ORIGINAL RESEARCH ARTICLE

ROLE OF BUCCAL LORAZEPAM IN DOMICILIARY/ OUT OF HOSPITAL MANAGEMENT OF SEIZURES

Gausai Dhanaram¹, Parakh Manish², Payal Vikas³, Meena Harimohan⁴, Singh Sumeet⁵, Sharma Sonam⁶

¹ Junior Specialist, Government Hospital, Balotra, Barmer, Rajasthan, India.
² Senior Professor and Consultant Paediatric Neurologist, Dr. S.N. Medical College, Jodhpur, Rajasthan, India.
³ Assistant Professor, Department of Paediatrics, Dr. S.N. Medical College, Jodhpur, Rajasthan, India.
⁴ Assistant Professor, Department of Paediatrics, Dr. S.N. Medical College, Jodhpur, Rajasthan, India.
⁵ Junior Resident, Department of Paediatrics, Dr. S.N. Medical College, Jodhpur, Rajasthan, India.
⁶ Junior Resident, Department of Paediatrics, Dr. S.N. Medical College, Jodhpur, Rajasthan, India.

CORRESPONDENCE ADDRESS:
Dr. Manish Parakh
A-314, Shastri Nagar, Opposite Hanwant School, Jodhpur (Raj) India 342003
Residence Telephones: 0091-291-2614335, 2432134
Cell phone: 0091-9414127335
Email id: manparkh@hotmail.com

ABSTRACT

Background and Aims: A prospective follow-up to study the role of buccal lorazepam and intranasal midazolam in pre-hospital/domiciliary/ out of hospital management of seizure in children with epilepsy in Pediatric Neurology Clinic in an urban tertiary care teaching hospital.

Methods: A total of 94 children with epilepsy were included and followed up for a maximum of 24 months. All caregivers were counseled in domiciliary/ out of hospital management of seizures and instructed to use Buccal lorazepam (0.01 mg/kg/dose) or intranasal midazolam for a seizure a lasting more than five minutes/ >3 seizures within 30 minutes for seizures occurring in pre-hospital setting where trained medical personnel were not available. A detailed enquiry regarding occurrence of seizures and use of drugs to control the seizure was done every 6 months on follow up visits.

Results: 54 patients (57.5%) had one or more seizures in a an out of hospital setting. Attendants of 22 patients used buccal lorazepam for acute management of seizures in a pre-hospital setting and 17 (77.2%) reported immediate cessation of the seizure event.
Drowsiness (13.6%), irritability (9.1%), sedation (4.5%), vomiting (4.5%), confusion (4.5%) and frothing from mouth (4.5%) were commonly reported side effects and no serious adverse effects were seen in any patient.

**Conclusion:** Buccal lorazepam is a cheap and effective drug which can be safely used by parents and other non-medical caregivers for acute management of a seizure in an out of hospital setting. It must however be complemented with effective pre-hospital/domiciliary seizure management training which is recommended to be included in Basic Life support training skill courses.

**Key words:** Buccal, Lorazepam, domiciliary, Seizure

**INTRODUCTION:**

Epilepsy is characterized by recurrent unprovoked seizures presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness. Despite advancements in pharmacologic and non-pharmacologic management of epilepsy, more than 33% of patients with epilepsy remain resistant and continue to have seizures during their lifetime[1]. Epileptic seizure, a common neurologic medical emergency is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in brain[2]. Recurrent seizures despite being on specific pharmacologic or non-pharmacologic management is associated with increased morbidity and mortality including chances of landing into status epilepticus in the affected individuals and also has an impact on the family and caregivers. One of the most dreaded issues in patients with epilepsy is a seizure outside hospital especially at home. In majority of rural India because of availability of few emergency room services, parents and caregivers have to transfer a convulsing child to nearest emergency room without proper transport facility which increases morbidity and mortality. Pre-hospital/Domiciliary management of a seizure with drugs that can be administered by parents and caregivers may be beneficial and can decrease morbidity and mortality associated with an out of the hospital seizure. Rectal diazepam, intranasal midazolam and recently buccal lorazepam are available in India for acute seizure management in an out of hospital setting.

