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Original Article

Long-term Outcome of Intravenous Lidocaine in Pediatric Cluster Seizures: A Preliminary Study

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ABSTRACT

Background: Cluster seizures are life-threatening conditions. They may easily evolve into status epilepticus and are reported in up to 20% to 30% of patients with epilepsy. Sometimes cluster seizures become drug resistant, leading to the use of unconventional therapies. One of these unconventional approaches may be the use of lidocaine, which is a sodium-channel-blocking drug mostly known as a local anesthetic and antiarrhythmic agent.

Methods: We describe the outcome of four children who were treated with continuous intravenous infusion of 2% lidocaine due to drug-resistant focal cluster seizures. Lidocaine was administered as an initial dose of 1 mg/kg/hour and, subsequently, was increased to 2 to 4 mg/kg/hour. The therapy was continued for five to 10 days. Patients remained under careful cardiological surveillance during the treatment.

Results: Complete seizure remission was achieved in all four children. None of the patients experienced adverse events. Although seizures recurred in all patients within an average time of 2.4 months, they appeared with reduced frequency, and within the follow-up period (mean 7.5 months) no additional cluster seizures occurred.

Conclusions: Treatment with lidocaine in pediatric cluster seizures may be useful and may be considered as a therapeutic option. Our patients encountered no side effects and experienced prolonged seizure remission, possibly resulting from the effect of lidocaine on sodium channels or from its anti-inflammatory properties. However, more studies are required to confirm the safety and long-term effectiveness of this approach. Clinicians should be aware of possible adverse effects and necessity of sustained cardiological surveillance during the treatment.

Introduction

Epilepsy is a chronic neurological disease. In about 60% of cases, it begins in childhood. The goal of treatment of epilepsy in children is complete seizure remission to prevent epileptic encephalopathy and developmental delay. Despite the development of numerous new antiepileptic drugs (AEDs), still 20% to 30% of patients have recurrent seizures and drug-resistant epilepsy.[1] Especially in epileptic syndromes like West, Lennox-Gastaut, or Dravet syndromes, complete seizure remission is very difficult to achieve. In some patients, seizures recur as cluster seizures or as status epilepticus despite the treatment with many AEDs.

Cluster seizures are life-threatening conditions requiring obligatory hospitalization.[2] However, they are not listed in the International League Against Epilepsy Commission on Classification and Terminology, and currently, there is no single strict definition of cluster seizures.[3,4] Cluster seizures are an intermediate stage between a single epileptic attack and status epilepticus.[5] In different studies, cluster seizures were mostly defined as the occurrence of four epileptic seizures within 48 hours, three epileptic seizures within 24 hours, or several seizures within one to two days.[4,6,7] In other studies, cluster seizures were defined as a three- or fourfold increase of seizure frequency.[4] In spite of lack of a

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strict definition, cluster seizures are reported in up to 20% to 30% of patients with epilepsy. Epilepsies with focal seizures are often associated with difficult-to-control and recurrent seizures. Seizures associated with frontal and temporal lobe epilepsies present the greatest tendency to occur in clusters that sometimes do not respond to standard AEDs like benzodiazepines, barbiturates, valproic acid (VPA), phenytoin (PHT), and levetiracetam (LEV).[6] In the face of such drug-resistant life-threatening situations, it is sometimes necessary to use unconventional therapies to stop the seizures and improve the patient's condition. One of these unconventional approaches may be the use of lidocaine.

Lidocaine is mostly known as a local anesthetic and class Ib antiarrhythmic agent. Owing to its action via sodium channels, it has also been considered as a possible AED.[8-12] The first use of lidocaine in seizures was described by Bernhard et al. in 1955.[13] Since then some authors have also reported an antiepileptic effect of lidocaine, mostly in neonates and young children.[8-12,14-16]

The aim of this study was to assess the efficacy and safety of intravenous (IV) infusion of lidocaine in individuals with drug-resistant cluster seizures. We believe this is the first report of the extended follow-up of children treated with lidocaine due to cluster seizures and the first study in the population of Poland and Middle Europe.

Materials and methods

We reviewed the records of patients younger than 18 years who had been hospitalized at the Department of Child Neurology, Medical University of Warsaw, Poland, between 2016 and 2018 and who experienced drug-resistant cluster seizures and were treated with continuous IV infusion of lidocaine.

