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Original Article

Efficacy of single dose of phenytoin/fosphenytoin in benign convulsions with mild gastroenteritis

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ABSTRACT

Background. This study evaluated the efficacy of a single dose of phenytoin/fosphenytoin (PHT) to control repetitive seizures in children with benign convulsions with mild gastroenteritis (CwG).

Methods. Children aged between 3 months and 5 years with CwG were retrospectively enrolled. Convulsions with mild gastroenteritis were defined as (a) seizures with acute gastroenteritis without fever or dehydration; (b) normal blood laboratory results; and (c) normal electroencephalography and brain imaging findings. Patients were divided into two groups according to whether or not intravenous PHT (10 mg/kg of phenytoin or phenytoin equivalents) was administered. Clinical manifestations and treatment efficacy were evaluated and compared.

Results. Ten of 41 children eligible for inclusion received PHT. Compared to children in the non-PHT group, those in the PHT group had a higher number of seizures (5.2 ± 2.3 vs. 1.6 ± 1.0, $P < 0.001$) and a lower serum sodium level (133.5 ± 3.2 mmol/L vs. 137.2 ± 2.6 mmol/L, $P = 0.001$). Initial serum sodium levels were negatively correlated with seizure frequency ($r = -0.438$, $P = 0.004$). In all patients, seizures were completely resolved with a single dose of PHT. There were no significant adverse effects from PHT.

Conclusions. A single dose of PHT can effectively treat CwG with repetitive seizures. The serum sodium channel may play a role in seizure severity.

Key words: phenytoin; fosphenytoin; sodium channel; benign convulsions; mild gastroenteritis.

Benign convulsions with mild gastroenteritis (CwG) are clinically diagnosed by afebrile seizures with mild gastroenteritis symptoms that are not accompanied by clinical signs of dehydration, electrolyte imbalance, or hypoglycemia, in previously healthy infants and young children aged 1 month to 6 years.[1,2] Although CwG has predominantly been reported in children of East Asian countries, cases in Europe and the United States of America have also been described.[3-9] In almost half of the affected patients, the seizures tend to occur in clusters over 1-2 days, but there is no long-term risk of recurrent seizures.[2,10] Benzodiazepines are commonly used as first-line antiseizure medications in the emergency department; however, these medications are not effective in children with repetitive seizures during acute CwG.[3] Although clustering seizures in CwG have shown a good prognosis without persistent neurologic complications, they can cause parental anxiety, and clinicians may repeat or administer unnecessarily high doses of antiseizure medications to control repetitive seizures.

Previous studies have reported the effectiveness of carbamazepine, phenobarbital, lidocaine or fosphenytoin in controlling repetitive seizures in CwG.[3,11-13] We hypothesized that voltage-gated sodium channels play a role in initiating

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seizures in CwG. In the present study, we evaluated the effectiveness of phenytoin/fosphenytoin (PHT), which has inhibitory effects on sodium channels, in controlling repetitive seizures in CwG. Patients with more than two seizures during the acute illness were treated with a lower dose of PHT than that used in previous studies, to minimize the risk of side effects. Patient's clinical characteristics and treatment responses were assessed.

Material and Methods

Patients

This was a retrospective study to evaluate the efficacy of PHT in controlling repetitive seizures in CwG patients aged between three months and five years who were admitted to Busan Paik Hospital in South Korea from January 2013 to December 2018. All patient records were reviewed to collect data on clinical manifestations, laboratory studies, electroencephalography (EEG), and brain magnetic resonance imaging (MRI) findings. Ethical approval for this study was provided by the institutional review board of Busan Paik Hospital (approval number: 180179). Written informed consent by the patients was waived due to the retrospective nature of our study.

In this study population, CwG was defined as follows: 1) seizures accompanied by acute gastroenteritis symptoms in previously healthy infants and children; 2) normal neurodevelopment and neurological examination findings; 3) normal laboratory findings without hyponatremia (serum sodium < 130 mg/dl), hypoglycemia (serum glucose ≤ 50 mg/dL), and cerebrospinal fluid (CSF) abnormalities; 4) normal EEG and brain imaging findings.[2] We excluded patients who were diagnosed with meningitis, encephalitis, or epilepsy and had seizures associated with fever during acute gastroenteritis.[2] Patients were divided into two groups according to whether they received intravenous PHT or not. A single dose of intravenous PHT was slowly administered over 30 minutes at a dose of 10 mg/kg for phenytoin from 2013 to 2016. Fosphenytoin was introduced at our institution in 2017 and children treated from 2017 to 2018 received 10 mg phenytoin equivalents (PE)/kg using the same rate of administration. We administered low doses of intravenous PHT, 10 mg/kg, because previous studies reported good efficacy with fewer adverse effects for low doses of antiseizure medications such as phenobarbital at a dose of 5–10 mg/kg[3,4,13], carbamazepine at a dose of 5 mg/kg[11], and phenytoin at a dose of 5–10 mg/kg[3] in controlling repetitive seizures.

