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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

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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.

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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).

2.6. Statistical analysis

A meta-analysis was not performed in this study due to the heterogeneity of data within the articles and the presence of a small number of predominantly retrospective studies.

3. Results

The results of the search strategy across all databases and other sources are summarized in Fig. 1. Seven hundred twenty-seven articles were identified, with 718 from the database search and 9 from the search of published meeting proceedings. Seventy-two duplicate references were removed, leaving 655 for analysis. By applying the inclusion/exclusion criteria to the title and abstract of the articles, we identified 65 articles that fit these criteria. Upon review of the reference sections of relevant review articles, 5 additional articles were added, leaving a total of 70 articles for second review. Of the 70 identified, 61 were from the database search and 9 were from published meeting proceedings. Applying the inclusion/exclusion criteria to the full text documents, only 13 articles were eligible for inclusion in the systematic review, with 11 from database and 2 from meeting proceeding sources. The 57 articles that were excluded were done so because they either did not report details around the administration of lidocaine for seizure control, were based on pediatric patients only, were non-relevant studies, or because they were review articles.

Of the 13 articles included in the review, all were original studies. There were 10 retrospective studies [14–21,25,26] and 3 prospective studies [22–24]. Within the retrospective studies, 6 were retrospective case series [14,15,17–19,25] and the remaining 4 were retrospective case reports [16,20,21,26]. All studies were based at single centers. The 3 prospective studies included in the systematic review were all prospective single arm studies with no control groups [22–24].

Across all studies, 76 patients were studied utilizing lidocaine for control of their SE/RSE (mean: 5.5 patients/study; range: 1–36 patients/study), with a total of 82 separate episodes of SE/RSE treated with lidocaine being documented. The age of patients studied ranged from 15 to 89 years. Two studies had small numbers of pediatric data included with their adult patients, which was inseparable [18,22]. This small number of pediatric patients (lowest recorded age of 15) were included as "adults" for the purpose of this study. One study failed to indicate the age of the participants [19], though it is suspected they were adult base on the pathology described. Study demographics and patient characteristics for the adult studies can be seen in Table 1, while treatment characteristics and seizure outcome are reported in Table 2.

The underlying pathology leading to SE/RSE within the 76 cases identified included: ischemic stroke (24), primary epilepsy (12), traumatic brain injury (TBI) (5), tumor (4), post-operative SE (4), infectious (3), idiopathic (3), metabolic (2), hypoxia (2), intracerebral hemorrhage (ICH) (1), and unspecified (16).