Inclusion criteria

All included children experienced drug-resistant cluster seizures. Based on the current literature we defined cluster seizures as at least a threefold increase in seizure frequency in patients with already diagnosed epilepsy (statistical definition) or at least two epileptic seizures within six hours in children in whom epilepsy was not previously diagnosed (clinical definition).[4]

Drug resistance was considered as the lack of complete cessation or more than 50% reduction in seizure frequency with the use of at least three classical AEDs including at least one first-line AED (benzodiazepines, i.e., diazepam, clonazepam [CLZ], lorazepam, midazolam) and at least two second-line AEDs (i.e., VPA, PHT, phenobarbital [PHB], LEV, or other classical AEDs depending on the type of seizures).

Therapeutic intervention

Owing to drug-resistant seizures, all our patients received an IV continuous infusion of 2% lidocaine at a preliminary dose of 1 mg/kg/hour, and then after at least six hours and cardiological assessment the dose was increased to 2 to 4 mg/kg/hour. The treatment was continued for five to 10 days. Other classical AEDs, which were used before, were also administered, and new AEDs were introduced at the end of lidocaine infusion.

Before administering lidocaine, we performed 12-channel electrocardiography, blood pressure measurement by sphygmomanometer, and blood testing (assessment of liver and kidney function, morphology, and ions) in every patient. During the treatment, patients were continuously monitored with heart rhythm, saturation, and blood pressure (using sphygmomanometer). Infusion of lidocaine was not begun or ceased if patient presented any contraindication to the use of lidocaine before or during the study (i.e., allergy for lidocaine, cardiac arrhythmia or sustained hypotension, impairment of liver or kidney function, suspicion or diagnosis of myasthenia gravis) or if the consent for the treatment with lidocaine was withdrawn.

The study was approved by the Bioethical Committee of the Medical University of Warsaw. Patients' parents and patients (if they were at least 16 years old) signed a consent form for treatment with IV lidocaine.

Objectives of the study

The primary objective of the study was at least a 75% reduction in seizure frequency after lidocaine infusion. The secondary objective was the evaluation of a safety profile and both short- and long-term outcomes of lidocaine IV infusion.

Results

The study group consisted of four patients (two girls and two boys) aged between two and 13 years (median age seven years), who experienced drug-resistant cluster seizures. Three of four patients (75%) were diagnosed and treated with epilepsy since early childhood. In their clinical course, they had been treated with many AEDs in different combinations (Table 1). However, sustained seizure remission (longer than a few months) was never achieved. Only one patient (patient no. 4) had not been previously diagnosed with epilepsy; however, in his medical history seizures began in early childhood.

During the lidocaine infusion complete seizure cessation was initially achieved in all children; however, after a few months seizures recurred (Table 2). Seizure remission persisted for the mean time of 2.4 months (ranged from 1.5 to three months). Nevertheless, the reduction of seizure frequency by about 80% to 100% sustained during a follow-up period (mean time of 7.5 months, ranged from three to 12 months) in all children.

Below we present the case reports of our patients. Details of lidocaine doses and duration of the infusion are summarized in Table 2.

Patient 1

This six-year-old girl with drug-resistant frontal lobe epilepsy and polymicrogyria was evaluated because of a significantly increased number of seizures (up to 70 to 100 per day).

At age one year, she was diagnosed with epilepsy after presenting with several dozen sudden tonic seizures of her right limbs with clonic movements of her left limbs, screaming with widely opened eyes, and pupillary dilitation. These episodes lasted for one to two minutes. Her psychomotor development was normal. Antiepileptic treatment was modified several times with transient improvement; nevertheless, seizures continued to occur every few days or weeks (Table 1). Brain magnetic resonance imaging (MRI) revealed extended right frontal lobe polymicrogyria. She was left-handed, and due to the significant risk of hemiparesis of her dominant side, she was not appropriate for surgical treatment.

After a few years, the morphology of her seizures changed. During the seizure, she presented with anxiety, screaming, an extension of the limbs (left more than right), autonomic signs (flushing), and pedal movements. Sometimes she expereinced transient paresis of the left leg after a very intense seizure. At age 5.5 years, she experienced two episodes of status epilepticus, and an external vagus nerve stimulator was implanted.

