ORIGINAL ARTICLE

Lidocaine for Status Epilepticus in Pediatrics

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ABSTRACT: ***Background:*** Our goal was to perform a systematic review of the literature on the use of intravenous lidocaine in pediatrics 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 Grading of Recommendations Assessment, Development, and Evaluation methodologies by two independent reviewers. ***Results:*** Overall, 20 original studies were identified, with 19 manuscripts and one meeting abstract. Two hundred and thirty-five pediatric patients were treated for 252 episodes of SE/RSE. Patients had varying numbers of antiepileptic drugs (two to eight) on board before lidocaine therapy. During 20 of the 252 (7.9%) episodes of SE/RSE, phenytoin was on board. The dose regimen of lidocaine varied, with some using bolus dosing alone; others used a combination of bolus and infusion therapy. Overall, 60.0% of seizures responded to lidocaine, with complete cessation and greater than 50% reduction seen in 57.6% and 12.3%, respectively. Patient outcomes were sparingly reported. ***Conclusions:*** There currently exists Oxford level 2b, Grading of Recommendations Assessment Developement, and Evaluation C evidence to support the consideration of lidocaine for SE and RSE in the pediatric population. Further prospective studies of lidocaine administration in this setting are warranted.

RÉSUMÉ: Traitement de l'état de mal épileptique par la lidocaïne en pédiatrie. ***Contexte :*** Nous avons effectué une revue systématique de la littérature à propos de l'utilisation de la lidocaïne par voie intraveineuse chez des enfants en état de mal épileptique (ÉMÉ) ou d'ÉMÉ résistant au traitement (ÉMÉR) afin de déterminer son impact sur le contrôle de l'ÉMÉ. ***Méthode :*** Nous avons recherché tous les articles sur ce sujet indexés dans MEDLINE, BIOSIS, EMBASE, Global Health, HealthStar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform (du début jusqu' à novembre 2014) ainsi que la documentation parallèle. Deux réviseurs indépendants ont utilisé l'Oxford and Grading of Recommendations Assessment, Development and Evaluation pour évaluer la qualité des études. ***Résultats :*** En tout, 20 études originales ont été identifiées, dont 19 manuscrits et un résumé. Deux cent trente-cinq patients d'âge pédiatrique ont ainsi été traités au cours de 252 épisodes d'ÉMÉ/ÉMÉR. Les patients recevaient plusieurs médicaments antiépileptiques (de 2 à 8) avant le traitement par la lidocaïne. Au cours de 20 des 252 épisodes d'ÉMÉ/ÉMÉR (7,9%), le patient recevait de la phénytoïne. La dose de lidocaïne était variable : certains ont reçu seulement un bolus alors que d'autres ont reçu la lidocaïne en bolus et en perfusion. En tout, 60% des crises ont répondu à la lidocaïne avec arrêt complet de la crise chez 57,6% des patients et plus de 50% de réduction chez 12,3% des patients. Peu d'information était rapportée sur l'issue chez les patients. ***Conclusions :*** Il y a actuellement des données de niveau 2b, selon le Grading of Recommendations Assessment, Development and Evaluation C, à l'appui de l'utilisation de la lidocaïne pour traiter l'ÉMÉ et l'ÉMÉR chez les patients d'âge pédiatrique. Il serait donc justifié de procéder à des études prospectives sur l'utilisation de la lidocaïne dans ce contexte.

Keywords: clinical pharmacology, epilepsy, epilepsy - pediatric, neurocritical care, neurology - neonatal, neurology - pediatric, pediatric neurology, pediatrics, seizures, status epilepticus

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Status epilepticus (SE) and refractory status epilepticus (RSE) can be difficult to manage in the pediatric and neonatal populations. Concerns over drug reactions and interactions in the developing child pose potential limitations to antiepileptic drug (AED) selection in the setting of SE and RSE.[1-3]

Current management options for SE and RSE in the pediatric/neonatal patient population include, but are not limited to: benzodiazepines, barbiturates, phenytoin, levetiracetam, carbamazepine, and lidocaine[4]—all of which have displayed varying efficacy at seizure control in SE and RSE.[4-7]

Lidocaine, a class Ib antiarrhythmic agent, has known sodium channel–based AED properties in both the adult and pediatric populations stemming back to the 1950s.[8-11] Its potential summative benefit in the presence of other sodium channel–mediated AEDs seem to be mediated by its amine chain motif and external sodium channel binding site.[12-14] Using lidocaine to treat

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seizures is common in the pediatric literature. Of interest within a recent survey, the third commonly prescribed AED for neonatal seizures was lidocaine.[4]

Given the use of lidocaine as an AED in the pediatric and neonatal populations as reported in the literature to date,[15-35] we decided to perform a systematic review to determine the effectiveness of lidocaine in controlling pediatric/neonatal SE and RSE.

Methods

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers[36] was conducted. The data were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[37] The review questions and search strategy were decided upon by the primary author (FAZ) and supervisor (MW).

