 (55.0)</td>
<td>104 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Age (months, median, IQR)</td>
<td>35.5 (17.75-54)</td>
<td>35.5 (19-60)</td>
<td>.523*a</td>
</tr>
<tr>
<td>Preexisting neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormality</td>
<td>11 (5.4)</td>
<td>20 (8.5)</td>
<td>.209</td>
</tr>
<tr>
<td>Convulsion semiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsions types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>160 (79.2)</td>
<td>183 (78.2)</td>
<td>.799</td>
</tr>
<tr>
<td>Focal</td>
<td>42 (20.8)</td>
<td>51 (21.8)</td>
<td></td>
</tr>
<tr>
<td>Status epileptic</td>
<td>47 (23.3)</td>
<td>68 (29.1)</td>
<td>.171</td>
</tr>
<tr>
<td>Serial convulsions</td>
<td>25 (12.4)</td>
<td>27 (11.5)</td>
<td>.788</td>
</tr>
<tr>
<td>Convulsions associated with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fever (T ≥38°C)</td>
<td>132 (65.3)</td>
<td>145 (62)</td>
<td>.470</td>
</tr>
<tr>
<td>Cause of convulsionsb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>119 (58.9)</td>
<td>154 (65.8)</td>
<td>.138</td>
</tr>
<tr>
<td>Epilepsy (idiopathic or not)</td>
<td>28 (13.9)</td>
<td>22 (9.4)</td>
<td>.145</td>
</tr>
<tr>
<td>Meningitis (bacterial or not)</td>
<td>17 (8.4)</td>
<td>17 (7.3)</td>
<td>.655</td>
</tr>
<tr>
<td>Others causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protracted febrile convulsions</td>
<td>33 (16.3)</td>
<td>36 (15.4)</td>
<td>.740</td>
</tr>
<tr>
<td>No specified</td>
<td>4 (2)</td>
<td>5 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
*aWilcoxon-Mann-Whitney test was used to compare median values.
*bFor patients with comorbidity, the diagnosis retained on the top of the list was considered.

234 (36%) in the lorazepam group (P = .481). About 6% of patients died within 24 hours in the diazepam group versus 3% in the lorazepam group (P = .133) (Table 2).

Treatment Failure Determinants

When considering the entire study population, a statistical relationship was found between status epilepticus on admission and further therapeutic failure (P < .001). Separate group analysis revealed a statistical association between presentation with status epilepticus or cerebral malaria and treatment failure (P < .001, P = .045, respectively) in the lorazepam group. There was a statistical association between presentation with meningitis and treatment failure (P = .03) in the diazepam group.

In order to predict short-term outcome, all seizure characteristics—focal, prolonged (status epilepticus), and repetition (serial)—as well as preexisting neurologic disorder, cerebral malaria, and meningitis were included in a logistic regression model. Two factors seemed to be predictive of a treatment failure: status epilepticus and the nature of the anticonvulsant administered. A child admitted for status epilepticus had two times more chance not to respond to the first dose of anticonvulsant drug (adjusted OR = 2.474, 95% CI = 1.594-3.841). The administration of sublingual lorazepam tripled the chance of treatment failure (OR = 2.948, 95% CI = 1.910-4.550).

Discussion

In this study, acute seizures in children were treated with two first-line anticonvulsants, intrarectal diazepam and sublingual lorazepam, according to their usually recommended mode of administration. Intrarectal diazepam seems to be more rapidly active than the sublingual lorazepam as it stops more seizures at the 5- and 10-minute intervals after administration. The difference between the two medications seems to diminish over time, possibly because of the natural history of seizures in children, in which most will ultimately spontaneously resolve. Preadmission circumstances play a critical role regarding the prognosis. Central nervous system infections such as meningitis seemed to play a deleterious role in the diazepam group. In any event, differences between the two medications exist in favor of diazepam when considering long-lasting seizures or the presence of status epilepticus.