At age six years she was admitted to our clinic due to the occurrence of cluster seizures (up to 70 to 100 per day—anxiety,

TABLE 1.
Characteristics of the Study Group

Patient	Sex	Age at Admission	Age at First Epileptic Seizure	Type of Epilepsy	Brain MRI Results	AEDs Used in the Past in Different Combination	Type of Seizures During the Admission	Seizure Frequency During the Admission	AEDs Used During the Admission before Lidocaine Infusion
Patient 1	Female	6 years	1 year	Frontal lobe epilepsy	Extensive pachygyria of the right frontal lobe	VPA, CBZ, oral and IV PHT, LEV, PHB, TPM, CLB, VGB, LAC, LTG, OXC, IM ACTH, IVIG, external vagus nerve stimulation	Focal seizures (frontal lobe seizures)	70–100/day	CLZ, DZP, CBZ, PHB, TPM, LEV
Patient 2	Female	2 years	5 months	Epilepsy with focal seizures	Polymicrogyria/ pachygyria of the left parietal lobe	VPA, LEV, LTG, vitamin B12 due to its deficiency	Focal clonic seizures of limbs with disturbed consciousness	40–50/day with evolution to status epilepticus	DZP, CLZ, VPA, PHB, TPM, ACTH, LEV, thiopental, PHT, ketamine
Patient 3	Male	13 years	Since infancy	Lennox-Gastaut syndrome	Agenesis of corpus callosum with cortico-subcortical atrophy	VPA, LEV, VGB, TPM, PHT, LAC, IVIG, acetazolamide	Focal tonic seizures (left side of the body)	Up to 45/day	DZP, CLZ, VPA, TPM
Patient 4	Male	8 years	2 years	Frontal lobe epilepsy	No abnormalities	He was not treated with AEDs before the admission	Focal seizures (frontal lobe seizures)	Up to 70/day	DZP, CLZ, VPA, LEV, TPM

Abbreviations:
ACTH = Tetracosactide
CBZ = Carbamazepine
CLB = Clobazam
CLZ = Clonazepam
DZP = Diazepam
IM = Intramuscular
IV = Intravenous
IVIG = Intravenous immunoglobulin
LAC = Lacosamide
LEV = Levetiracetam
LTG = Lamotrigine
MRI = Magnetic resonance imaging
OXC = Oxcarbazepine
PHB = Phenobarbital
PHT = Phenytoin
TPM = Topiramate
VGB = Vigabatrin
VPA = Valproic acid

TABLE 2.
Characteristics and Effectiveness of Lidocaine IV infusion

Patient	Initial Dose of Lidocaine (mg/kg/hour)	Targeted Dose of Lidocaine (mg/kg/hour)	Time Between Dosage Increase	Duration of Lidocaine Infusion	Other AEDs Used with (Simultaneously) or After Lidocaine Infusion	Effect of the Treatment	Follow-up				
							Duration of the Follow-up	Time of Seizure Recurrence	Frequency of Seizures at the Time of Follow-up	AEDs Used at the Time of Follow-up	Seizure Reduction Compared With Admission
Patient 1	1	2	6 hours	10 days	LEV, PHT*	Complete seizure remission	12 months	3 months	1–2/week	LEV, PHT*	Nearly 100%
Patient 2	1	4	6 hours	5 days	PHT*, PHB*	Complete seizure remission	3 months	2 months	5–10/week	CLZ*, TPM*, VPA*	More than 90%
Patient 3	1	2	6 hours	5 days	VPA*, TPM*, PHT*, acetazolamide	Complete seizure remission	11 months	3 months	4–8/month	VPA*, TPM*, PHT*, acetazolamide	Nearly 100%
Patient 4	1	2	6 hours	5 days	CBZ*, PHT* and acetazolamide	Complete seizure remission	4 months	1 and 5 months	Mostly 3/day, Sometimes up to 10–15/day	CBZ*, LEV, LAC*	More than 80%

Abbreviations:
CBZ = Carbamazepine
CLZ = Clonazepam
LAC = Lacosamide
LEV = Levetiracetam
PHT = Phenytoin
PHB = Phenobarbital
TPM = Topiramate
VPA = Valproic acid
* Drugs acting via blocking sodium channels

limb extension, pedal movements). Before admission, she had been treated with oral carbamazepine (CBZ) and LEV. Initially, we began treatment with IV CLZ and other benzodiazepines; however, seizures were still observed. Subsequently, CBZ, IV PHB and then topiramate (TPM), and LEV were implemented but did not reduce the number of seizures. Therefore, after a cardiological assessment, we began an IV infusion of 2% lidocaine (Table 2). After a dozen hours, complete seizure remission was achieved and she returned to her baseline functioning. Lidocaine infusion was continued for 10 days, and oral PHT with LEV (CBZ was withdrawn) was simultaneously introduced at the end of lidocaine infusion. Before discharge from the hospital, 30- to 60-minute electroencephalography (EEG) confirmed the improvement.