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 children? 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, pediatric patients (age younger than 18 years), any language, and the use of lidocaine for seizure control in SE. Exclusion criteria were adult and animal studies. Any non-English studies were translated.

Search Strategy

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

As well, meeting proceedings for the past 5 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, American Association of Neurological Surgeons, Congress of Neurological Surgeons, European Neurosurgical Society, World Federation of Neurological Surgeons, American Neurology Association, American Academy of Neurology, American Epilepsy Society, European Federation of Neurological Science, World Congress of Neurology, Society of Critical Care Medicine, Neurocritical Care Society, and the World Federation of Societies of Intensive and Critical Care Medicine, American Society for Anesthesiologists, World Federation of Societies of Anesthesiologist, Australian Society of Anesthesiologists, International Anesthesia Research Society, Society of Neurosurgical Anesthesiology and Critical Care, Society for Neuroscience in Anesthesiology and Critical Care, and the Japanese Society of Neuroanesthesia and Critical Care.

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

Study Selection

Using two reviewers (FAZ and KJZ), 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 the articles 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).

Data Collection

Data were 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 administration used, timing to administration of drug, duration of drug administration, time to effect of drug, how many other AEDs were used before lidocaine, degree of seizure control, adverse effects, and patient outcome.

Quality of Evidence Assessment

Assessment of the level of evidence for each included study was conducted by two independent reviewers (FAZ and MW) using the Oxford criteria[38] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria[39-44] for level of evidence.

The Oxford criteria consist of a five-level grading system for literature. Level 1 is split into subcategories 1a, 1b, and 1c, which represent a systematic review of randomized control trials with homogeneity, individual randomized control trials 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 randomized control trials, 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 (CJK).

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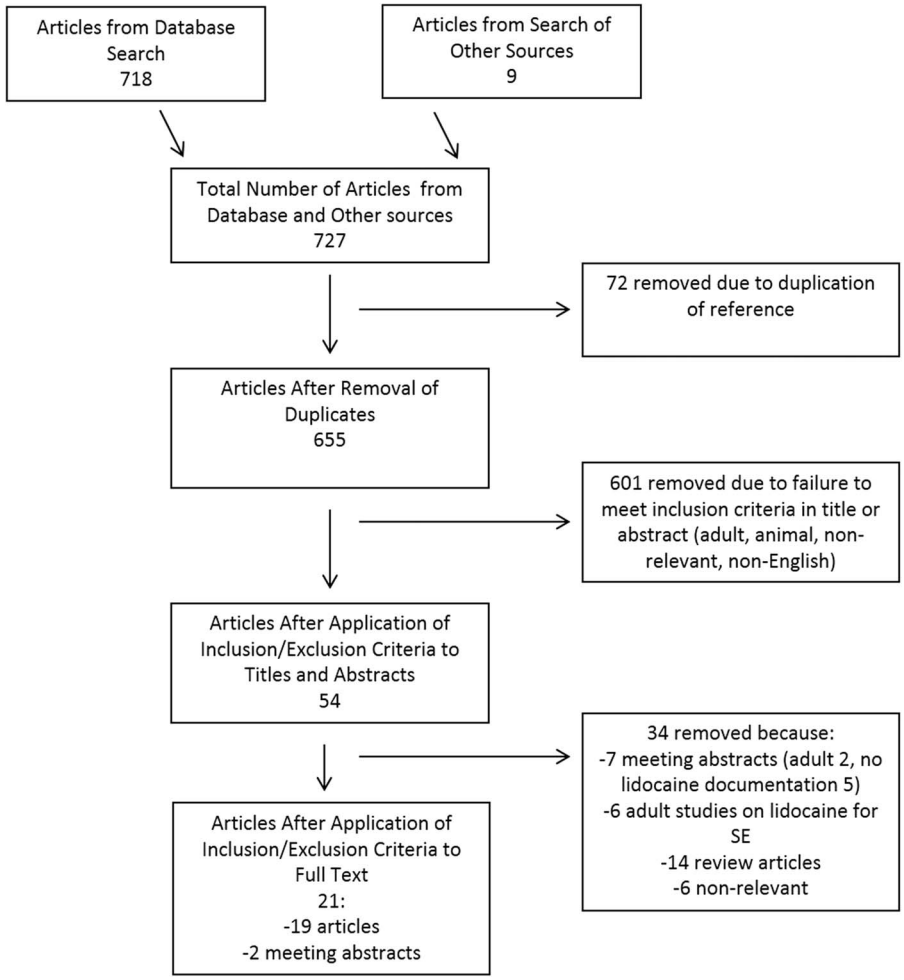

Figure 1: *Flow diagram of search results.*

Statistical Analysis

A meta-analysis was not performed in this study because of the heterogeneity of data within the articles and the small number of low-quality studies.

