Seizure 31 (2015) 41–48

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Lidocaine for status epilepticus in adults

F.A. Zeiler [a,*], K.J. Zeiler [a,1], C.J. Kazina [a,2], J. Teitelbaum [b,c,3], L.M. Gillman [d,e,4], M. West [a,2]

[a] Section of Neurosurgery, Department of Surgery, University of Manitoba, Winnipeg, Canada
[b] Section of Neurocritical Care, Montreal Neurological Institute, McGill, Montreal, Canada
[c] Section of Neurology, Montreal Neurological Institute, McGill, Montreal, Canada
[d] Section of Critical Care Medicine, Department of Medicine, University of Manitoba, Winnipeg, Canada
[e] Section of General Surgery, Department of Surgery, University of Manitoba, Winnipeg, Canada

ARTICLE INFO

Article history:
Received 27 April 2015
Received in revised form 26 June 2015
Accepted 3 July 2015

Keywords:
Lidocaine
Status epilepticus
Refractory
Adult

ABSTRACT

Introduction: Our goal was to perform a systematic review of the literature on the use of intravenous lidocaine in adults for status epilepticus (SE) and refractory status epilepticus (RSE) to determine its impact on seizure control.
Methods: All articles from MEDLINE, BIOSIS, EMBASE, Global Health, HealthStar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform (inception to November 2014), and gray literature were searched. The strength of evidence was adjudicated using both the Oxford and GRADE methodology by two independent reviewers.
Results: Overall, 13 studies were identified, with 11 manuscripts and 2 meeting abstracts. Seventy-six adult patients were treated for 82 episodes of SE/RSE. Patients had varying numbers of anti-epileptic drugs (AEDs), 1–12, on board prior to lidocaine therapy. During 69 of the 82 (84.1%) episodes of SE/RSE, phenytoin was on board. The dose regimen of lidocaine varied, with some utilizing bolus dosing alone; others utilizing a combination of bolus and infusion therapy.

Overall, 70.7% of seizures responded to lidocaine, with complete cessation and greater than 50% reduction seen in 64.1% and 6.1% respectively. Patient outcomes were sparingly reported.
Conclusions: There currently exists level 4, GRADE C evidence to support the consideration of lidocaine for SE and RSE in the adult population. Thus there is currently weak evidence to support the use of lidocaine in this context. Further prospective studies of lidocaine administration in this setting are warranted.

1. Introduction

Refractory status epilepticus (RSE), defined as the failure of seizure response to a first line benzodiazepine and second line anti-epileptic drug (AED), poses a therapeutic challenge [1]. Numerous different therapies have been utilized in attempts to control RSE, including various AEDs with different receptor targets [1,2], therapeutic hypothermia [3], volatile inhalational anesthetic agents [4,5], urgent vagal nerve stimulator (VNS) insertion [6,7], and even electroconvulsive therapy [8].

Common AED targets include gamma-aminobutyric acid (GABA), GABA transaminase, sodium channels, calcium channels and n-methyl D-aspartate (NMDA) receptors [1,2]. Both sodium channel and GABA mediated AED are the most commonly utilized medications for seizures, and form the backbone of initial therapy for RSE [1,2,9]. Phenytoin, diphenytoin and carbamazapine are the common sodium channel antagonists utilized in the management of seizures [9].

Lidocaine, a class Ib anti-arrhythmic agent and local anesthetic agent, has emerged within the pediatric literature as an AED in neonatal status epilepticus (SE) [10,11]. Of interest, despite also acting as a sodium channel antagonist, lidocaine has displayed efficacy in seizure control in cases of SE and RSE in the presence of phenytoin [12].

* Corresponding author at: GB-1 820 Sherbrook Street, Winnipeg, MB, Canada R3A 1R9. Tel.: +1 204 228 6623.
E-mail addresses: umzeiler@cc.umanitoba.ca (F.A. Zeiler), kaitlinzeiler@gmail.com (K.J. Zeiler).
[1] Address: GB-1 820 Sherbrook Street, Winnipeg, MB, Canada R3A 1R9.
[2] Address: Section of Neurosurgery, University of Manitoba, GB-1 820 Sherbrook Street, Winnipeg, MB, Canada R1A 1R9.
[3] Address: Montreal Neurological Institute, 3801 rue University, Montréal, QC, Canada H3A 2B4.
[4] Address: Section of General Surgery and Critical Care Medicine, Z3053 St. Boniface General Hospital, Winnipeg, MB, Canada. Tel.: +1 204 237 2568.

http://dx.doi.org/10.1016/j.seizure.2015.07.003
1059-1311/

The reason for the added effect of lidocaine in the setting of previous sodium channel antagonist administration likely stems from the drug's amine chain, not present in other commonly used sodium channel based AEDs [13]. This allows binding of both compounds with aromatic based motifs, like phenytoin and tricyclic anti-depressants, and those with amine chain motifs, like lidocaine, at different sites on the sodium channels leading to a combined effect [13].