During lidocaine infusion, she remained under strict cardiological surveillance. The treatment was well tolerated without adverse effects.

Seizures recurred three months later. After one year she was treated with oral LEV and PHT. Seizures were still observed, however, with significantly reduced frequency—one to two seizures per week.

Patient 2

This two-year-old girl with drug-resistant focal seizures, polymicrogyria or pachygyria, and developmental delay was admitted due to the occurrence of cluster seizures (two to three seizures per hour, several dozens of seizures per day) with evolution to status epilepticus.

First seizures were observed at age five months (disturbed consciousness with deviation of eyes and clonic movements of left or right limbs). Sometimes paroxysmal muscle hypotension, eyelid myoclonus with pupil extension, perioral movements, and limb tremors were also observed. Treatment had been initiated with VPA and LEV. She had been treated with many AEDs in different combinations; however, seizures were still observed (Table 1). Her brain MRI disclosed polymicrogyria in the left parietal lobe.

She was admitted to our clinic due to a significant increase in seizure frequency (focal clonic seizures of limbs, about 40 to 50 per day) during upper respiratory tract infection. First, diazepam (DZP) and IV CLZ had been implemented without improvement. Subsequently, we started IV infusion of VPA and then PHB, however, with no effect. Third, TPM and intramuscular tetracosactide were also introduced. Owing to the inefficiency of the treatment and evolution to status epilepticus, she was transferred to the intensive care unit and was treated with thiopental, VPA, LEV, TPM, IV infusion of midanium, IV PHT, ketamine. Despite the polytherapy, seizures still occurred, and after cardiological evaluation, we decided to treat her with IV infusion of 2% lidocaine (Table 2). After a dozen hours, complete seizure remission was achieved and she returned to baseline functioning. Subsequently, oral PHT and PHB were continued. Before discharge from the hospital, a 30- to 60-minute EEG confirmed the improvement.

During the lidocaine treatment, she remained under strict cardiological surveillance. She tolerated a lidocaine infusion well, without any adverse events.

Seizure remission lasted for two months with treatment of CLZ, TPM, and VPA. Subsequently, seizures recurred, however, with reduced frequency (five to 10 per week). Cluster seizures were not observed.

Patient 3

This 13-year-old boy with cerebral palsy (spastic tetraparesis), Lennox-Gastaut syndrome, and developmental delay was evaluated because of an increased number of seizures appearing in clusters—up to 45 per day.

His psychomotor development had been delayed since infancy and he had cerebral palsy (spastic tetraparesis). Brain MRI revealed agenesis of corpus callosum with a typical extension of lateral ventricles. Later a brain MRI showed additional cortico-subcortical atrophy.

First epileptic seizures (focal tonic seizures) had occurred in infancy. At ages 1.5 and 2.5 years, he experienced two episodes of status epilepticus with generalized tonic-clonic seizures. At age 10 years, he experienced status epilepticus every three to four months. Since age 12 years an increased number of polymorphic seizures, especially short myoclonic seizures of upper limbs (up to several dozens), were observed. He was treated with several AEDs in different combinations; however, permanent seizure remission was never achieved (Table 1).

During his admission at age 13 years, up to 45 seizures per day were observed (focal seizures with turning to the left), sometimes every five to 15 minutes. First, he was treated with benzodiazepines without improvement. Subsequently, IV infusion of VPA and oral TPM were introduced. After a dozen hours without further improvement, we decided to start IV infusion of lidocaine (Table 2). After a few hours, seizure reduction and then complete remission was achieved. Lidocaine infusion was continued for five days, and oral PHT was introduced at the end of lidocaine infusion. The patient returned to baseline functioning, and 30- to 60-minute EEG confirmed improvement. At discharge, he was treated with VPA, TPM, PHT, and acetazolamide.