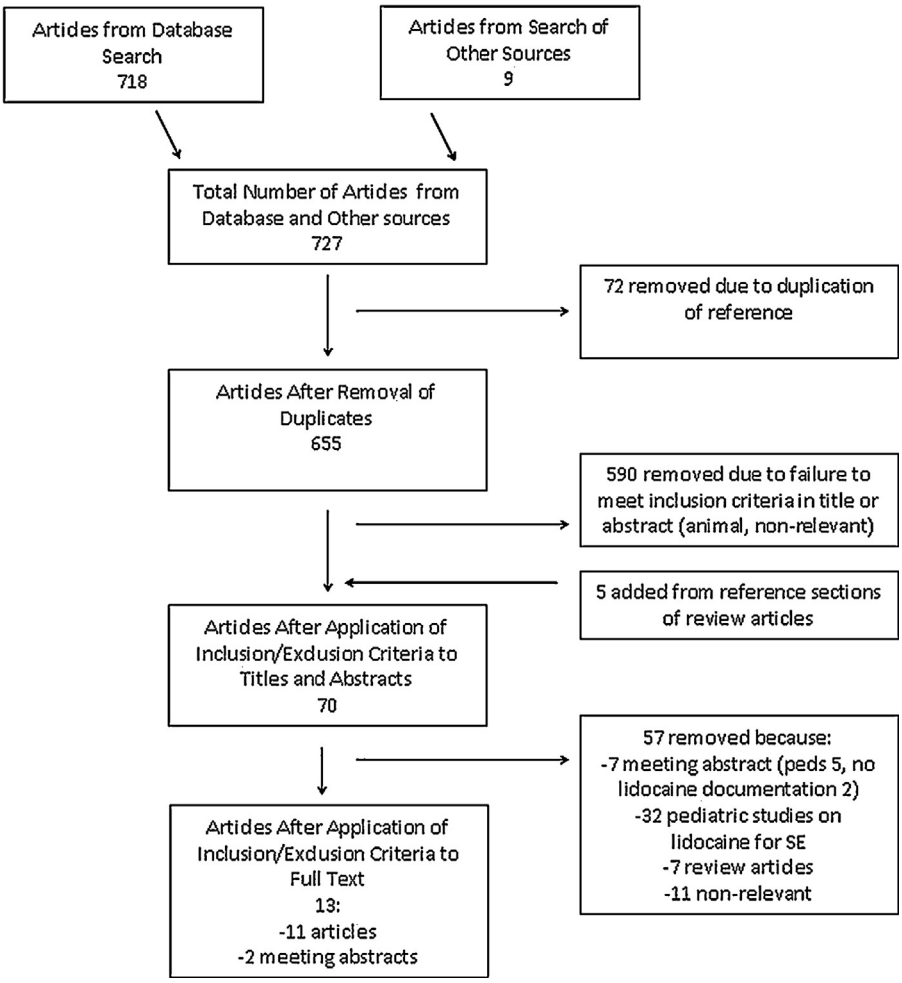

Fig. 1. Flow diagram of search results.

Table 1
Adult study characteristics and patient demographics.

Reference	Number of patients treated with lidocaine	Study type/ design	Study setting	Article location	Mean age (years)	Etiology of seizures	Mean # Meds prior to lidocaine	Mean time until lidocaine administration (days)
Aggarwal and Wali [14]	3	Retrospective case series	Single center	Journal	30.0 (range: 30–50)	Idiopathic (1); primary epilepsy (1); TBI (1)	2	Unknown
Bernhard et al. [15]	9	Retrospective case series	Single center	Journal	34.8 (range: 20–68)	Primary epilepsy (3); post-op SE (4); tumor (1); TBI (1)	Unknown	3–48 h
Cervenka et al. [16]	1	Retrospective case report	Single center	Journal	49	Inflammatory cerebritis	12 (including 4 IV anesthetics)	12 days
De Giorgio et al. [17]	2	Retrospective case series	Single center	Journal	23 and 37	Primary epilepsy (1); tumor (1)	4 and 2 (both had 1 IV anesthetic)	Unknown
Lemmen et al. [18] [a]	4	Retrospective case series	Single center	Journal	15–61	Primary epilepsy (3); SDH (1)	2.3 (range: 1–3)	Unknown
Moddel et al. [19]	6	Retrospective case series	Single center	Meeting abstract	Unknown	Stroke (1); hypoxia post-arrest (2); AIDS (1); tumor (1); unknown (1)	Range: 2–5 (2 IV anesthetics in 5, 3 in 1)	Unknown
Morris [20]	1	Retrospective case report	Single center	Journal	83	ICH	3	48 h
Nandakumar et al. [21]	1	Retrospective case report	Single center	Meeting abstract	24	NORSE	6 (3 IV anesthetics)	14 days
Pascual et al. [22] [a]	36	Prospective single arm	Single center	Journal	16–89	Cerebrovascular (23); metabolic (2); not specified (11) 29/36 generalized SE 7/36 focal SE	2 (range: 1–2)	20 min
Pascual et al. [23]	8	Prospective single arm	Single center	Journal	69 (range: 25–87)	Unknown (5); tumor (1); primary epilepsy poor medication adherence (1); meningitis (1) 6/8 generalized SE 2/8 focal SE	1.4 (range: 0–3)	Unknown
Taverner and Bain [24]	3	Prospective single arm (12 injections during 12 seizure episodes – randomly assigned placebo or lidocaine)	Single center	Journal	49.7 (range: 31–65)	Primary epilepsy (3)	1 (range: 0–3)	
Fernandez-Torre et al. [25]	1 (6 patients total, only 1 received lido)	Retrospective case series	Single center	Journal	59	Post-TBI (focal SE)	8	Unknown
Westreich and Kneller [26]	1	Retrospective case report	Single center	Journal	45	Post-TBI (focal SE)	4	48 h

AED = anti-epileptic drug; IV = intravenous; TBI = traumatic brain injury; SE = status epilepticus; SDH = subdural hematoma; ICH = intracerebral hemorrhage; NORSE = new onset resistant status epilepticus; min = minute; h = hours.
[a] Lemmen et al. [18] and Pascual et al. [22] are studies containing small numbers of pediatric patients, of which the data cannot be extracted from the adult information. Thus these studies were considered to be adult studies, with the pediatric data included in the analysis.