Short-Term Efficacy and Primary Outcome

Although in many cases seizure activity will resolve spontaneously, cessation of the seizures remains the primary goal to achieve in emergency cases. This is required because of the increasing risk of evolution toward status epilepticus and secondary morbidity if seizures last longer.8,9 In this perspective, intrarectal diazepam seems to have a greater rate of efficacy than sublingual lorazepam (38% vs 28% after 5 minutes and 79% vs 56% at 10 minutes). With intrarectal diazepam, 50% of seizures could be stopped within 6.3 minutes versus almost 8.9 minutes for sublingual lorazepam. That means that...
despite a tricky mode of preparation and administration, a plasma concentration level adequate to control seizures is reached faster than with sublingual lorazepam.

Pharmacokinetics of lorazepam has been discussed in several studies comparing different routes of administration. Anderson et al.12 have suggested that buccal absorption of lorazepam could impair its efficacy. They have demonstrated that detection of lorazepam in plasma takes 2.6 and 0.6 minutes, respectively, when administered sublingually and intranasally. In their study, the mean peak levels achieved were 14 to 16 ng/mL.12 By comparison, plasma diazepam concentrations of 200 ng/mL can be reached within 10 minutes following intranasal administration.13 Molyneux et al.14 of the Malawi College of Medicine also found that buccal lorazepam was 30% less effective than intravenous administration, leading them to interrupt their study. Furthermore, Chamberlain et al.15 have shown that it is necessary to reach lorazepam plasma level of at least between 60 and 80 ng/mL in order to obtain effective seizure control. A lack of effective seizure control can occur if the level falls below a threshold of 40 ng/mL. Based on this recently reported pharmacokinetic profile of sublingual lorazepam,12 Srinivas16 suggested that intranasal and sublingual dosing needs to be at least 8 mg (independent of child weight) to achieve target levels for a meaningful clinical outcome. However, in a study by Arya et al.,17 the efficacy rate of intranasal lorazepam administered to children at a dose of 0.1 mg/kg was surprisingly high at 83%. This suggests that pharmacokinetic profile is not the only important factor to consider in analyzing sublingual lorazepam efficacy. Underlying diseases, seizure characteristics,18 and specific factors relevant to African children (eg, malaria, malnutrition, protein binding states) could be factors that play an important role in the low efficacy of sublingual lorazepam in our settings.

Table 2. Secondary Endpoints.

<table>
<thead>
<tr>
<th></th>
<th>Diazepam (n = 202)</th>
<th>Lorazepam (n = 234)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Seizure recurrence within 24 hours</td>
<td>80 (39.6%)</td>
<td>85 (36.3%)</td>
<td>.481</td>
</tr>
<tr>
<td>Dead within 24 hours</td>
<td>12 (6%)</td>
<td>7 (3%)</td>
<td>.133</td>
</tr>
</tbody>
</table>

When the two treatment groups are considered separately, status epilepticus was a significant predictor of treatment failure only in children treated with sublingual lorazepam, whereas meningitis appears as a predictor of treatment failure in the diazepam group (OR = 3.2, 95% CI = 1.1-8.9). These results suggest that the efficacy of intrarectal diazepam in convulsing children suffering from meningitis might need to be assessed in our settings through studies targeting this specific population.

Intermediary Outcomes

Twenty to 30 minutes after administration, both medications exhibited more similarity in their profile of activity, with at least some overlapping of confidence intervals (Figure 3). This is consistent with their respective pharmacokinetic features. Delayed activity of the sublingual lorazepam may be due to the slowness of its absorption. This has also been reported by Anderson et al.12 and Rey et al.,20 although plasma concentration levels were different depending on the route of administration. This is of some importance and may influence the decision to ultimately repeat administration of one or another medication. Based on its usual rapidity of absorption and action, repetition of intrarectal diazepam could be done quite early (as soon as 5-10 minutes after the first dose). For sublingual lorazepam, it would be necessary to wait a few more minutes before giving a second administration. An untested but theoretically superior alternative would be to switch to a more rapidly active medication such as intrarectal diazepam rather than to repeat lorazepam.

