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Clinical Study

Lorazepam or diazepam for convulsive status epilepticus: A meta-analysis

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ABSTRACT

Convulsive status epilepticus (CSE) is a neurological emergency in adults and children. However, whether a particular benzodiazepine is of superior efficacy and safety in management of CSE is controversial. We performed a meta-analysis to compare the outcome of lorazepam and diazepam for treating CSE. We searched the PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases from 1966 to February 2014. No language restriction was applied. Reference lists of all the selected articles were hand-searched for any additional trials. Trial quality was assessed using the modified Jadad scale and the Consolidated Standards Of Reporting Trials (CONSORT) checklist. Two authors independently extracted data from all eligible studies, including study design, participants, interventions, and outcomes. The data was analyzed using fixed-effects or random-effects models with mean differences and risk ratios for continuous and dichotomous variables, respectively. A total of six studies involving 970 patients were included in this analysis. The majority of patients were children (n = 574) and 396 patients were adults. Meta-analysis showed no significant difference between the two treatment groups regarding seizure control and adverse effects regardless of patient age. This meta-analysis demonstrates that diazepam and lorazepam have equal efficacy and side effects for treating CSE in adults and children, and either can be chosen as a reasonable first-line therapy. More high quality randomized controlled trials are needed to support this finding.

1. Introduction

Convulsive status epilepticus (CSE) is defined as either two or more convulsions without complete recovery of consciousness between seizures (intermittent CSE) or as a single prolonged seizure that lasts for at least 30 minutes (continuous CSE). CSE is a common neurological emergency in adults and children [1]. The mortality and morbidity of CSE are related to its duration, and therefore early control is important. However, the best initial drug treatment remains uncertain [2].

For many years, diazepam was used as the first line treatment for CSE [3]. Recently, lorazepam has been demonstrated to be effective in the treatment of status epilepticus in adults [4,5] and children [1,6]. However, despite many experts advocating its use as a first-line treatment, lorazepam is not yet approved by the USA Food and Drug Administration for this indication[6]. Additionally, many studies have suggested that lorazepam is superior to diazepam as a first-line therapy because of improved seizure outcomes and lower rates of respiratory depression [7]. However, many published guidelines still recommend diazepam.

The purpose of this systematic review is to combine the data from all available randomized controlled trials (RCT) to compare the clinical results of using lorazepam or diazepam for treating CSE.

2. Methods

2.1. Inclusion criteria

Prospective RCT were included. The study population included patients with generalized CSE. All patients underwent treatment with lorazepam or diazepam to control their status epilepticus. The main outcome measures included seizure control and adverse effects. Successful treatment was defined as cessation of seizure activity within 10–15 minutes of the first intervention.

2.2. Search methods

We searched the PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases. Two

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authors independently searched for relevant studies from 1966 to February 2014. The search strategy was created with the assistance of a librarian using a combination of terms, such as "lorazepam", "diazepam", "epilepticus", "status epilepticus", "SE", "convulsive status epilepticus", "CSE", "prospective", "randomized controlled trials", "meta-analysis", and "systematic review". We limited searches to RCT, systematic reviews, and meta-analyses and imposed no language or other limitations. The electronic search was complemented by hand searches of the reference lists. Figure 1 provides further detail of the search strategy.

2.3. Selection of studies

Two reviewers (Wu and Zhang) independently screened the titles and abstracts of the studies identified by the search strategy and discarded clearly irrelevant studies. The same two reviewers also independently applied the selection criteria to the studies retrieved by the literature search. They resolved disagreement by discussion, and if any uncertainty remained, they consulted an additional reviewer and expert (Xue) who made the final decision.

2.4. Methodological quality assessment

Two reviewers independently assessed the quality of the studies, and the revised Jadad Scale was used to assessment the quality. This scale includes the randomization process (2 points), allocation concealment (2 points), appropriateness of blinding (2 points), and a description of dropouts and withdrawals (1 point). The total score is 7 points, with a score of 0–3 indicating poor quality, and 4–7 points indicating high quality. The Consolidated Standards on Reporting Trials (CONSORT) checklist and scoring system was used to evaluate the quality of included trials: scores of 18–22 correspond to an excellent study quality; 13–17 correspond to a good study quality; 8–12 correspond to a fair study quality; and $\leqslant$7 correspond to a poor study quality.