Results

The results of the search strategy across all databases and other sources are summarized in Figure 1. Overall, a total of 727 articles were identified, with 718 from the database search and nine 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 54 articles that fit these criteria. Of the 54 identified, 45 were from the database search and nine were from published meeting proceedings. Applying the inclusion/exclusion criteria to the full-text documents, only 21 articles were eligible for inclusion in the systematic review, with 19 from the database and two from meeting proceeding sources. The 33 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 adult patients only, were nonrelevant studies, or because they were review articles. Upon review of the reference sections of relevant review articles, no additional articles were added.

Of the 21 articles included in the review, 20 were original studies,[15-26,28-35] with one companion abstract publication identified.[27] The companion abstract was included for completeness[27] and was not included for the rest of the review to avoid duplication of patient data. There were 15 original retrospective studies[15,16,18,20,21,23-26,28,30,32-35] and five prospective studies.[17,19,22,29,31] Within the retrospective studies, 12 were retrospective case series[15,16,18,20,21,24,26,28,30,32,34,35] and the remaining three were retrospective case reports.[23,25,33] All studies were based in single centers. The five prospective studies included three prospective single-arm studies[22,29,31] and two randomized control trials.[17,19] The two randomized control trials compared lidocaine to benzodiazepine (midazolam or clonazepam) in the setting of RSE.

Across all studies, 235 patients were studied using lidocaine for control of their SE/RSE (mean: 11.8 patients/study; range: 1-46 patients/study), with a total of 252 separate episodes of SE/RSE treated with lidocaine documented. Sixteen patients were studied as controls, using benzodiazepine-based therapies in the setting of RSE.[17,19] The age of patients studied ranged from 25 weeks' gestational age to 16 years. Study demographics and patient characteristics for the pediatric studies can be seen in Table 1, whereas treatment characteristics and seizure outcome are reported in Table 2.

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Table 1: Pediatric 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 before lidocaine	Mean time until lidocaine administration (days)
Aggarwal et al[15]	1 (4 patients total; only 1 pediatric)	Retrospective case series	Single center	Journal	16	Primary GTC epilepsy	2	Unknown
Bernhard et al[16]	1 (10 patients total; only 1 pediatric)	Retrospective case series	Single Center	Journal	3	Primary focal epilepsy Focal SE (1)	0	Unknown
Boylan et al[17]	5 (11 neonates randomized overall; only 5 received lido)	Prospective Randomized (All received phenobarb; if fail, after 12 hours then randomized to midaz or lido or clonaz as second-line therapy)	Multicenter	Journal	29-42 weeks GA	Hypoxic ischemic encephalopathy (8); Intracranial hemorrhage (2); prematurity (1)	1	12 hours
Dan et al[18]	2 (6 children, only 2 Tx with lido)	Retrospective case series	Single center	Journal	9 and 10	Unknown (1); cortical dysplasia (1)	7 (range: 6-8)	Unknown
Fallah et al[19]	20	Prospective randomized trial (comparing midazolam to lidocaine in RSE)	Single center	Journal	3.8 (range: 0.1-12 years)	Idiopathic (3); primary epilepsy (17)	3 (diazepam, phenytoin, phenobarb)	35 minutes
Hamano et al[20]	37 (53 episodes of SE)	Retrospective case series	Single center	Journal	3.6 (range: 0.2-15.1 years)	Primary epilepsy (19); acute encephalitis (14); febrile seizures (4) 53 total SE episodes: -40 generalized SE -14 focal SE	2-3	Unknown
Hellstrom-Westas et al[21]	46	Retrospective case series	Single center	Journal	25-43 weeks GA	asphyxia (25); ICH (9); meningitis (4); cardiac disease (1); SIDS (2); metabolic (1); septicemia (1); idiopathic (3)	1 to 2 (phenobarb in all, 22 received diazepam)	Unknown
Hellstrom-Westas et al[22]	24	Prospective single arm	Single center	Journal	26-42 weeks GA	Asphyxia (15); ICH (6); hypoxia (2); hypoglycemia (1)	1 to 3 (phenobarb in all, 21 received diazepam)	Unknown
Kobayashi et al[23]	1	Retrospective case report	Single center	Journal	6	Primary epilepsy	5	Unknown
Kwon et al[24]	7	Retrospective case series	Single center	Meeting abstract	2.6 years (range: 0.2-10 years)	Unknown	1	Unknown
Lago et al[25]	1	Retrospective case report	Single center	Journal	39 weeks GA	TS	3	Unknown