The country of origin of the manuscripts were as follows: USA [16–18,20,25,26], Spain [22,23,25], UK [21,24], Germany [19], India [14], and Sweden [15].

3.1. Lidocaine treatment characteristics

Duration of treatment prior to lidocaine administration was documented in 6 studies, ranging from 20 min to 14 days, with patients on various numbers of AEDs prior to lidocaine, with the mean number of AEDs ranging from 1 to 12 with most patient treatments typically consisting of a combination of oral AED and intravenous anesthetic agents. Of note, in 69 of the 82 (84.1%) SE/RSE episodes described, phenytoin was on board during lidocaine administration. All AED's reported were typically on board during the lidocaine treatment. Similarly, the duration of lidocaine treatment was described in 7 of the 13 studies, with treatment duration ranging from one time bolus dosing, up to 84 h continuous intravenous infusion. No one was discharged home on lidocaine therapy for their seizures.

The literature on lidocaine use for control of SE/RSE in the adult population yielded 13 studies. Within these 13 studies [14–26], 6 utilized bolus dosing of lidocaine in isolation [14,15,19,23,24,26], ranging from 100 to 400 mg IV, with a common weight based dosing of 1–3 mg/kg. One study utilized continuous infusions of lidocaine only [19], with dosing ranging from 2 to 4 mg/kg/h.

Finally, some studies utilized only bolus dosing of lidocaine, followed by continuous infusions [15,17,19,20,22]. The initial bolus ranged from 25 mg up to 3 mg/kg intravenously, with the number of boluses received prior to the initiation of infusion ranging from 1 to 4. The infusion rates ranged up to 3 mg/kg/h. Lidocaine treatment characteristics can be seen in Table 2.

Table 2
Adult articles–lidocaine treatment characteristics, seizure response, and outcome.

Reference	Number of patients treated with lidocaine	Lidocaine dose	Mean duration of lidocaine administration (days)	PHT on board	Electrographic seizure response	Recurrence after withdrawal of lidocaine	Adverse effects to lidocaine	Patient outcome
Aggarwal and Wali [14]	3	100 mg IV over 1 min	Single bolus dose	3/3	Seizure control in all within 45 s	Unknown; 1 case controlled for 12 h after single dose	None	Unknown (2); died (1)
Bernhard et al. [15]	9	7 had infusions: 1–3 mg/kg/h 2 had bolus dose: 0.6–3 mg/kg once	Infusions: 12–24 h	0/9	Seizures control in 7/9 Failure in 2/9	3 had recurrences	None	Unknown
Cervenka et al. [16]	1	Unknown	Unknown	1/1	Failed	N/A	None	Seizure control with ketogenic diet and surgery
De Giorgio et al. [17]	2	1 mg/kg IV bolus followed by infusion 1–2 mg/min	Unknown	1/2	Seizure control within 1 h	None	None	Unknown
Lemmen et al. [18][a]	4	1 patient bolus: 30 mg 3 patients: combination 30 mg bolus and infusion 100–300 mg/h	Infusions: 8–48 h	4/4	Seizure control in all	None	None	Unknown
Moddel et al. [19]	6	Continuous infusion: 2–4 mg/kg/h	Unknown	6/6	4/6 seizure control 2/6 no response	¼ with control recurred with withdrawal	None	Unclear: dead (1); palliative care (1); unknown (4)
Morris [20]	1	25 mg × 4 over 15 min, then 2 mg/min infusion	84 h	1/1	Seizure control	None	None	Independent
Nandakumar et al. [21]	1	Unknown	Unknown	1/1	No response	No response	None described	Died
Pascual et al. [22][a]	36 (42 episodes of SE)	Group A: Respiratory depressed group - No benzo Group B: Normal Resp status - Received benzo upfront Lidocaine: bolus 1.5–2 mg/kg ×2, if not response infusion at 3–4 mg/kg/h	Unknown	42/42 episodes	*First Bolus (n = 42):* - 12 complete responses - 19 temporary response - 11 no response *Second Bolus (n = 30):* - 12 complete response - 7 temporary - 11 no response *Infusion (n = 8):* - 3 no response - 3 complete response - 2 = 50% reduction in seizures	23/42 complete response no recurrence 14/42 no response 2/42 50% reduction 3/42 recurred after withdrawal	Hypotension (2) Cardiorespiratory arrest (1): prolonged uncontrolled RSE, 6 h of lidocaine infusion achieved control, but patient arrested	Dead (5); unknown in remaining (27)
Pascual et al. [23]	8	100 mg IV bolus 1 or 2 times (7) Infusion (1) = dose not specified	Bolus dosing (7); infusion (1) = duration not specified	8/8	Complete response in 5: - 2 × bolus = 3 Failure (temporary response) in 3 Time to response: 3 min–6 h	Infusion patient recurred after withdrawal (1) Temporary response in 2 with single bolus	Cardiac arrest in 1 patient 6 h after 2nd bolus dose.	Unclear: 1 = home, 1 = died, 6 = unknown
Taverner and Bain [24]	3	200–400 mg IV bolus doses = 6 doses in total Each patient also received 6 random doses of placebo = saline	Bolus only	0/3	"Increases interval between fits" – statistically significant compared to placebo Linear relationship of dose to response	In all 3 patients	None	Unknown
Fernandez-Torre et al. [25]	1	Unknown	Unknown	1/1	No response	No response	None described	Died
Westreich and Kneller [26]	1	150 mg bolus, then 1 g IV over 1 h, then 1 g IV over 6 h	1 h	1/1	Seizure cessation in 5 min	No recurrence	None	Home