The efficacy of PHT was evaluated in the acute phase of CwG. Vital signs, including body temperature, blood pressure, pulse rate, respiratory rate, and percutaneous oxygen saturation were monitored during and after seizures, and when administering antiseizure medications. All patients were hospitalized and discharged when they had been seizure-free for more than 24 hours.

Clinical data including age, sex, preceding gastroenteritis symptoms, the interval from gastroenteritis symptoms to seizure onset, seizure characteristics (semiology, duration, frequency, and interval between the first seizure and the last seizure), benzodiazepine usage during the acute seizure period, length of hospital stay, previous history of seizures and antiseizure medications, were collected for each patient.

Laboratory tests

The following laboratory tests were performed in all patients at the time of presentation to the emergency department: complete blood cell count, electrolyte panel, serum glucose, C-reactive protein, and liver enzymes. The positive rate of stool rotavirus or norovirus, EEG features, CSF analysis and brain MRI findings were also reviewed. We conducted an immunochromatographic assay using the SD BIOLINE Rotavirus Rapid kit (Standard Diagnostics, Inc., Korea) for the detection of group A rotavirus in fecal specimens. For

the detection of norovirus, a QuickNavi®-Norovirus 2 kit was used according to the manufacturer's instructions. The rotavirus and norovirus antigen tests were performed until 2014. A stool multiplex real-time RT-PCR with Allplex GI-Virus Assay (Seegene, Seoul, Korea), detecting norovirus, rotavirus, adenovirus, and astrovirus was introduced in our hospital when it became available in 2015.

Statistical analyses

All statistical analyses were performed using SPSS for Windows, version 26.0 (SPSS Inc., an IBM Company, Chicago, Illinois, USA). Numerical variables were assessed for the assumption of normality of variables by the Shapiro Wilk test. Continuous variables are presented as mean ± standard deviation or median (interquartile range) and qualitative variables are expressed as percentages. The comparisons were performed through the Student's t-test when the continuous variable was distributed normally or Mann-Whitney U test when the variable was not distributed normally. Pearson's chi-squared test or Fisher's exact test were used for categorical variables. Fisher's exact test was used for cases where the expected frequency is less than 5. Two-tailed null hypotheses of no difference were rejected if *P* values were less than 0.05. The association between serum sodium level and frequency of seizures in all patients was evaluated using the Pearson correlation coefficients.

Results

Patients' clinical findings

Forty-six children with CwG were enrolled during the study period, of whom 41 were included in the analysis (Fig. 1). The average age was 18.1 ± 10.4 (range, 3–56) months and 18 (44%) were male (Table I). Gastroenteritis symptoms of vomiting and diarrhea were observed in 33 (81%) and 36 (88%) patients, respectively, and they occurred within three days before the onset of seizures. Three patients had previously experienced febrile seizures. The most common semiology of seizure was a generalized motor seizure (85%), and the majority of seizures (98%) were shorter than five minutes. Repetitive seizures were observed in 23 patients (56%) and 13 patients (32%) had more than three seizures. None of the participants experienced prolonged seizures that lasted >15 minutes. Brain MRI was performed in 40 patients and interictal EEG in 39 patients, both of which showed no abnormalities. Six of 32 patients returned positive tests for rotavirus and nine of 20 patients returned positive tests for norovirus. Cerebrospinal fluid tests were performed on 13 patients and were normal.