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Table 1. *Continued*

Reference	Number of patients treated with lidocaine	Study type/design	Study setting	Article location	Mean age (years)	Etiology of seizures	Mean # meds before lidocaine	Mean time until lidocaine administration (days)
Lin et al[26]*	4 (9 total; only 4 Tx with lido)	Retrospective case series	Single center	Journal	10 years (range: 9.1-14.5 years)	AERRPS	4	Unknown
Lin et al[27]*	3	Retrospective case series	Single center	Meeting abstract	Range: 6-14 years	AERRPS	Unknown	9.3 days (range: 9-10 days)
Lundqvist et al[28]	30	Retrospective case series	Single center	Journal	Unknown	Unknown	1-2 (benzodiazepine infusions in all)	Unknown
Malingre et al[29]	20	Prospective single arm	Single center	Journal	Unknown "neonates"	Unknown	2 (phenobarb in all; either midaz or clonaz as second agent)	Unknown
Okumura et al[30]	1 (2 cases; only 1 Tx with lido)	Retrospective case series	Single center	Journal	7 and 8	Acute encephalopathy NYD	3	Unknown
Rey et al[31]	13	Prospective single arm	Single center	Journal	29-42 weeks GA	Asphyxia (10); hypernatremia (1); *Listeria* (1); unknown (1)	2 (all had phenobarb and diazepam)	0.2-4.3 days
Shany et al[32]	22 (30 total; 22 Tx with lido, 8 with midaz)	Retrospective case series	Single center	Journal	1.5-9 years	Asphyxia (30)	2 (phenobarb and benzo)	Unknown
Wakamoto et al[33]	1	Retrospective case report	Single center	Journal	7.5	Encephalitis Focal SE	2	Unknown
Wallin et al[34]	3	Retrospective case series	Single center	Journal	Unknown "neonates"	asphyxia (2); idiopathic (1)	(Phenobarb and diazepam in all)	3.6 days (range: 2-6)
Yamamoto et al[35]	16 (65 total studied; 49 midaz only, 10 lido only, 6 both)	Retrospective case series	Multicenter	Journal	25-41 weeks GA	Undefined number of varying pathologies	6.3% Hypotension, hypersecretion, abdominal distension	

AERRPS, acute encephalitis with refractory repetitive partial seizures; benzo, benzodiazepine; clonaz, clonazepam; GA, gestational age; GTC, generalized tonic clonic; lido, lidocaine; midaz, midazolam; NYD, not yet diagnosed; phenobarb, phenobarbital; TS, tuberous sclerosis; Tx, treatment.

*Lin et al[26] and Lin et al[27] contain duplicate data, with only the data from Lin et al[26] included in the final summary of data. Lin et al[27] is the published meeting abstract of Lin et al.[26]

A variety of underlying pathology leading to SE/RSE was reported within the 234 cases treated with lidocaine. The most commonly reported pathology was hypoxia/anoxia, primary epilepsy, encephalitis, and intracerebral hemorrhage. A large number of studies failed to specify the underlying cause of SE/RSE.

Pre-Lidocaine Treatment Characteristics

Duration of treatment before lidocaine administration was documented in five studies, ranging from 35 minutes to 10 days. Patients were on various numbers of AEDs before lidocaine, with the mean number of AEDs ranging from two to eight with most patient treatments typically consisting of a combination of oral AED and intravenous anesthetic agents. Of note, in 20 of the 234 (8.5%) SE/RSE episodes described, phenytoin was on board during lidocaine administration. All AEDs reported as being used in management were typically on board during the lidocaine treatment. Similarly, the duration of lidocaine treatment was described in 10 of the 20 studies, with treatment duration ranging from one time bolus dosing, up to 36 days of continuous intravenous infusion. One patient was discharged with lidocaine transdermal patches, eventually being transitioned to mexilitine.[23]

Lidocaine Treatment Characteristics

The Retrospective Studies

The literature on lidocaine use for control of SE/RSE in the pediatric population yielded 15 retrospective studies.[15,16,18,20,21,23-26,28,30,32-35] Within these 15 studies, one used bolus dosing of lidocaine in isolation,[15] with a dose of 100 mg intravenously once.

Four studies used continuous infusions of lidocaine only,[23,26,28,34] with dosing ranging from 1 to 8 mg/kg/hour. Of note, one of these studies[23] transitioned from continuos infusion to lidocaine transdermal patch for maintenance therapy in a single patient. Duration of the lidocaine infusion was documented in only one study from this group, with duration ranging from 0.5 to 2.5 days.[28]

Six studies used bolus dosing of lidocaine, followed by continuous infusions.[16,20,21,24,25,32] The initial bolus ranged from 0.91 mg/kg to 4 mg/kg intravenously, typically given over 20 minutes (when documented). The infusion rates ranged up to 2 to 6 mg/kg/hour. The duration of the lidocaine infusions in this group of studies varied from 1 to 36 days, with three manuscripts failing to document duration of therapy.[20,24,32]

Finally, four studies failed to document the details of lidocaine dosing and administration.[18,30,33,35] Lidocaine treatment characteristics can be seen in Table 2.

