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Review article

Efficacy and safety of anti-epileptic drugs in patients with active convulsive seizures when no IV access is available: Systematic review and meta-analysis☆

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ABSTRACT

Objectives: To explore the existing evidence for anti-convulsant drugs and their routes of administration in treating acute seizures in children and adults when intravenous access is not available.
Methods: All major databases including Medline *via* Ovid, PubMed, Cochrane CENTRAL, Embase, and Google Scholar were searched till May 2015. Randomized and quasi-randomized controlled trials comparing two anti-convulsant drugs (at least one comparator being administered through non-intravenous route) for treatment of acute seizures were included.
Outcome measures: Primary outcome measure was proportion of children with clinical seizure cessation within 10 min of drug administration. Secondary outcome measures were time taken to clinical seizure cessation from the time of admission and from the time of drug administration, and incidence of significant adverse effects.
Results: Out of the 19,165 citations, 26 studies were finally included. Regarding the primary outcome measure, the quality of evidence was 'moderate' for following 3 comparisons: buccal midazolam being superior to per-rectal diazepam (RR 1.14; 95% CI, 1.06–1.24), intra-nasal lorazepam being same as intravenous lorazepam (RR 1.04; 95% CI, 0.89–1.22) and intramuscular paraldehyde (RR 1.22; 95% CI, 0.99–1.52). The quality of evidence was 'very-low' for 1 comparison: per-rectal lorazepam being superior to per-rectal diazepam (RR 3.17; 95% CI, 1.63–6.14). The quality of evidence was 'low' for following 2 comparisons: sub-lingual lorazepam being inferior to rectal diazepam (RR 0.71; 95% CI, 0.62–0.81), and intranasal midazolam being superior to per-rectal diazepam (RR 1.14; 95% CI, 1.05–1.25). The rest of the comparisons did not show any difference, but the quality of evidence was 'low' to 'very low'. The time to seizure cessation after drug administration was lower in the intravenous group. However, time to seizure cessation after presentation (includes time for drug administration) was lower in the non-intravenous group. Significant adverse effects were infrequently reported and when present, were similar in both the groups.
Conclusions: When intravenous access is not available, non-intravenous routes of administration of benzodiazepines should be considered for the control of acute seizures in children/adults. The preference may be guided by availability, expertise and social preference. [PROSPERO No: CRD42015019012].

Abbreviations: IVD, intravenous diazepam; IVL, intravenous lorazepam; INL, intranasal lorazepam; INM, intranasal midazolam; SLL, sublingual lorazepam; PRD, per-rectal diazepam; IVM, intravenous midazolam; BCM, buccal midazolam; IMP, intramuscular paraldehyde; IMM, intramuscular midazolam.

☆ Clinical Trial Registration: This review is registered with the PROSPERO database registry (CRD42015019012).

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1. Introduction

The treatment for acute convulsive seizure is aimed at earliest cessation of seizure in order to prevent progression to status epilepticus, cardio-respiratory compromise, and cerebral damage. Absence of timely intervention may lead to a protracted seizure episode that is more difficult to control with significant subsequent neurological morbidity and mortality.

Dispensing antiepileptic drugs intravenously is the fastest route of administration; however, achieving peripheral venous access may be difficult in a convulsing child. This situation is compounded by resource constraints and lack of trained personnel. Similarly, venous access is not possible in home settings by parents/caregivers. However, the optimal agent and route of administration for resource constrained or pre-hospital treatment of acute convulsive seizures including status epilepticus is not known. The ideal anti-convulsant drug is one which can be given safely and easily, should be rapidly acting, has minimum cardio-respiratory adverse effects, has a long lasting effect, and is cost-effective.

Rectal diazepam was commonly used to control convulsive seizures in pre-hospital settings but concerns over social acceptability and convenience have stimulated a search for better alternatives. We explored the existing evidence for anti-convulsant drugs and various routes of administration in treating acute seizures in children and adults when intravenous access is not available. A recent Cochrane review for the status epilepticus (Prasad et al., 2014) did not focus on the drugs by non-intravenous routes and included only 4 studies (Chamberlain et al., 1997; Ahmad et al., 2006; Silbergleit et al., 2012; Appleton et al., 1995) relevant to our topic. This review of evidence was a part of the process of formulating World Health Organization (WHO), Mental Health Gap Action Programme (mhGAP) and Emergency Triage Assessment and Treatment (ETAT) guidelines (Web reference).

2. Methods

This review is registered with the PROSPERO database registry (CRD42015019012).

2.1. Types of studies

Randomized and quasi-randomized controlled trials, irrespective of blinding were included.

2.2. Types of participants

Patients (>1 month of age) of both sexes with acute convulsive seizures being treated in the hospital or in the outpatient or community setting were included. Participants included those presenting *de novo* with a first convulsion and those with an established diagnosis of epilepsy. All causes of the convulsion (including convulsive status epilepticus) were included. Those receiving anticonvulsants before study enrollment were excluded.

2.3. Types of intervention

Trials comparing two anti-convulsant drugs (at least one comparator being through non-intravenous route) for treatment of acute convulsive seizures were included. Specific drugs included midazolam, diazepam, lorazepam and paraldehyde. The different routes of drug administration were analyzed that included per-rectal, intranasal, buccal, sub-lingual and intra-muscular routes.

2.4. Types of outcome measures

2.4.1. Primary outcome measures

1. Proportion of study participants with clinical seizure cessation within 10 min of drug administration.

2.4.2. Secondary outcome measures

1. Time taken to clinical seizure cessation from the time of admission (in minutes).
2. Time taken to clinical seizure cessation from the time of drug administration (in minutes).
3. Incidence of significant adverse effects: significant respiratory depression requiring ventilation, apneas, bradypneas, and hypotension.