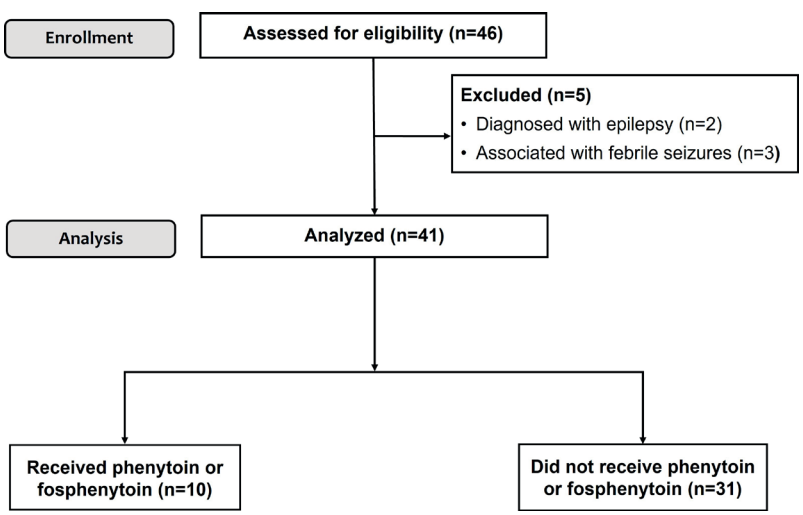

Fig. 1. Study flow chart describing the study population.

Table I. Comparison of clinical findings between groups.*

Variables	PHT group (n = 10)	Non-PHT group (n = 31)	p
Age at diagnosis, mean±SD	17.2 ± 5.3	18.4 ± 11.6	0.76[a]
Male sex	4 (40)	14 (45)	1.0[b]
Vomiting	8 (80)	25 (81)	1.0[b]
Diarrhea	8 (80)	28 (90)	0.58[b]
Latency to seizure onset**			0.43[b]
< 24 hours	2 (20)	7 (23)	
24–48 hours	8 (80)	18 (58)	
48–72 hours	0 (0)	6 (19)	
Two or more seizures	10 (100)	13 (42)	0.002[b]
Three or more seizures	10 (100)	3 (42)	< 0.001[b]
Number of seizures, mean±SD	5.2 ± 2.3	1.6 ± 1.0	< 0.001[a]
Interval from 1st seizure to last (hours), median (IQR)	8 (6–11)	6 (5–11)	0.47[c]
Seizure semiology			1.0[b]
Focal to bilateral tonic-clonic	1 (10.0)	5 (16)	
Apparently generalized	9 (90.0)	26 (84)	
Seizure duration			1.0[b]
< 1 min	1 (10)	5 (16)	
1–5 min	9 (90)	25 (81)	
> 5 min	0 (0)	1 (3)	
Use of initial lorazepam	10 (100)	7 (23)	< 0.001[b]
Length of hospital stay (days), median (IQR)	3 (3–5)	3 (2–4)	0.13[c]

P values refer to comparisons across the two groups. *Data are indicated as number (percentage) unless indicated otherwise.
**Latency to seizure onset was defined as the interval between the onset of gastroenteritis and the onset of seizures.
Abbreviations: IQR, interquartile range; PHT, phenytoin or fosphenytoin.; SD, standard deviation.
[a]Student's t-test, [b]Fisher's exact test, [c]Mann Whitney-U test

Clinical and laboratory characteristics in the PHT group

Ten children were administered a single dose of PHT to control repetitive seizures; phenytoin was administered to six patients and fosphenytoin to four (Table II). The clinical characteristics and laboratory findings were compared between the two groups according to whether (PHT group) or not (non-PHT group) they received phenytoin or fosphenytoin (Tables I and III). There was no significant difference in clinical characteristics such as age, sex, gastroenteritis symptoms, the interval between the onset of gastroenteritis and seizures, seizure semiology and duration between the groups (Table I).

Patients in the PHT group had more seizures before treatment than the non-PHT group had in total (5.2 ± 2.3 vs. 1.6 ± 1.0, $P < 0.001$) and all patients who received PHT had three or more seizures during the acute period, although the median interval from the onset of the first seizure to the last seizure was not significantly different between groups. All patients in the PHT group experienced recurrent seizures despite receiving an initial dose of intravenous lorazepam; therefore, a single dose of PHT was administered, which resolved the seizures for all 10 patients. No other antiseizure medications, aside from lorazepam, were administered to patients in the non-PHT group. Seizures were controlled in seven patients in the non-PHT group who received an initial dose of intravenous lorazepam. The seizures ceased spontaneously in the remaining 24 patients of the non-PHT group, and these patients did not require lorazepam.

Table II. Clinical manifestations of 10 patients who received phenytoin or fosphenytoin.