mg = milligram; kg = kilogram; h = hour; min = minute; IV = intravenous; SE = status epilepticus; RSE = refractory status epilepticus.
[a] Lemmen et al. [18] and Pascual et al. [22] are studies containing small numbers of pediatric patients, of which the data cannot be extracted from the adult information. Thus these studies were considered to be adult studies, with the pediatric data included in the analysis.

3.2. Seizure response

Overall, 58 of the 82 (70.7%) SE/RSE episodes studied displayed seizure response to lidocaine administration. Complete seizure control upon lidocaine administration occurred in 53 of the 82 (64.6%) SE/RSE episodes documented. A greater than 50% reduction in seizure frequency occurred in 5 of the 82 (6.1%) SE/RSE episodes described. Failure of lidocaine treatment occurred in 24 of 82 (29.2%) episodes.

In those patients with phenytoin on board during lidocaine administration, there were 69 discrete SE/RSE episodes recorded. Lidocaine administration resulted in seizure reduction in 47 of these 69 (68.1%) episodes, with 45 of 69 (65.2%) and 2 of 69 (2.9%) resulting in complete seizure control and greater than 50% seizure reduction, respectively. Twenty-two of these 69 (31.9%) SE/RSE episodes failed lidocaine administration when phenytoin was already on board.

Within the group of patients treated with lidocaine in the absence of phenytoin on board there were 13 discrete SE/RSE episodes described. Complete seizure cessation with lidocaine administration occurred in 8 of the 13 (61.5%) SE/RSE episodes. Three of the 13 (23.1%) SE/RSE episodes treated with lidocaine resulted in greater than 50% reduction in seizures. Failure of lidocaine therapy occurred in 2 of the 13 (15.4%) of the SE/RSE episodes described.

Recurrence of seizures upon withdrawal of lidocaine occurred in 13 of the 58 (22.4%) responsive SE/RSE episodes.

3.3. Adverse effects of lidocaine

Only two studies documented adverse events related to lidocaine administration [22,23]. One study displayed 2 cases of hypotension with lidocaine bolus dosing [22]. Cardiorespiratory arrest was seen in 2 patients [22,23]. One patient had received 6 h of continuous lidocaine infusion with control of RSE around the 6 h mark from onset. The patient arrested with failed resuscitation attempts [22]. The second patient suffered a fatal cardiac arrest 6 h after 2 bolus doses of lidocaine were administered [23].

3.4. Outcome

Patient outcome was reported sparingly in most studies as the main focus of these reports was the success/failure of lidocaine treatment. This data can be seen in Table 2.

3.5. Level of evidence for lidocaine

Based on two independent reviewers, there were a total of 13 studies reviewed with 12 representing Oxford level 4 evidence for the administration of lidocaine for SE/RSE [14–21,23–26]. One prospective single arm study was deemed Oxford level 2b evidence for the administration of lidocaine for SE/RSE.