The Prospective Studies

The literature on lidocaine use for control of SE/RSE in the pediatric population yielded five prospective studies.[17,19,22,29,31] Within these, three were prospective single-arm studies. The first study was a prospective study of 24 patients with unspecified underlying etiology, treated with a 1.6 to 2.2 mg/kg bolus, followed by a continuous infusion at 4.7 to 6.3 mg/kg/hour, for a duration of 0.1 to 9.3 days.[22] The second study was a prospective study of 20 patients with unspecified underlying etiology, treated with 2 mg/kg intravenous bolus of lidocaine over 10 minutes, followed by continuous infusion for 36 hours.[29] The infusion protocol was as follows: 6 mg/kg/hour for 12 hours, then 4 mg/kg/hour for 12 hours, and finally 2 mg/kg/hour for 12 hours. The final prospective single-arm study followed 13 patients with hypoxia as the predominant underlying etiology.[31] These patients were administered continuous lidocaine infusions via the following protocol: 4 mg/kg/hour for 1 day, then 2 mg/kg/hour for 1 day, and finally 1 mg/kg/hour for 1 day for a total treatment duration of 3 days.

The two remaining prospective studies identified in this review were randomized control trials comparing lidocaine to benzodiazepine-based therapy.[17,19]

The first study was a randomized control trial of 11 patients with hypoxia as the predominant etiology of their SE. These patients had all received phenobarbitone as the first-line AED, and if failure of seizure control was noted at 12 hours they were randomized to one of three groups. One group (n = 5) received lidocaine bolus of 4 mg/kg over 20 minutes, followed by a continuous infusion at 2 mg/kg/hour for an unspecified duration. If failure of lidocaine occurred at this point, the infusion dose was escalated to 4 mg/kg/hour for 12 hours. If the seizures still failed to respond at this point the patient was removed from the trial. Another group (n = 3) received a midazolam bolus of 60 mcg/kg followed by an infusion of 150 mcg/kg/hour for 12 hours. If failure of midazolam occurred at this point, the infusion dose was escalated to 300 mcg/kg/hour for 12 hours. If the seizures still failed to respond at this point, the patient was removed from the trial. The final group (n = 3) received clonazepam at an unspecified dose and duration.

The second randomized trial followed 20 patients with primary epilepsy as predominant etiology of their SE.[19] These patients all received diazepam (0.2-0.3 mg/kg intravenous load twice), phenytoin (15-20 mg/kg intravenous load), and phenobarbitone (10 mg/kg intravenous load over 10 minutes). If failure of these three AEDs occurred, patients were enrolled and randomized to receive either midazolam or lidocaine therapy. The midazolam group (n = 10) received 0.15 mg/kg bolus followed by a continuous infusion of 1 to 6 mcg/kg/hour, titrated to effect, for a treatment duration of 24 hours. The lidocaine group (n = 10) received a 1 mg/kg bolus; if no response, then a second dose was given after 15 minutes followed by a continuous infusion at 5 mg/kg/hour for 12 hours. The infusion was then titrated off by 0.5 mg/kg/hour on an hourly basis. If a patient from either group failed, then therapy was stopped and pentobarbital was started.

Seizure Response

Overall, 174 of the 252 (69.0%) SE/RSE episodes studied displayed seizure response to lidocaine administration. Complete seizure control upon lidocaine administration occurred in 143 of the 252 (57.6%) SE/RSE episodes documented. A greater than 50% reduction in seizure frequency occurred in 31 of the 252 (12.3%) SE/RSE episodes described. Failure of lidocaine treatment occurred in 78 of 252 (30.9%) episodes.

In those patients with phenytoin on board during lidocaine administration, there were 20 discrete SE/RSE episodes recorded. Lidocaine administration resulted in seizure reduction in 12 of these 20 (60.0%) episodes, with all resulting in complete seizure control. Eight of these 20 (40.0%) SE/RSE episodes failed lidocaine administration when phenytoin was already on board.