During treatment, our patient was continuously cardiologically monitored. He tolerated the treatment well, without any adverse events.

Three months later seizures recurred. After 11 months tonic seizures were observed with a frequency of four to eight per month. There were no cluster seizures.

Patient 4

This eight-year-old boy, without a history of epilepsy, was admitted to our clinic due to the occurrence of up to 70 epileptic seizures per day. At age two years, paroxysmal episodes occurred, mostly during night sleep—he suddenly woke up, screamed with frightening and flushing face, and pedal movements. Those incidents lasted up to two minutes and were observed several times during the night. His psychomotor development was normal.

During his admission at eight years of age, seizures (with the morphology as previously described) occurred with frequency up to 70 per day, only during sleep and primarily during the night. First, he was treated with benzodiazepines (IV diazepam and CLZ) and then with IV infusion of VPA. No improvement was achieved. Subsequently, LEV and TPM were introduced with slight improvement; however, about 40 to 50 seizures per day were still reported. Owing to the inefficiency of standard antiepileptic treatment, we decided to treat him with an IV infusion of lidocaine (Table 2). During the second day of therapy, complete seizure remission was achieved, and treatment was continued for five days with simultaneous oral CBZ, PHT, and acetazolamide introduction.

During the lidocaine infusion, he was continuously cardiologically monitored. He tolerated the treatment well, without any adverse effects.

During seizures, EEG recordings revealed ictal discharges in frontal lobes. An EEG (30- to 60-minute recording), before discharge from the hospital, was normal. Brain MRI revealed no abnormalities. He was diagnosed with frontal lobe epilepsy.

After 1.5 months his seizures recurred, however, with significantly reduced frequency, up to 15 per day. Antiepileptic treatment was modified—acetazolamide and PHT were withdrawn and LEV with lacosamide was added to CBZ. After four months,

seizures were still observed—mostly three seizures per day, sometimes up to 10 to 15 per day.

Discussion

Owing to the very high seizure frequency, cluster seizures are life-threatening conditions. These seizures may easily evolve into status epilepticus, which can be associated with brain damage, and, subsequently, neurological and intellectual deficits.[15,17] Therefore, all patients with cluster seizures require quick seizure cessation and hospitalization in an intensive care unit.[2]

We present four patients with drug-resistant cluster seizures to whom we administered an unconventional treatment with continuous IV infusion of 2% lidocaine with significant improvement (Table 2). Lidocaine is mostly known as a local anesthetic and class Ib antiarrhythmic drug. However, due to its mechanism of action, it has also considered as an AED mostly in neonatal and pediatric status epilepticus.[8,11,12,14-16]

The mechanism of action of lidocaine is related to its blocking of sodium channels, which are voltage-gated proteins activated during depolarization and responsible for cellular activation.[8-10,18,19] A significant group of classical AEDs also act via sodium channels (e.g., CBZ, PHT).[1] However, unlike other AEDs, which include two phenyl groups, the lidocaine molecule contains an aromatic (phenyl) and a tertiary amine group (Fig).[19,20] The different chemical structure may explain the effectiveness of lidocaine in treating our patients despite an ineffectiveness of other AEDs.[20-22] The occurrence of both a phenyl and a tertiary amine group allows lidocaine to bind and block sodium channels not only via an aromatic site (as other classical AEDs) but also by additional amine site situated externally to aromatic binding.[21,23] In a study of 261 episodes of status epilepticus, Hattori et al. reported that nearly half of patients who did not respond to PHT responded to lidocaine.[15]