Eleven of 13 studies met GRADE D level of evidence [14–21,23,25,26], while the remaining 2 met GRADE C level of evidence [22,24]. Summary of the level of evidence can be seen in Table 3.

Table 3
Adult studies – Oxford and GRADE level of evidence.

Reference	Study type	Oxford [29] level of evidence	GRADE [30–35] level of evidence
Aggarwal and Wali [14]	Retrospective case series	4	D
Bernhard et al. [15]	Retrospective case series	4	D
Cervenka et al. [16]	Retrospective case report	4	D
De Giorgio et al. [17]	Retrospective case series	4	D
Lemmen et al. [18] [a]	Retrospective case series	4	D
Moddel et al. [19]	Retrospective case series	4	D
Morris [20]	Retrospective case series	4	D
Nandakumar et al. [21]	Retrospective case series	4	D
Pascual et al. [22] [a]	Prospective single arm	2b	C
Pascual et al. [23]	Prospective single arm	4	D
Taverner and Bain [24]	Prospective single arm	4	C
Fernandez-Torre et al. [25]	Retrospective case series	4	D
Westreich and Kneller [26]	Retrospective case report	4	D

[a] Lemmen et al. [18] and Pascual et al. [22] are studies containing small numbers of pediatric patients, of which the data cannot be extracted from the adult information. Thus these studies were considered to be adult studies, with the pediatric data included in the analysis.

4. Discussion

Lidocaine is a type Ib anti-arrhythmic agent and sodium channel antagonist commonly utilized in the cardiac and pain literature. It is via its sodium channel blockage that neural conduction is reduced and impeded, leading to its anti-arrhythmic and anesthetic properties. Given these effects at the neuronal sodium channel, lidocaine's role as an AED has been investigated [12,14–26].

Unlike other sodium channel blocking AEDs, such as phenytoin (also a class Ib anti-arrhythmic), its structure includes an aromatic and amine chain motif allowing for binding to the sodium channel via both the channels pore-lining phenyl binding site [36,37], or via the external amine chain site, both of which lead to the reduction of ion transport across the cellular membrane. Other sodium channel based AEDs typically only carry a diphenyl motif, solely allowing binding at the pore-lining phenyl sites [13], blocking sodium ion transport. Thus, lidocaine can potentially add further sodium channel blockade in the setting of refractory seizures where other sodium channel antagonists are on board, via interaction with the external amine binding site.

To date small case series have appeared since the 1950s describing the use of lidocaine as an AED, with the majority of the literature focused on the pediatric population. Current literature suggests a trend to improved responsiveness in the neonate population, which may suggest a differential response rate depending on the degree of brain maturation. This however has yet to be substantiated. Given the success of lidocaine as an AED in the setting of neonatal and pediatric seizures [10–12], we elected to perform a systematic review of the literature in order to determine its effect on SE and RSE in the adult population.

Through our review we identified 13 articles pertaining to the reported usage of lidocaine for adult SE/RSE [14–26], with 11 published manuscripts and 2 published meeting abstracts. A total of 76 patients were described in these articles, with 82 distinct episodes of SE/RSE being treated with lidocaine. The majority of the studies were retrospective case reports/series, with only 3 being prospective single arm studies. Looking at the primary outcome of our study (seizure control), 70.7% of these SE/RSE episodes responded to lidocaine administration, with 64.3% complete seizure control rates. Of interest, during 69 of the SE/RSE episodes, phenytoin was on board during lidocaine administration, with 68.1% displaying seizure response to lidocaine. Recurrence of seizures after lidocaine withdrawal occurred in 22.4% of SE/RSE episodes. In the secondary outcomes, few adverse events were reported with lidocaine administration, though those reported were significant. Patient outcome data was too sparingly documented for any conclusions to be made. Twelve studies were

Oxford level 4 for quality, with one representing Oxford level 2b. Eleven studies were GRADE D, with 2 representing GRADE C level of evidence. A meta-analysis was not possible given the heterogeneous nature of the studies available. Thus, based on this review, we can currently provide Oxford level 4, GRADE C recommendations for the use of lidocaine for adult SE/RSE. This constitutes weak evidence to support the use of lidocaine in this context. The current lack of more robust studies impairs our ability to draw more definitive conclusions on the impact of lidocaine for SE/RSE in adults.