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Table 2: Pediatric 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 during lidocaine	Electrographic seizure response	Recurrence after withdrawal of lidocaine	Adverse effects to lidocaine	Patient outcome
Aggarwal et al[15]	1	100 mg IV x 1	Single bolus	1/1	Immediate cessation	Yes; control for 12 hours	None	Unknown
Bernhard et al[16]	1	4 mg/kg IV x 1 4-6 mg/kg/hour infusion started after recurrence	24 hours	0/1	Transient decrease in seizures and cessation of SE	Yes	None	Achieved pre-SE baseline
Boylan et al[17]	5 (6 other randomized patients: 3 treated with midaz, 3 with clonaz)	Phenobarbitone at 40 mg/kg was ongoing Lidocaine = 4 mg/kg over 20 min then 2 mg/kg/hour for 12 hours, if failure then 4 mg/kg/hour Midazolam = 60 mcg/kg load than 150 mcg/kg/hour for 12 hours, if failure then 300 mcg/kg/hr Clonazepam = unspecified dose	12 hours of each therapy, if no response, then increase infusions for another 12 hours. If failure of increased dose, patient removed from trial.	0/5	2/5 lidocaine patients became seizure-free 1/5 had 80% reduction in seizures on EEG All other infants (midaz group, or increased dosing of lido/midaz, or clonaz group) had no response	Unknown	None	Lidocaine group = 3/5 severe limitations, 2/5 died Midazolam = 1/3 mild impairment, 1/3 moderate, 1/3 died Clonazepam = 1/3 moderate impairment, 1/3 died, 1/3 LTFU
Dan et al[18]	2	Unknown	Unknown	1/2	Failed in both	Unknown	None	Died (1); required IA and no impact on outcome (1)
Fallah et al[19]	10 (randomized patients: 10 with midaz; 10 with lido)	All patients: A. Diazepam (0.2-0.3 mg/kg bolus x2) B. Phenytoin (15-20 mg/kg load) C. Phenobarbitone (10 mg/kg over 10 minutes) If failed above then randomized: Midaz group (n = 10): 0.15 mg/kg bolus then 1 mcg/kg/hour infusion titrated up to 6 mcg/kg until control -Continued for 24 hours if effective, then titrated off Lidocaine group (n = 10): 1 mg/kg bolus; repeat if no response in 15 minutes, then infusion at 1 mg/kg/hour titrated to 5 mg/kg/hour until control -Continued for 12 hours at this dose then titrated off by 0.5 mg/kg/hour *if either medication failed, they were stopped and pentobarb started	12 hours	10/10	Lidocaine 5/10 seizure cessation: -2/5 with first bolus -2/5 with second bolus -1/5 with infusion Midazolam 2/10 seizure cessation	Unknown	Transient bradycardia (1)	Unknown
Hamano et al[20]	37 (53 episodes of SE)	Bolus dose: 0.91-3.33 mg/kg Infusion: 2.59 mg/kg/hour (range: 2-4 mg/kg/hour)	Unknown	0/37	Stopped seizures in 19/53 episodes of SE within 5 minutes of Tx	Unknown	Decreased SpO_2 in 1 patient temporarily	Unknown

Hellstrom-Westas et al[21]	46	Bolus dose: 1-2 mg/kg Infusion: up to 6 mg/kg/hr	3.5 days (range: 0-12 days)	0/46	38/46 patients had seizure cessation: -Bolus of 2 mg/kg stopped seizures in 15/21 within 5 minutes, and 5/29 in 30 minutes -Bolus of 1-1.5 mg/kg stopped seizures in only 3/6 -Seizures usually recurred with maintenance under 6 mg/kg/hour	No; only recurred initially if infusion <6 mg/kg/hour	Decrease in HR by 10-40 beats/minute (20); Increase in HR by 30-40 beats/minute (2); BP change (7)	Unknown
Hellstrom-Westas et al[22]	24	Bolus dose: 1.6-2.2 mg/kg Infusion: 4.7-6.3 mg/kg/hour	3.1 days (range: 0.1-9.3 days)	Unknown	15/24 immediate cessation of seizures 3/24 seizure reduction 6/24 transient/no response	Recurrence in 4/24	Metabolic acidosis (1)	Unknown
Kobayashi et al[23]	1	Infusion: 1 mg/kg/hour Lidocaine tape used for maintenance: 18 mg/tape; 4 tapes every 8 hours	Transitioned to mexiletine	1/1	Immediate response to infusion	None	None	At baseline
Kwon et al[24]	7	Bolus dose: 1-2 mg/kg Infusion: 2-4 mg/kg/hour	14 days (range: 4-36 days)	0/7	2/7 complete seizure cessation 3/7 had <50% reduction in seizures 2/7 no response	None	3/7 hypotension	Unknown
Lago et al[25]	1	Bolus dose: 2 mg/kg Infusion: 6 mg/kg/hour	Unknown	1/1	Failed	None	None	Died
Lin et al[26]*	4 (9 total; only 4 Tx with lido)	Infusion: 6-8 mg/kg/hour	Unknown	4/4	Complete response in 4/4	None	None	Died (1); vegetative (1); moderate impairment (1); mild impairment (1)
Lin et al[27]*	3	Infusion: 6-8 mg/kg/hour	Unknown	Unknown	Complete response in 3/3	None	None	Transitioned to topiramate and other AEDs
Lundqvist et al[28]	30	Bolus dose (n = 1) Infusions: 4-8 mg/kg/hour	1.8 days (range: 0.5-2.5 days)	0/30	16/30 patients had complete cessation of seizures 3/30 had reduction in seizures 1/30 had an incomplete response	Unknown	None	Unknown
Malingre et al[29]	20 (21 episodes of SE)	Bolus dose: 2 mg/kg over 10 minutes Infusion: 6 mg/kg/hour for 12 hours; then 4 mg/kg/hour for 12 hours; then 2 mg/kg/hour for 12 hours	36 hours	0/20	11/20 had cessation of seizures 5/20 had reduction in seizures 5/20 had no response	Unknown	None	Unknown