Rectal diazepam is available as an enema and suppository and Midazolam is available is an intranasal preparation. Although effective, rectal route of administration of diazepam is culturally not very acceptable and the newer preparations are expensive. If not administered appropriately, the drug absorption and distribution is not optimal and render it ineffective. Intranasal midazolam is easier to administer during a seizure but is not distributed evenly and
absorption from nasal route may be more erratic due to the secretions accumulating in nose during a seizure. Buccal Lorazepam administered during a seizure have been a part of the acute seizure management protocol of many centres worldwide but is not used in India because of non-availability of a buccal preparation for this purpose. In the past two years, a cheap buccal preparation of Lorazepam is now available in India. The current study was designed with an objective to evaluate the role of buccal lorazepam in acute prehospital management of childhood seizures.

METHODS:

The present study was conducted in the Pediatric Neurology Clinic, Department of Pediatrics, Umaid hospital for Women and Children, Dr. S.N. Medical College, Jodhpur over a 12 month period. The study was approved by Ethical Committee of Medical College Jodhpur. All patients with childhood epilepsy (due to any aetiology) attending the Pediatric Neurology Clinic were enrolled in the study. Children below the age of 3 months, having a history suggestive of allergy or intolerance to benzodiazepines or having serious side effects requiring hospitalization were not included in the study.

The patients were worked up as per standard protocols and were prescribed specific anticonvulsants for management of the epileptic disorder. In addition, at least two of the family members accompanying the child were trained by the attending physician in pre-hospital/ domiciliary seizure management as mentioned in the parent/ caregiver instruction leaflet for Pre-hospital/ domiciliary management of seizure episode. A copy of the leaflet detailing the instructions in both English and Hindi (Figure 1) was given to the attendants and were instructed to share the information with other adult family members living with the child.

1. Parents have been taught in details about the rescue plan for out of hospital/ domicially seizure management as-

   a. Evacuation from accident zone, turning prone to prevent aspiration, use of intranasal midazolam or sublingual lorazepam and early transport to the nearest emergency room.

   b. Lorazepam 1 mg MD (sublore 1mg) to be used sublingually as 1 tablet or midazolam 1.25 spray as 3 spray in each nostril for single seizure lasting >5 minutes or more than 3 seizures in 30 minutes. Can be repeated once if the seizure lasts more than 3 minutes.
Attendants were instructed to use Lorazepam mouth dissolving tablet by placing between gum and lower lip in a dose as per the chart below (Table 1). Mouth dissolving Lorazepam is available in 1mg, 2 mg and 4 mg strength.

<table>
<thead>
<tr>
<th>Weight</th>
<th>Dose to be given</th>
<th>1/2 tablet of 1mg preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7.5 kg</td>
<td>0.5 mg</td>
<td></td>
</tr>
<tr>
<td>7.5-12.5 kg</td>
<td>1 mg</td>
<td>1/2 tablet of 1mg preparation</td>
</tr>
<tr>
<td>12.5-17.5 kg</td>
<td>1.5 mg</td>
<td>1 1/2 tablet of 1mg preparation</td>
</tr>
<tr>
<td>17.5kg-22.5kg</td>
<td>2 mg</td>
<td>1 tablet of 2 mg preparation</td>
</tr>
<tr>
<td>22.5kg-27.5kg</td>
<td>2.5mg</td>
<td>1 1/2 tablet of 2mg preparation</td>
</tr>
<tr>
<td>27.5kg-32.5kg</td>
<td>3 mg</td>
<td>1 tablet of 2mg preparation and 1 tablet of 1mg preparation</td>
</tr>
<tr>
<td>&gt;32.5 kg</td>
<td>4mg</td>
<td>1 tablet of 4mg preparation</td>
</tr>
</tbody>
</table>
Use of Midazolam nasal spray (as per doses schedule provided by the manufacturer) was demonstrated using a dummy spray bottle (Table 2). The use of either mouth dissolving lorazepam or Midazolam was to be done only if a seizure lasted more than approximately five minutes or more than three seizures in 30 minutes. Attendants were instructed that five minutes are only an approximate estimation and they did not need to use a clock/timer to use the same. In case the child had a seizure/cluster of seizures during the follow up period, Parents/Attendants/Caregivers were instructed to note down the following in a diary later on the same day:

1. Number of seizures during the follow up period
2. Whether the seizures occurred in a cluster or were isolated events. If clusters, then parents were instructed to note down the number of seizures in the cluster
3. Approximate duration of the seizure and whether Buccal Lorazepam or Midazolam spray was used to terminate the seizure
4. Approximate time when the seizure stopped after administering Buccal Lorazepam or Midazolam spray
5. Number of tablets of Buccal Lorazepam or Midazolam sprays used to terminate the seizure
6. All side effects and adverse events occurring in the next 48 hours

All the attendants were instructed to attend neurology clinic for regular follow up and those not coming for a regular follow up were contacted by phone and were persuaded to come for a regular follow up. All the patients in the study were followed up for a minimum of 6 months to a maximum of 24 months from their time of registration. On every follow up visit apart from the ongoing or new issues related to his/her illness, appropriate treatment compliance was also restressed and antiepileptic treatment reviewed and changed as indicated. A detailed history of the number of seizures that occurred since previous follow up, the total duration of a seizure or cluster of seizures and whether the attendants required mouth dissolving lorazepam or midazolam nasal spray for termination of seizure was recorded. In case no medication was used, the reasons for the same were also recorded. The approximate time taken for seizure termination and side effects reported by caregivers after the use of medication to abort seizures were recorded. In this study the end of the seizure episode (clinically) was defined as the cessation of visible epileptic phenomena or return of purposeful response to external stimuli for the aforementioned purpose and if the seizure did
not end within 10 minutes of drug administration, the treatment was deemed to be ineffective. The prehospital/domiciliary seizure management of the epileptic fit was re-stressed and re-taught on every follow up visit.

RESULTS:
A total of 165 patients diagnosed as Epilepsy (due to any etiology) attended Pediatric Neurology clinic in the one year study duration. Families of 94 of these children consented to participate in the study and were followed up for a maximum of 24 months. 58 (61.7%) were males and 36 (38.3%) were females and 49 (52.1%) had history suggestive of generalized seizures and 45 (47.9%) had focal seizures (Table I).

A follow up of 18 months was completed for 46.8% (44) patients, 12 months for 37.2% (35) patients, 6 months for 8.5% (8) patients and 24 months for 7.4% (7) patients. After registration in the Pediatric Neurology Clinic and starting appropriate anticonvulsant drugs, 42.5% (n=40) patients remained seizure free whereas 57.5% (n=54) patients had one or more seizures during the follow up (Table II). Out of 54 patients who had recurrence of seizure during their follow up, 26 patients had a seizure of more than five minutes and four patients had more than three seizures in 30 minutes. Amongst these 30 patients 22 (73.3%) patients were administered buccal lorazepam by their parents/caregivers/other attendants and in none of the patients intranasal midazolam was used.

Out of 22 patients in whom buccal lorazepam was used, seizures were aborted within a minute in 17 (77.2%) patients and no response was observed even after 10 minutes in remaining 5 (22.8%) patients. In 11 patients buccal lorazepam was used every time when there was recurrence of a seizure and nine (81.2%) of these patients had cessation of seizure every time buccal lorazepam was used (Table III). None of these patients landed in status epilepticus.

Drowsiness was reported in 13.6% (n=3) patients, Irritability (9.1%), vomiting (4.5%), confusion (4.5%) and frothing from mouth (4.5%) were other reported side effects. No serious adverse event was observed in any patients.

DISCUSSION:
Seizure, a common neurologic medical emergency, continues to be associated with significant morbidity and mortality in the pediatric age group and affects 4-7% of children[3]. Early domiciliary/prehospital treatment of seizures in the community, school, or home with drugs that can be administered by parents, teachers, nonmedical personnel and even
paramedics may be beneficial and can decrease morbidity and mortality[4]. In planning domiciliary therapy, the safety, ease of administration, choice of drug, route of therapy, and the practicability of familiarization by the user are important issues. Various drugs administered through different routes have been tried in the management of acute seizures.