Two reviewers independently extracted the data using a standardized form. A consensus method was used to resolve disagreements, and a third reviewer was consulted if disagreements persisted.

2.5. Statistical analysis

For dichotomous variables, we derived the relative risks and 95% confidence intervals (CI) for each outcome. For continuous variables, we calculated the mean differences and 95% CI for each outcome. We performed the meta-analysis using a fixed-effect model if no significant heterogeneity was present. To assess heterogeneity between studies, we performed a chi-square test and estimated the I^2 statistic. A random-effects model was selected to account for heterogeneity in the design and patient selection among the included studies. Subgroup analyses were conducted for different outcomes.

3. Results

A search of the PubMed, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar databases retrieved 952 articles. We excluded 249 duplicate and 358 unrelated articles after we reviewed the titles and abstracts. After reading the full text, six papers were selected for this meta-analysis. Figure 2 summarizes the study selection process.

All six studies were published in English [2,4,6,8–10] (Table 1). These studies included a total population of 970 participants, 574 children [6,9,10] and 396 adults [2,4,8]. Four hundred ninety-nine patients were treated with diazepam and 471 patients were treated with lorazepam. All of these studies reported seizure control and adverse effects as the main outcomes.

3.1. Methodological quality

All six trials had level II evidence. Using the revised Jadad Scale, all studies were of high quality. All of the RCT were evaluated using the CONSORT checklist and scoring system, and two studies had scores of 8–12, three studies had scores of 13–17, one study had a score of >17, meaning all of the RCT had satisfactory quality scores. The details are described in Table 2.

3.2. Seizure control in adults

Three of the included trials [2,4,8] reported seizure control in adults (Table 3), and the pooled analysis across these studies found no significant difference between the diazepam and lorazepam groups (odds ratio [OR], 0.73, 95% CI 0.35–1.55; $I^2 = 0.0\%$, $p = 0.157$). There was no evidence of heterogeneity (Fig. 3). The primary efficacy outcome was defined as the cessation of a status epilepticus within 10 minutes of the initial dose in two selected studies [4,8]. One study defined the primary outcome as the cessation of a status epilepticus within 20 minutes of the initial dose [2]. A sensitivity analysis was performed that excluded the study published in 1998 [2], and no significant difference was found between the diazepam and lorazepam groups (OR, 0.73, 95% CI 0.46–1.15; $I^2 = 0.0\%$, $p = 0.175$). The results of the pooled analysis were stable.

3.3. Seizure control in children

Three trials [6,9,10] examined seizure control in children (Table 3), and the pooled analysis across these studies found no significant difference between the diazepam and lorazepam groups (OR, 0.95, 95% CI 0.73–1.22; $I^2 = 0.0\%$, $p = 0.677$). There was no evidence of heterogeneity (Fig. 4). However, the primary efficacy outcome was defined as cessation of status epilepticus within 10 minutes of the initial dose in two selected studies [6,10], while one study defined the primary outcome as the cessation of a status epilepticus within 1 minute of the initial dose [9]. A sensitivity analysis was performed that excluded the study published in 1995 [9], and no significant difference was found between the

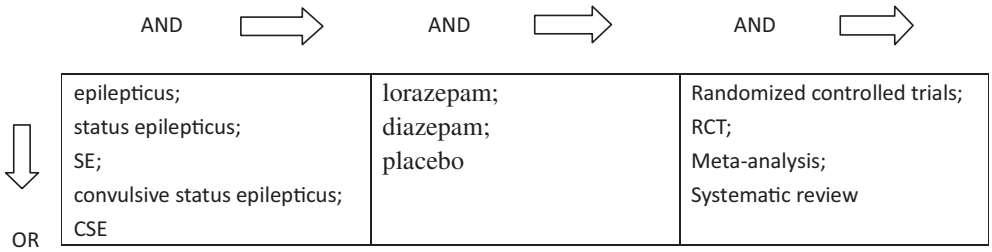

Fig. 1. Keywords and Boolean (logical) operators used in the database searches.