Patient no.	Age (Months)	Sex	Number of seizures before PHT	Interval from the first to last seizure (h)	Administered antiseizure medications	Causative virus	Initial serum sodium level (mmol/L)	Follow up serum sodium level (mmol/L)
1	22	Male	5	8	Lorazepam, phenytoin	Unknown	130	136
2	13	Female	3	3	Lorazepam, phenytoin	Rotavirus	130	137
3	23	Male	4	9	Lorazepam, phenytoin	Rotavirus	140	142
4	6	Male	10	10	Lorazepam, phenytoin	Unknown	132	134
5	15	Female	7	8.5	Lorazepam, phenytoin	Norovirus	133	138
6	24	Female	3	7	Lorazepam, phenytoin	Unknown	136	139
7	17	Female	7	6.5	Lorazepam, fosphenytoin	Norovirus	132	135
8	18	Female	6	16	Lorazepam, fosphenytoin	Norovirus	136	139
9	17	Female	4	13	Lorazepam, fosphenytoin	Unknown	135	136
10	17	Male	3	4	Lorazepam, fosphenytoin	Norovirus	131	139

PHT: phenytoin or fosphenytoin.

Table III. Comparison of laboratory parameters between the two groups.

Variables	PHT group (n=10)	Non-PHT group (n=31)	p
Peripheral WBC (/mm^3)	10738 ± 3155	9294 ± 4674	0.37[a]
Hemoglobin (g/dL)	12.0 ± 0.8	12.2 ± 0.9	0.60[a]
C-reactive protein (mg/dL)	0.12 ± 0.18	0.42 ± 0.71	0.19[a]
Sodium on admission (mmol/L)	133.5 ± 3.2	137.2 ± 2.6	0.001[a]
Hyponatremia on admission*	7 (70)	7 (23)	0.02[b]
Sodium after 1–2 days of admission (mmol/L)	137.5 ± 2.4	138.9 ± 1.7	0.06[a]
Calcium (mg/dL)	9.9 ± 0.6	9.7 ± 0.6	0.57[a]
Ionized calcium (mmol/L)	1.09 ± 0.15	0.94 ± 0.27	0.09[a]
Venous glucose (mg/dL)	86.5 ± 21.2	87.2 ± 18.6	0.92[a]
Positive test for rotavirus	2/9 (22)	4/23 (17)	1.00[b]
Positive test for norovirus	4/5 (80)	5/15 (33)	0.13[b]

Note: Values are expressed as mean ± standard deviation or number of patients (%). The denominator is the number of patients for which data is available, and the numerator is the number of patients corresponding to the variable. *Number of patients with hyponatremia, defined as a serum sodium level of 130–135 mmol/L. Abbreviations: PHT, phenytoin or fosphenytoin; WBC, white blood cell.
[a]Student's t-test, [b]Fisher's exact test

No significant differences in laboratory findings including complete blood cell count, C-reactive protein, serum calcium, glucose level, or positive rates of rotavirus or norovirus were found between the two groups. However, the average initial sodium level was lower in the PHT group (133.5 ± 3.2 mmol/L vs. 137.2 ± 2.6 mmol/L, *P* = 0.001). The follow-up mean sodium level one or two days after PHT administration was 137.5 ± 2.4 mmol/L, with no significant difference compared to the non-PHT group. No patients required treatment for hyponatremia. In this cohort, low serum sodium levels correlated with more frequent seizures, although the size of the correlation was low (r = -0.438, *P* = 0.004). There were no meaningful adverse effects associated with the administration of phenytoin or fosphenytoin.

Discussion

In the present cohort study of children with CwG, PHT demonstrated good efficacy and safety for controlling repetitive seizures. After administration of 10 mg/kg of phenytoin or 10 mg PE/kg of fosphenytoin, all children showed complete cessation of seizures that were not controlled by initial lorazepam therapy. The initial serum sodium level was lower in children who received PHT than in those who did not, and this improved after one or two days. The sodium level negatively correlated with the frequency of seizures although the size of the correlation was low. The results of this study suggest that PHT is an effective drug for controlling repetitive seizures and that sodium channel abnormalities may be the cause of repetitive seizures in CwG.

In this study, about half of the patients (n = 23, 56%) had two or more seizures with the same semiology within 24 h. Lorazepam was administered to 17 patients (41%) with two or more seizures during the acute phase, but it was not effective in 10 patients (59%); however, the administration of PHT was effective in controlling repetitive seizures for these patients. Seizures spontaneously resolved in the remaining six patients who experienced two or more seizures without the administration of any additional antiseizure medications. These findings are consistent with those of the prior studies, which demonstrated that repetitive seizures could occur in CwG and that these may be refractory to benzodiazepine.[3,7,14-16] Previous studies reported that benzodiazepine therapy as a first-line treatment is effective at preventing further seizures in 25–59% of CwG patients, indicating the necessity of identifying other treatment strategies.[3,7,15,17]