In a hospital setup, intravenous diazepam, midazolam or lorazepam is commonly used for control of acute seizures, but it requires prompt establishment of an intravenous line and has the disadvantage of being a respiratory depressant.[5]

Rectal diazepam has been used successfully for pre-hospital and in-hospital treatment of acute seizures.[6] However; its use may be socially embarrassing and undesirable. It also requires special equipment and arrangement to administer it, which is difficult to be arranged in pre-hospital setting like homes, schools and day care centers. It is not always reliable owing to its variable bioavailability and wide range of serum concentration.[7,8] There is also a risk of child abuse.

Midazolam, a benzodiazepine, has been described as an alternative rescue medication in the management of acute seizures.[9,10] Recent studies have demonstrated intranasal midazolam to be effective in the management of acute childhood seizures as it was found to end seizures within 1 to 2 minutes of intranasal administration. [11,12] However the absorption from nasal route may be erratic and unreliable; also higher cost limits its use in poor community in developing countries.

Episodes of acute seizures have also been treated with buccal diazepam and buccal/sublingual lorazepam.[13,14] Sublingual/buccal lorazepam is cheap and easy to administer. Lorazepam is a high-potency short-to-intermediate-acting 3-hydroxy benzodiazepine drug which has all five intrinsic benzodiazepine effects; anxiolytic, amnesic, sedative/hypnotic, anticonvulsant and muscle relaxant.[15,16] Lorazepam is used for the short-term treatment of anxiety, insomnia, acute seizures including status epilepticus and sedation of hospitalized patients, as well as sedation of aggressive patients.[17]

Lorazepam (buccal/sublingual) is particularly useful for acute management of seizures because it is a fast-acting medication, used easily in hospital and domiciliary setting but swallowing it before its full dissolution reduces its effectiveness. It is a part of pre-hospital and in-hospital management protocols in almost all hospitals in the western hemisphere. In India, however it is not commonly used because of unavailability of a buccal preparation until recently. Besides, most of the discharge instructions and outpatient clinic prescriptions for epilepsy patients hardly ever mention, educate and stress pre-hospital/ out of hospital
management of acute seizures that can be given by parents and caregivers. Appropriate pre-hospital management of acute seizures is known to reduce morbidity and mortality in patients with epilepsy.

The current study was done to evaluate the role of buccal lorazepam in acute pre-hospital management of seizure in children with epilepsy. In our study after registration in Pediatric Neurology Clinic and starting appropriate anticonvulsant drugs 42.5% (n=40) patients remained seizure free whereas 57.5% (n=54) patients had seizures on one or more occasions (Table II). Recurrence of a seizure even when the patient was regularly receiving anticonvulsant was more in patients with generalized seizures (68.6%) than in partial seizures (54.3%). There seems to be a general consensus that both adults and children with newly diagnosed epilepsy have only a 65–75% chance of entering long-term remission.[18,20]

Amongst the patients who had seizures in an out of hospital setting, 73.3% (22) were administered buccal lorazepam by their caregivers/attendants while intranasal midazolam was not used in any of them. In 8 (26.7%) patients none of the drugs were used for acute seizure management in an out of hospital setting. Parents of 6 (75%) of these patients mentioned that they were reluctant to use either buccal lorazepam or intranasal midazolam as a part of the pre-hospital/domiciliary seizure management despite detailing the same in the clinic or at discharge due to apprehension of doing something wrong. They also mentioned that they did not remember and recall instructions given to them regarding management of seizure. In fact these were also the parents who did not follow instructions for evacuating the patient to a safer area and also proper positioning during a seizure. All these patients were however immediately taken to the nearest emergency room (Primary health centre, Subcenter or a Private hospital). None of these parents took the patient to a traditional faith healer. Parents of two patients mentioned that they were not properly counselled. Parents/ Caregivers of 18 patients mentioned that they did not buy intranasal midazolam because it was costly.

In the current study mouth dissolving lorazepam was used in 22 patients and seizures were aborted within a minute of its use in 77.2% of them and no response was observed in remaining 22.8% patients (Table III). Mouth dissolving lorazepam was used for every recurrence of seizure in eleven patients and 81.2% of these patients reported cessation of seizure every time buccal lorazepam was used. None of these patients landed in status epilepticus. Drowsiness was reported in 13.6% (n=3) patients. Irritability (9.1%), vomiting (4.5%), confusion (4.5%) and frothing from mouth (4.5%) were other reported side effects. No serious adverse effect was observed in any patients. These results are comparable to
another study done by Yager and Seshia who have studied the efficacy of sublingual lorazepam for serial seizures in ten children using initial dose of 0.05mg/kg and reported good response in eight children (80%) while partial response was observed in the remaining two patients and none of the patients landed in status epilepticus. Side effects were minimal and included drowsiness, unsteadiness and nausea for up to one day.