Table 2. *Continued*

Reference	Number of patients treated with lidocaine	Lidocaine dose	Mean duration of lidocaine administration (days)	PHT on board during lidocaine	Electrographic seizure response	Recurrence after withdrawal of lidocaine	Adverse effects to lidocaine	Patient outcome
Okumura et al[30]	1 (2 cases; only 1 Tx with lido)	Unknown	Unknown	1/1	Failure	Unknown	Unknown	Moderate impairment, controlled on multiple AEDs
Rey et al[31]	13	Infusions: 4 mg/kg/hour for 1 day; then 3 mg/kg/hour for 1 day; then 2 mg/kg/hour for 1 day, then 1 mg/kg/hour for 1 day	4 days	0/13	11/13 (85%) seizure control (effect within 13 hours of starting lido)	Unknown	None	Unknown
Shany et al[32]	22 (30 total; 22 Tx with lido, 8 with midaz)	Bolus dose: 2 mg/kg over 20 minutes Infusion: 4 to 6 mg/kg/hour	Unknown	0/22	11/22 seizure control 6/22 partial response 5/22 no response	Unknown	None	Died (5); major disability (7); no complication (9)
Wakamoto et al[33]	1	Unknown	Unknown	1/1	Failure	Unknown	Unknown	Died
Wallin et al[34]	3	Infusion up to 6.8 mg/kg/hour	3 days (1); 3 weeks (1); 3 months (1)	0/3	All responded to therapy	No; recurrence on initial withdrawal in case 2 and 3, but not after prolonged infusion	None	Unknown
Yamamoto et al[35]	16 (65 total studied; 49 midaz only, 10 lido only, 6 both)	Not clear; mean dose 1.8 mg/kg/hour during Tx period	Unknown	Not clear	4/16 complete seizure cessation 9/16 reduction in seizures by >50% 3/16 reduction in seizures by <50% or failure	Unclear	6.3% hypotension, hypersecretion, abdominal distension	Unclear

BP, blood pressure; IV, intravenous; midaz, midazolam; rehab, rehabilitation center; Tx, treatment.

*Lin et al[26] and Lin et al[27] contain duplicate data, with only the data from Lin et al[26] included in the final summary of data. Lin et al[27] is the published meeting abstract of Lin et al.[26]

Table 3: Pediatric studies: Oxford and GRADE level of evidence

Reference	Study type	Oxford[38] level of evidence	GRADE[39-44] level of evidence
Aggarwal et al	Retrospective case series	4	D
Aggarwal et al[15]	Retrospective case series	4	D
Bernhard et al[16]	Prospective randomized trial	2b	C
Boylan et al[17]	Retrospective case series	4	D
Dan et al[18]	Prospective randomized trial	2b	B
Fallah et al[19]	Retrospective case series	4	D
Hamano et al[20]	Retrospective case series	4	D
Hellstrom-Westas et al[21]	Prospective single arm	2b	C
Hellstrom-Westas et al[22]	Retrospective case report	4	D
Kobayashi et al[23]	Retrospective case series	4	D
Kwon et al[24]	Retrospective case report	4	D
Lago et al[25]	Retrospective case series	4	D
Lin et al[26]*	Retrospective case series	4	D
Lin et al[27]	Retrospective case report	4	D
Lundqvist et al[28]*	Prospective single arm	2b	B
Malingre et al[29]	Retrospective case report	4	D
Okumura et al[30]	Prospective Single arm	2b	C
Rey et al[31]	Retrospective case series	4	D
Shany et al[32]	Retrospective case report	4	D
Wakamoto et al[33]	Retrospective case series	4	D
Wallin et al[34]	Retrospective case series	4	D
Yamamoto et al[35]	Retrospective case series	4	D

*Lin et al[26] and Lin et al[27] contain duplicate data, with only the data from Lin et al[26] included in the final summary of data. Lin et al[27] is the published meeting abstract of Lin et al.[26]

In comparison, analyzing those patients treated with lidocaine without phenytoin on board recorded a total of 232 discrete SE/RSE episodes. Complete seizure response to lidocaine administration occurred in 131 of the 232 (56.5%) of the SE/RSE episodes. Failure of lidocaine therapy occurred in 70 of the 232 (30.1%) of the SE/RSE episodes described.

Focusing on the randomized trials[17,19] comparing lidocaine treatment to benzodiazepine-based therapy for SE/RSE, one study displayed a 60.0% seizure response rate to lidocaine (either cessation or >50% reduction in seizures), with the benzodiazepine groups failing to demonstrate seizure response.[17] The second randomized trial displayed a 50% seizure response rate to lidocaine in the setting of RSE, with only a 20% response rate in the midazolam group.[19]

Recurrence of seizures upon withdrawal of lidocaine occurred in six of the 78 (7.7%) responsive SE/RSE episodes. Recurrence rates were unspecified in 174 of the SE/RSE episodes.

Adverse Effects of Lidocaine

Only six studies documented adverse events related to lidocaine administration.[19-22,25,35] Bradycardia and hypotension were noted in 30 and 11 patients, respectively. Other less commonly reported complications were: tachycardia (two), metabolic acidosis (one), and decreased oxygen saturations (one).