Long-Term Outcomes

Our study did not reveal a statistically significant difference between the two treatment groups as far as 24-hour seizure recurrence and 24-hour mortality were concerned (P = .48 and P = .13). Sublingual lorazepam thus seems to be as efficacious as intrarectal diazepam on these crude 24-hour outcome measures, although our study was not powered to assess mortality. Sublingual lorazepam is absorbed slowly compared to other administration routes (intravenous, intramuscular, and intranasal), but after the first 30 minutes, pharmacokinetic profiles are not different12,21 although it is possible to find differences in lorazepam serum concentrations after its administration by different routes in a single patient or when comparing individuals within the same study group placed in the same conditions.21 This seems to be confirmed by a recent report in which intravenous lorazepam was equally effective as intranasal lorazepam in the treatment of prolonged seizures.17

Intrarectal diazepam is reported to be rapidly absorbed and to produce high serum diazepam concentrations within 10 minutes in most children.13 However, the duration of action is shorter for diazepam (<2 hours) than for lorazepam (up to 72 hours) and does not correlate with the plasma concentration-time profiles of these drugs. The physicochemical properties of benzodiazepines (lipid solubility and protein binding) regulate their rate and extent of entry into the brain and cerebrospinal fluid. The
duration of the pharmacological activity of benzodiazepines may be to some extent related to the affinity of these compounds for the benzodiazepine receptors in the brain: lorazepam has higher affinities than diazepam. These advantages may help explain the delayed efficacy of sublingual lorazepam noted in this study.

Although the efficacy of sublingual lorazepam is delayed, thanks to its duration of action longer than for diazepam, the diazepam group has exactly the same outcome at 24 hours. This can be explained by the pharmacokinetic properties of diazepam. It has been shown that the metabolites of diazepam (N-desmethyldiazepam, the oxazepam, and temazepam) are pharmacologically active. The N-desmethyldiazepam can even accumulate in blood to concentrations 7-fold higher than diazepam and contribute significantly to the pharmacological effect of diazepam.

Study Limitations
Our study was not a double-blind randomized clinical trial. Double-blinding would have avoided a certain degree of potential bias because of the knowledge of administered drug by the nursing staff. Another weakness is that this study was not an intention-to-treat trial. In view of the need to depart from a rigid time-based protocol, patients who defecated within 10 minutes following the administration of intrarectal diazepam were excluded from the study. This approach has probably disadvantaged the buccal lorazepam, but the number of patients excluded for this reason was small. Some children who received sublingual lorazepam could have lost it in their saliva, preventing them from achieving adequate plasma concentrations and effective seizure control.

Conclusion
Sublingual lorazepam at a dose of 0.1 mg/kg appears less effective compared to intrarectal diazepam at a dose of 0.5 mg/kg in African children presenting with seizures lasting more than 5 minutes. Although sublingual lorazepam would appear to be an attractive treatment option because of its easy administration, its use could be justified only in circumstances where intrarectal diazepam is unavailable, impractical to use, or its administration would be delayed.

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Author Contributions
CKKM, JPM, JMD, EMM, and RMKM designed the study. CKKM, DMK, CM, and JPM were clinical leads in the participating centers; they collected and entered the data. CKKM maintained the database. CKKM, EMM, TDW, JK, JMW, and JPM analyzed the data. All investigators contributed to the writing of the final draft of the report.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval
The study protocol was approved by the Liège Regional Hospital/Citadelle ethics committee (no. 1093) and has been confirmed by the ethics committees of the National University of Rwanda (no. 006) and of the School of Public Health of the University of Kinshasa (no. 055). Because of the need for an immediate intervention in such a situation of lasting convulsions, informed consent have been obtained from the parents after clinical stabilization and subsequent detailed explanations of the study protocol and aims.

References