Our study demonstrated the superior efficacy of PHT to control repetitive seizures compared to lorazepam, supporting prior studies that reported that antiseizure medications with inhibitory effects on voltage-dependent neuronal sodium channels seem to be effective for CwG.[3,4,11,12,15,16,18,19] Nakazawa et al.[12] reported the efficacy and tolerance of fosphenytoin in children with CwG. Fourteen of 16 patients (88%) experienced no further seizures after administration of fosphenytoin (median dose, 22.5 mg/kg) and no side effects from the medication. Our patients received only a half loading dose of PHT (10 mg/kg) to avoid side effects, but this was effective at controlling repetitive seizures. No patients experienced side effects of PHT such as hypotension, cardiac arrhythmia, or local skin reactions because low doses of PHT were slowly injected over 30 minutes and continuous blood pressure and cardiac rhythm monitoring were conducted by attending physicians and nurses. Some previous studies have reported that low-dose carbamazepine (5 mg/kg/day) or lidocaine that blocks voltage-gated sodium channels also showed good efficacy in controlling repetitive seizures in CwG.[3,11,16,19] However, patients with repetitive seizures usually cannot take carbamazepine orally because they are generally drowsy after seizures. Furthermore, it is not easy to insert a nasogastric tube as these patients may also experience recurrent vomiting with CwG. Lidocaine infusion has not been approved for controlling seizures and cannot be administered as an antiseizure

medication. A recent Japanese small cohort study demonstrated the efficacy of intravenous phenobarbital to prevent further seizures in CwG.[13] Their randomized, placebo-controlled trial showed that a single dose of 10 mg/kg of phenobarbital was effective in all seven patients in the phenobarbital group, and five of six patients in the placebo group had recurrent seizures after administration of normal saline. Phenobarbital not only stimulates GABA-A receptor subunits to induce hyperpolarization, but also selectively blocks the inactive form of closed sodium channels.[16,20] However, excessive somnolence, drowsiness, and unsteadiness can be problematic side effects of phenobarbital usage.[19]

It is not clear why antiseizure medications that block sodium channels are more effective than benzodiazepines for CwG. Weng et al.[21] tried to identify pathogenic variants of neuronal sodium channel alpha 1 subunits (*SCN1A*) in 12 patients with CwG. However, no pathogenic variants in the *SCN1A* gene were identified in their study.[21] Our study showed that serum sodium was lower in patients who received PHT than in those who did not, and this was significantly associated with the number of seizures patients experienced, although the changes in sodium levels were within the normal range. These results suggest that modulators of sodium channels or single nucleotide polymorphism of sodium channels may be responsible for provoking repetitive seizures in CwG. Motoyama et al.[16] demonstrated that serum sodium and chloride levels in patients with seizures were lower than those without seizures in rotavirus gastroenteritis, indicating the possible relevance of sodium channels in CwG. Additionally, other studies also reported similar results of lower serum sodium levels associated with CwG.[22,23] However, no studies have defined the pathomechanism of CwG so far. The implication of decreased sodium levels in the PHT group and some negative correlation between sodium levels and the number of seizures in the setting of CwG are uncertain and merit future research.

Our study has some limitations. First, this was a single center study with a small sample size, and the study design was a retrospective observational study. Prospective randomized controlled studies from larger cohorts are required to define the efficacy and safety of PHT for the control of repetitive seizures in CwG. Second, the efficacy and safety of PHT could not be compared with other antiseizure medications such as phenobarbital. Further comparative studies with other antiseizure medications will be necessary to confirm the effectiveness of PHT in controlling repetitive seizures. Third, we did not evaluate long-term follow-up data. However, the results of this study are valuable because they demonstrate that a single low dose of PHT was effective at resolving seizures during admission, and there were no cases of recurrent seizures after discharge. Several previous studies have also demonstrated the excellent prognosis of CwG.[2,14,23-25] Finally, we did not evaluate the mechanism by which sodium channels contribute to CwG pathogenesis.

In conclusion, the present study suggests that a single dose of PHT in CwG effectively and safely controlled repetitive seizures. Further studies should be conducted to demonstrate the efficacy of PHT compared with other antiseizure medications in CwG and the possible mechanism of action associated with sodium channels.

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Ethical approval

This work was approved by the institutional review board of Busan Paik Hospital (approval number: 180179). Written informed consent by the patients was waived due to a retrospective nature of our study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BLL; data collection: KSL, BLL; analysis and interpretation: BLL; draft manuscript: KSL, BLL. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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