Outcome

Patient outcome was reported sparingly in most studies because the main focus of these reports was the success/failure of lidocaine treatment. In those studies that reported such data, outcomes were as follows: dead (13), major morbidity (14), moderate morbidity (4), and minor/no morbidity (13). These data can be seen in Table 2.

Level of Evidence for Lidocaine

Based on two independent reviewers, there were a total of 20 original studies reviewed with five representing Oxford level 2b evidence for the administration of lidocaine in pediatric SE/RSE.[17,19,22,29,31] Fifteen studies represented Oxford level 4 evidence for lidocaine administration in pediatric SE/RSE.[15,16,18,20,1,23-26,27,28,30,32-35]

Two of the 20 studies met GRADE B level of evidence,[19,29] three met GRADE C evidence,[17,22,31] whereas the remaining 15 met GRADE D level of evidence.[15,16,18,20,1,23-26,27,28,30,32-35] Summary of the level of evidence can be seen in Table 3.

Discussion

Lidocaine is a type Ib antiarrhythmic agent and sodium channel antagonist commonly used in the cardiac and pain literature. It

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is through its sodium channel blockage that neural conduction is reduced and impeded, leading to its antiarrhythmic 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 antiarrhythmic), 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,[27,28] 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 because of 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. 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 to determine its effect on SE and RSE in the adult population.

Through our review, we identified 20 original articles pertaining to the reported usage of lidocaine for control of SE/RSE in the pediatric population. Nineteen were published manuscripts, whereas one was a published meeting abstract. A total of 235 patients were described in these articles with 252 discrete episodes of SE/RSE treated with lidocaine therapy. Sixteen patients were identified as prospectively enrolled control subjects, receiving benzodiazepine-based therapy in comparison to lidocaine.

The majority of the studies were retrospective case reports/series, with only five being prospective in nature. Looking at the primary outcome of our study (seizure control), 69.0% of the SE/RSE episodes responded to lidocaine therapy via seizure cessation or greater than 50% reduction in seizures. Complete seizure cessation was noted in 57.6%, greater than 50% reduction in 12.3%, and failure of lidocaine therapy was noted in 30.9%. Comparing those patients with and without phenytoin on board during lidocaine administration, seizure cessation occurred in 60.0% and 56.6%, respectively. In the secondary outcomes, bradycardia and hypotension were commonly reported. Unfortunately, patient outcome data were too sparingly documented for any strong conclusion on the impact of lidocaine therapy in pediatric SE/RSE. A meta-analysis was not possible given the heterogeneous, retrospective nature of the studies available. Based on this review, we can currently provide Oxford level 2b, GRADE C, recommendations for the use of lidocaine for pediatric SE/RSE.

Some important points have arisen from our review. First, the seizure response rate of 69.0% with lidocaine administration in a population of medically refractory cases is quite high compared with other therapies for RSE.[45] This may represent a significant publication bias, focused on publishing only positive results with lidocaine for SE/RSE. Second, the seizure cessation rate of 60.0% to lidocaine whereas phenytoin has already been administered highlights the effectiveness of this medication in the presence of another sodium channel agent, as further emphasized by the 56.5% cessation rate for those patients not on phenytoin during lidocaine therapy. The effect of the external sodium channel binding motif of lidocaine, not possessed by phenytoin, is the likely reason for the seemingly "additive" benefit of lidocaine in the presence of another sodium channel based AED. Third, the two randomized trials,[17,19] though small, did demonstrate superior seizure control with lidocaine therapy compared to benzodiazepines when utilized as a second[17] or fourth[19] line agent in SE/RSE. Fourth, the seizure recurrence following withdrawal of lidocaine therapy was scarcely described, likely secondary to publication bias or underreporting. Lidocaine 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. Fifth, there did not appear to be a trend to increased efficacy in any particular underlying etiology treated within the studies. Finally, the number of complications described was not insignificant. Hypotension and bradycardia with lidocaine administration likely stems from the class Ib antiarrhythmic effects of lidocaine. It was not clear from the studies included in this review as to whether these side effects occurred during bolus dosing or continuous administration. Similarly, the dose of lidocaine therapy was likely to correlate with these side effects, though not commented on in the studies.

Our review has significant limitations. First, the small number of studies identified, all with small patient populations, makes it difficult to generalize to all pediatric 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 these data, to recommend a treatment regimen based on lidocaine. Fourth, the outcome data were 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. 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 pediatric SE/RSE. Despite these significant limitations, we believe the data provide evidence for the potential benefit of lidocaine therapy in the setting of pediatric SE/RSE.

Future prospective analysis of lidocaine treatment during 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 third-line agent in adult SE/RSE, in comparison to other commonly used agents also should be conducted.

Conclusions

There currently is Oxford level 2b, GRADE C, evidence to support the use of lidocaine for SE and RSE in the pediatric population. Further prospective studies of lidocaine administration in this setting are warranted.

Disclosures

The authors have nothing to disclose.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/cjn.2015.278.

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