Some important points have arisen from our review. First, the seizure response rate of 70.7% with lidocaine administration in a population of medically refractory cases is quite high compared to other therapies for RSE [38]. This likely represents a significant publication bias, focused on publishing only positive results with lidocaine for SE/RSE. Second, the seizure cessation rate of 65.2% in response to lidocaine when phenytoin has already been administered highlights the effectiveness of this medication in the presence of another sodium channel agent, as further emphasized by the 61.5% cessation rate for those patients not on phenytoin during lidocaine therapy. This likely represents the effect of the external sodium channel binding motif of lidocaine, not possessed by other sodium channel AEDs. Third, the seizure recurrence with withdrawal of lidocaine therapy was 22.4%, emphasizing that this treatment is not a long-term solution, but an option during crisis. Seizure response to lidocaine should be met with ongoing adjustment of oral AEDs with the goal of discontinuing intravenous anesthetic agents. Fourth, there did not appear to be a trend to increased efficacy in any particular underlying etiology treated within the studies. Fifth, the majority of the studies originated in the USA or Western Europe. This is slightly different when compared to those in the neonate populations which have a Japanese predominance. Thus, there may be a potential for regional variation in the application and response of lidocaine for SE/RSE. Finally, the number of complications described was low, with only two patients developing hypotension. The two cases of cardiorespiratory arrest during the treatment of RSE are difficult to solely attribute to lidocaine therapy given the complexity of treatment and critical illness. However, given that we cannot completely exclude lidocaine as the cause of arrest given the available data, we include these two cases as complications of therapy.

Our review has significant limitations. First, the small number of studies identified, all with small patient populations, makes it difficult to generalize to all adult SE/RSE patients. Second, the predominantly retrospective heterogeneous nature of the data makes it difficult to perform a meaningful meta-analysis, resulting in a strictly descriptive analysis. Third, the heterogeneity of prior treatments, time to lidocaine administration, and lidocaine dosage and duration leave the data on seizure responsiveness difficult to interpret. It is even more difficult, on the basis of this data, to recommend a treatment regimen based on lidocaine. Fourth, the outcome data was poorly recorded in the majority of the studies identified. As such, formal comments on the impact of lidocaine therapy on patient outcome during SE/RSE cannot be made at this time. Fifth, a small number of pediatric patients may have been included in the synthesis of data, and thus our results may not reflect an entirely "adult" population. Two manuscripts describe patients under the age of 18 [18,22], however we were unable to separate their data from the adult population. Similarly, one study [19] failed to document the age of the patients. Though we suspect, based on the pathology described, that these patients were adults, they very well may be younger than 18 years of age. Sixth, the range of ages seen in this review is important. There may be a correlation of responsiveness to lidocaine and the degree of brain maturation. Thus, younger patients may be more adept to responding, as seen in the neonates, whereas the elderly may not be as responsive. We were unable to determine a trend to responsiveness in younger adult patients however. This is an area of potential future research. Seventh, we intentionally excluded non-English manuscripts from the review. Though we did not identify any abstracts of non-English origin that may have been of interest, we may have missed some non-English manuscripts in the process which focused on lidocaine for SE/RSE in adults. As a result, our review may not be entirely inclusive. Finally, as previously mentioned, there is likely a significant publication bias in the literature favoring the publication of only positive results with lidocaine therapy for adult SE/RSE. Despite these significant limitations, we believe the data provides evidence for the potential benefit of lidocaine therapy in the setting of adult SE/RSE.

Future prospective analysis of lidocaine treatment during adult SE/RSE should be conducted. Formal comparison between phenytoin and lidocaine in a randomized fashion may prove interesting. Furthermore, prospective evaluation of lidocaine as the 3rd line agent in adult SE/RSE, in comparison to other commonly utilized agents should be conducted. In addition, there exists room for multicenter RCT in RSE comparing lidocaine to other commonly utilized agents such as midazolam or thiopentone. Prior to embarking on such endeavors however, we need to outline a means for accurate and comprehensive outcome assessment, as this is currently lacking in the available literature.

5. Conclusions

There currently exists level 4, GRADE C evidence to support the consideration of lidocaine for SE and RSE in the adult population. This constitutes weak evidence to support the use of lidocaine in this context. Further prospective studies of lidocaine administration in this setting are warranted.

Conflicts of interest

None of the authors have any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.07.003.

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