Moreover, the seizure remission and reduction lasting in our patients for a few months after lidocaine infusion may also suggest a long-term antiepileptic effect of lidocaine. Although a persisting seizure remission may be due to subsequently introduced PHT and other AEDs, the ineffectiveness of PHT in the medical history of our patients suggests an additional supportive effect of lidocaine on PHT efficacy.[8,9,21,24] PHT and lidocaine share a non-identical but overlapping binding side of the sodium channel.[21,24] Wang et al. reported that novel lidocaine/PHT hybrid molecule was a better binder to the sodium channel than PHT itself owing to the consistency of overlapping binding regions.[24] Therefore, the use of lidocaine, which binds in a different, overlapping, site of the receptor, may be effective during the crisis and facilitate the action of PHT for further seizure control. Another explanation for longer seizure remission after lidocaine infusion may be because of its anti-inflammatory effects.[19] There is evidence of a link between inflammation and epilepsy. Inflammation and proinflammatory cytokines are active in the brain tissue of patients with epilepsy and are playing a role in epileptogenesis, epilepsy, and status epilepticus[25,26] On the other hand, seizures, especially when persistent like cluster seizures or status epilepticus, also induce brain inflammation and increase the release of proinflammatory cytokines.[26] Cytokine interleukin (IL)-1β is particularly suggested to induce an excitatory effect on neurons, whereas anti-inflammatory IL-1Ra acts as an anticonvulsant agent.[25-28] Although lidocaine is not used as an anti-inflammatory agent, lidocaine exerts various effects on inflammatory cells, for example, blocking the release of proconvulsive Il-1β and stimulating the secretion of anticonvulsive and anti-inflammatory IL-1Ra.[19,28] Therefore in individuals with intense seizure activity like cluster seizures, it is possible that the anti-inflammatory effect of lidocaine together with its antiseizure properties contribute to seizure cessation and prolonged remission. Nevertheless, further researches are required to study these hypotheses.

An additional benefit of the use of lidocaine, compared with classical AEDs, is its lack of sedative properties.[29] This property may be an indication to use lidocaine even as a first-line treatment in patients in whom it is preferable to avoid respiratory depression or disturbances of consciousness or as a second-line treatment in patients not responding to diazepam.[29,30] Pascual et al. reported that lidocaine might also be safely implemented in patients with pulmonary diseases and reduced pulmonary reserve.[29]

Nevertheless, lidocaine may also cause adverse effects, mostly cardiological events, i.e., bradycardia, arrhythmias (including heart block), hypotension, transient decreases of saturation, and cardiovascular depression.[15,19,31] Weeke et al., in a study of 521 infants who were treated with lidocaine due to seizures, reported cardiological events in 11 children; however, the relation between the side effects and the lidocaine was plausible in only seven infants (1.3%), and bradycardia was observed in all of these patients.[31] Other side effects included 2:1 atrioventricular block (two patients), systemic hypotension (one patient), and asystole (one patient).[31] In a systematic review of 235 pediatric patients treated with lidocaine due to status epilepticus, bradycardia and hypotension were reported in 30 and 11 children, respectively.[8] Other less common complications were tachycardia (two patients), metabolic acidosis (one patient), and decreased saturation (one patient).[8]

Despite cardiological effects, lidocaine may also cause neurological toxicity, for example, dizziness, numbness, sleepiness, anxiety, and even seizures.[19,31] The influence of lidocaine on the central nervous system depends on the dose. At low doses, lidocaine exerts anticonvulsive effect, whereas higher doses may result in seizures.[32] Hattori et al. reported that lidocaine blood concentration exceeding 10 μg/mL (10 mL/L) can induce seizures.[15] Weeke et al. considered lidocaine blood concentration below 5 mg/L as less frequently related to adverse events.[31] The risk of other side effects is also increasing with the dose. In the group with 261 episodes of status epilepticus, Hattori et al. reported 14 adverse events (5.3%) that were judged to be definitely associated with lidocaine, and the risk significantly increased when the doses exceeded 4 mg/kg/hour.[15] Moreover, doses that exceeded 3.5 mg/kg/hour did not result in better efficacy.[15] However, in the study of 30 neonates treated with IV lidocaine (dosage 4 to 8 mg/kg/hour) due to status epilepticus, Lundqvist et al. reported side effects in only one child who experienced bradycardia during infusion.[11] Nevertheless, to reduce the risk of side effects rather lower doses of lidocaine (not exceeding 4 mg/kg/hour) should be implemented.[15,31] Lidocaine plasma concentration may also be monitored to reduce the risk of side effects. In our group, seizure control was achieved mostly at a lidocaine dose of 2 mg/kg/hour.