The majority of the literature to date on the use of lidocaine in SE and RSE is based in the pediatric population, with stronger evidence in the neonate population for its efficacy. This difference may reflect different stages of brain maturation and thus responsiveness to therapy. Given this, we were curious as to the literature on adult subjects [14–26]. The goal of our study was to perform a systematic review of the literature to determine the effect of lidocaine on adult SE and RSE.

2. Methods

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers [27] was conducted. The data was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [28]. The review questions and search strategy were decided upon by the primary author (FZ) and supervisor (MW).

2.1. Search question, population, inclusion and exclusion criteria

The question posed for systematic review was: What is the effectiveness of lidocaine for control of SE in human adults? The inclusion age range was age 18 or older. A small number of patients with age less than 18 were included, due to the inability to separate their data from the adults in the parent manuscripts. All studies, prospective and retrospective of any size based on human subjects were included. The reason for an all-inclusive search was based on the small number of studies of any type identified by the primary author during a preliminary search of MEDLINE.

The primary outcome measure was electrographic seizure control. Secondary outcome measures were patient outcome (if reported), and adverse effects of lidocaine treatment.

Inclusion criteria were: All studies including human subjects whether prospective or retrospective, all study sizes, adult patients (age 18 or greater), and the use of lidocaine for seizure control in SE. Exclusion criteria were: pediatric, non-English and animal studies.

2.2. Search strategy

MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from 1946 (inception) to November 2014 were searched using individualized search strategies for each database. The search strategy for MEDLINE can be seen in Appendix A of the supplementary material, with a similar search strategy utilized for the other databases. In addition, the World Health Organizations International Clinical Trials Registry Platform was searched looking for studies planned or underway.

As well, meeting proceedings for the last 10 years, looking for ongoing and unpublished work based on lidocaine use for seizures, were examined. The meeting proceedings of the following professional societies were searched: Canadian Neurological Sciences Federation (CNSF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), European Neurosurgical Society (ENSS), World Federation of Neurological Surgeons (WFNS), American Neurology Association (ANA), American Academy of Neurology (AAN), American Epilepsy Society (AES), European Federation of Neurological Science (EFNS), World Congress of Neurology (WCN), Society of Critical Care Medicine (SCCM), Neurocritical Care Society (NCS), and the World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), American Society for Anesthesiologists (ASA), World Federation of Societies of Anesthesiologist (WFSA), Australian Society of Anesthesiologists, International Anesthesia Research Society (IARS), Society of Neurosurgical Anesthesiology and Critical Care (SNACC), Society for Neuroscience in Anesthesiology and Critical Care, and the Japanese Society of Neuroanesthesia and Critical Care (JSNCC).

Finally, reference lists of any review articles or systematic reviews on seizure management were reviewed for relevant studies on lidocaine usage for seizure control.

2.3. Study selection

Utilizing two reviewers (FZ and KZ), a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently screened all titles and abstracts of the returned articles to decide if they met the inclusion criteria. Second, full text of the chosen articles was then assessed to confirm if they met the inclusion criteria and that the primary outcome of seizure control was reported in the study. Any discrepancies between the two reviewers were resolved by a third independent reviewer (MW).

2.4. Data collection

Data was extracted from the selected articles and stored in an electronic database. Data fields included: patient demographics, type of study (prospective or retrospective), number of patients, dose and route of lidocaine used, timing to administration of drug, duration of drug administration, time to effect of drug, how many other AEDs were utilized prior to lidocaine, degree of seizure control, adverse effects, and patient outcome.

2.5. Quality of evidence assessment

Assessment of the level of evidence for each included study was conducted by two independent reviewers (FZ and MW), utilizing the Oxford criteria [29] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria [30–35] for level of evidence.

The Oxford criteria consist of a 5 level grading system for literature. Level 1 is split into subcategories 1a, 1b, and 1c which represent a systematic review of randomized control trials (RCT) with homogeneity, individual RCT with narrow confidence interval, and all or none studies respectively. Oxford level 2 is split into 2a, 2b, and 2c representing systematic review of cohort studies with homogeneity of data, individual cohort study or low quality RCT, and outcomes research respectively. Oxford level 3 is split into 3a and 3b representing systematic review of case-control studies with homogeneity of data and individual case-control study respectively. Oxford level 4 represents case-series and poor cohort studies. Finally, Oxford level 5 represents expert opinion.

The GRADE level of evidence is split into 4 levels: A, B, C and D. GRADE level A represents high evidence with multiple high quality studies having consistent results. GRADE level B represents moderate evidence with one high quality study, or multiple low quality studies. GRADE level C evidence represents low evidence with one or more studies with severe limitations. Finally, GRADE level D represents very low evidence based on either expert opinion or few studies with severe limitations.

Any discrepancies between the grading of the two reviewers were resolved via discussion and a third reviewer when required (CK).