The study concludes that buccal lorazepam is a cheap, safe and convenient to use option to abort a seizure in a setting where emergency medical services and prompt transportation to emergency room is not feasible or available as is the case in many suburban and rural areas of India and other developing countries. It must however be complemented with effective pre-hospital/domiciliary seizure management training. Based on the aforementioned study we also wish to make recommendations to include a pre-hospital/Emergency room/ domiciliary seizure management protocol in Basic life support skill training.

**KEY MESSAGE:**

What is already known: Effective management of seizures in an out of hospital setting can reduce morbidity and mortality in epilepsy patients.

What this study adds: Buccal lorazepam is a cheap, safe and convenient to use option for out of hospital management of seizures. Effective pre-hospital/domiciliary management of acute seizure by parents/caregivers reduces morbidity and chances of landing into subsequent status epilepticus. Pre-hospital/domiciliary acute seizure management training should be included in Basic Life support skill training.

<table>
<thead>
<tr>
<th></th>
<th>Male (n=58)</th>
<th>Female (n=36)</th>
<th>Total (n=94)</th>
<th>x2, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n, %</td>
<td>n, %</td>
<td>n, %</td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>32 (55.2%)</td>
<td>17 (47.2%)</td>
<td>49 (52.1%)</td>
<td>0.56, 0.45</td>
</tr>
<tr>
<td>Partial</td>
<td>26 (44.8%)</td>
<td>19 (52.8%)</td>
<td>45 (47.9%)</td>
<td></td>
</tr>
<tr>
<td>Specific syndromes</td>
<td>17 (29.3%)</td>
<td>9 (25.0%)</td>
<td>26 (27.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Classification of Seizures (electro-clinical)
Table 2: EPILEPSY PATIENTS WHO DEVELOPED SEIZURES AFTER REGISTRATION IN PEDIATRIC NEUROLOGY CLINIC

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th></th>
<th>Female</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GE</td>
<td>PE</td>
<td>Total</td>
<td>GE</td>
<td>PE</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>n=32</td>
<td>n=26</td>
<td>n=58</td>
<td>n=17</td>
<td>n=19</td>
<td>n=36</td>
</tr>
<tr>
<td>&lt; 5 minutes</td>
<td>12</td>
<td>6</td>
<td>18</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>duration</td>
<td>37.4%</td>
<td>23.1%</td>
<td>31.0%</td>
<td>35.3%</td>
<td>21.1%</td>
<td>27.8%</td>
</tr>
<tr>
<td>&gt;5 minutes</td>
<td>10</td>
<td>8</td>
<td>18</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>duration</td>
<td>31.3%</td>
<td>30.8%</td>
<td>31.0%</td>
<td>29.4%</td>
<td>15.8%</td>
<td>22.2%</td>
</tr>
<tr>
<td>No seizures</td>
<td>10</td>
<td>12</td>
<td>22</td>
<td>6</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>31.3%</td>
<td>46.2%</td>
<td>37.9%</td>
<td>35.3%</td>
<td>63.2%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

GE versus PE - $x^2=4.1$  
$p = 0.1$
Male versus female - $x^2=1.46$  
$p=0.48$

Table 3: RESPONSE OF SUBLINGUAL LORAZEPAM IN EPILEPSY PATIENTS

<table>
<thead>
<tr>
<th>No. of patients used Lorazepam</th>
<th>Once</th>
<th>Multiple times</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Seizures stopped</td>
<td>8 (72.7%)</td>
<td>9 (81.8%)</td>
<td>17 (77.2%)</td>
</tr>
<tr>
<td>No response</td>
<td>3 (27.3%)</td>
<td>2 (18.2%)</td>
<td>5 (22.8%)</td>
</tr>
</tbody>
</table>

REFERENCES:


19. Cockerell OC, Johnson AI, Sander JWA, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. Epilepsia 1997;38:3–46.