Weeke et al. observed that a shorter duration of lidocaine infusion also reduces the risk of adverse effects[31]; they also reported that concomitant compromised cardiac function, impaired liver function, and hypocalcemia increase the risk. Therefore patients should be carefully cardiologically evaluated, and ions levels and liver function should be assessed before lidocaine infusion. All our patients were carefully cardiologically assessed before the treatment and continuously monitored during the infusion. Moreover, to reduce cardiological risk, the dose of lidocaine was gradually increased. The initial dose was 1 mg/kg/hour, and then after six hours it was increased to 2 to 4 mg/kg/hour (average 2.5 mg/kg/hour; median 2 mg/kg/hour) (Table 2). Despite the use of low or middle doses of lidocaine, seizure remission was achieved in all our patients, which may

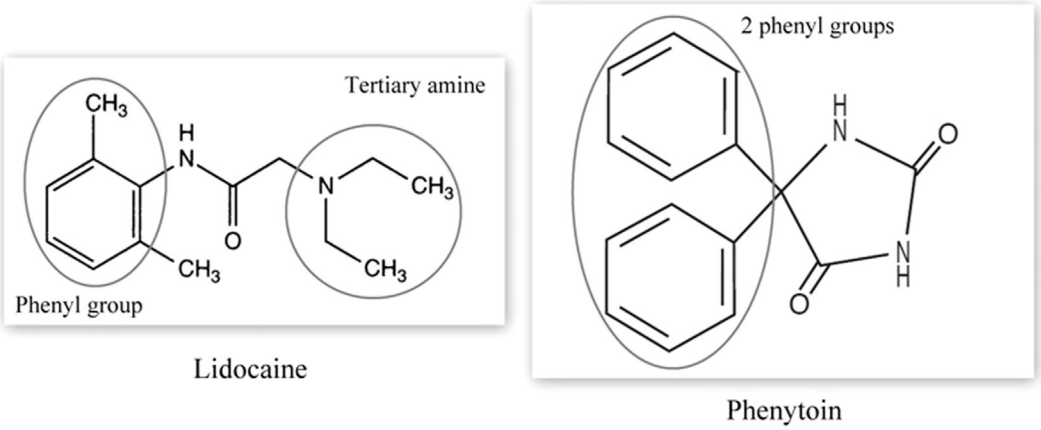

FIGURE. Comparison of the chemical structure of lidocaine and phenytoin.

suggest a good antiepileptic effect of IV infusion of lidocaine. Unfortunately, after a few months, seizures recurred in all children and they had to be treated with at least two AEDs. However, cluster seizures were not observed. Moreover, the frequency of seizures was also reduced. These results together with difficulties with prolonged IV administration and lack of an oral form of lidocaine suggest that lidocaine may be a rather good option during crisis than for long-term treatment. However, as seizure remission and reduction persisted after lidocaine withdrawal, it may also suggest a long-term antiepileptic effect of lidocaine.

Although lidocaine may potentially facilitate the antiepileptic effect of PHT for further seizure control and all our patients received PHT after lidocaine infusion, concurrent use of both drugs increases the risk of cardiological and neurological side effects.[15,31-33] Therefore the simultaneous or subsequent use of both drugs requires clinicians' awareness and careful cardiological and neurological monitoring.

Limitations of the study

Owing to the rare occurrence of drug-resistant cluster seizures, the study group was small and there was no control group. We did not monitor the blood concentration of lidocaine. Nevertheless, we believe that despite the small study group, this report may be useful and supportive for clinical decisions and provide valuable data about the possible long-term effect of lidocaine on seizure control. However, more studies are required for confirmation and better understanding of this possible long-term antiepileptic effect of lidocaine.

Conclusions

We believe this is the first report of the long-term outcome of the use of lidocaine in pediatric cluster seizures and the first report in the population of Poland and Middle Europe. Lidocaine has not been considered as a first-line or long-term therapy, possibly because of the concern for side effects and the inability to continue oral treatment. Nevertheless, treatment with lidocaine may be useful and may be considered as a therapeutic option during crisis, especially when other AEDs are not effective. In addition, lidocaine may support long-term seizure control or reduction due to a supportive effect on other AEDs and anti-inflammatory properties. Considering the risk of adverse effects, patients should be carefully assessed before the treatment and continuously cardiologically monitored during the infusion. Lidocaine infusion should be discontinued immediately when arrhythmia or other side effects occur.

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Authors' contributions: J.S. designed the study, collected data and wrote the manuscript. M.S. collected and analyzed data and wrote the manuscript. S.J. participated in study design, data analysis, and manuscript revision and editing.

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