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Original article

Efficacy of phenobarbital for benign convulsions with mild gastroenteritis: A randomized, placebo-controlled trial

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Abstract

Objective: This study was performed to evaluate the efficacy and safety of intravenous phenobarbital (PB) for benign convulsions with mild gastroenteritis (CwG).

Methods: A randomized, single-blind, placebo-controlled trial involving patients with CwG was conducted at the Japanese Red Cross Society Himeji Hospital. Patients with CwG who had experienced two or more seizures were eligible. Patients were excluded if any anticonvulsant was used before enrollment. Patients who were allocated to the PB group were administered 10 mg/kg of PB intravenously. Patients who were allocated to the placebo group were administered 20 ml of normal saline.

Results: From April 2016 to October 2018, 13 of 24 patients with CwG were randomized (PB group, n = 7; placebo group, n = 6; age, 1–3 years). Five of six patients in the placebo group had seizures after administration of placebo. However, patients in the PB group had no seizures after administration of PB, with a significant difference in efficacy between the two groups (P = 0.005). Five patients who had seizures after administration of normal saline were administered 10 mg/kg of PB, and no patients had a seizure thereafter. No significant differences were found in heart rate, blood pressure, or saturation of percutaneous oxygen between the two groups.

Conclusion: This is the first randomized controlled trial to evaluate the efficacy of an anticonvulsant for CwG. Intravenous PB at 10 mg/kg is effective and well tolerated for CwG.

Keywords: Benign convulsions; Gastroenteritis; Phenobarbital; Efficacy; Randomized controlled trial

1. Introduction

Benign convulsions with mild gastroenteritis (CwG) are benign provoked seizures in children aged 6 months to 3 years. CwG was first described by Morooka [1] in 1982 in Japan. CwG is characterized by (1) previously healthy infants and young children aged 6 months to 3 years, (2) afebrile brief seizures occurring between the first and fifth days of mild gastroenteritis, (3) the tendency for seizures to occur repetitively in clusters, (4) mild dehydration (<5%) and no metabolic abnormalities or electrolyte imbalance. (5) a normal interictal electroencephalogram, and (6) a good prognosis without sequelae [2–5].

Previous studies have shown that carbamazepine, phenobarbital (PB), fosphenytoin, and lidocaine are effective for CwG, whereas diazepam is less effective [2,3,6–10]. Nevertheless, randomized controlled studies of the treatment of CwG have not been reported.

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Therefore, the current study was performed to investigate the efficacy and safety of PB compared with placebo for treatment of seizures with CwG.

2. Methods

2.1. Study design

This single-center, randomized, single-blind, placebo-controlled trial of PB for patients with CwG was conducted at the Japanese Red Cross Society Himeji Hospital. This trial was carried out from April 2016 to October 2018. The study protocol and informed consent documents were approved by the institutional review board of the Japanese Red Cross Society Himeji Hospital. Written informed consent was obtained from the patients' parents prior to enrollment.

2.2. Patients

Patients with CwG who had experienced two or more seizures were eligible. CwG was defined as follows: (1) seizures accompanied by symptoms of gastroenteritis without clinical signs of dehydration, hypoglycemia, or electrolyte derangement in patients aged 6 months to 3 years with normal psychomotor development and normal neurological findings, and (2) maintenance of the body temperature at <38.0 °C before and after the seizures. Patients with both febrile seizures (body temperature of ≥38.0 °C) and afebrile seizures during a single episode of gastroenteritis were included.

Patients were excluded if they had at least one of the following: a seizure lasting for >5 min; use of any anticonvulsant, such as diazepam, for current seizures; a duration of >6 h since the last seizure; a history of unprovoked seizures; and previous participation in this study.

2.3. Randomization and interventions

Patients were randomly allocated to two groups (PB or placebo) in a 1:1 ratio using a block size of 10 by the sealed envelope method. Patients who were allocated to the PB group were intravenously administered 10 mg/kg of PB dissolved in 20 ml of normal saline (NS) for injection in 10 min. Patients who were allocated to the placebo group were administered 20 ml of NS in 10 min. The patients and their families were blinded to the treatment allocation, and all doctors and nurses were made aware of the drugs. If patients who were allocated to the placebo group had a seizure after administration of NS, 10 mg/kg of PB was administered. If patients had a seizure after administration of 10 mg/kg of PB, an additional 5 mg/kg of PB was administered. Heart rate, blood pressure, and saturation of percutaneous oxygen (SpO_2) were recorded immediately before and after administration of each drug. All patients were hospitalized, and they were discharged if they had developed no seizures for >24 h.

2.4. Statistical analysis

Categorical data were compared by the χ^2 test or Fisher's exact test. Continuous data were compared by the Wilcoxon rank sum test. The paired *t*-test was used to evaluate the significance of changes from before treatment in each group. A difference of $P < 0.05$ was considered significant. All statistical analyses were performed using JMP Version 10.0.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

During the study period, 24 patients with CwG visited the Japanese Red Cross Society Himeji Hospital. Of these patients, 13 were randomly allocated to the PB or placebo group (Fig. 1). Table 1 shows the clinical characteristics of the study groups. The mean ± standard deviation age of the patients was 2.3 ± 0.76 years, and the median age was 2.1 years. Among the 13 patients, 6 were boys and 7 were girls. Three patients had a history of CwG. No significant differences in clinical data, including age, sex, weight, number of seizures before treatment, interval from the last seizure to treatment, and pathogens, were found between the two groups. The median interval between the onset of gastroenteritis and seizures was 2 days (range, 1–4 days). All seizures were generalized and brief (<5 min).

Fig. 2 shows the clinical course of the patients. Five of six patients in the placebo group had seizures after administration of NS. However, patients in the PB group had no seizures after administration of PB, indicating a significant difference in efficacy between the two groups ($P = 0.005$). Five patients who had seizures after administration of NS were administered 10 mg/kg of PB, and none of these patients had a seizure

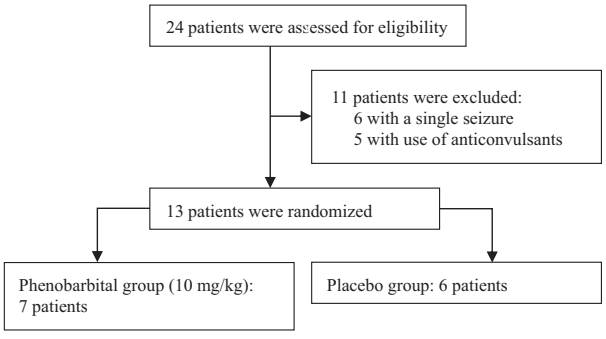

Fig. 1. Study flow chart.

Table 1
Clinical characteristics of the patients.

	Phenobarbital group (n = 7)	Placebo group (n = 6)	P value
Age, months*	29.1 (10.7)	25.8 (7.4)	0.61
Male, n (%)	5 (71.4)	1 (16.7)	0.10
Weight in kg*	12.6 (2.4)	10.5 (1.5)	0.07
Number of seizures before treatment*	3.4 (1.0)	4.2 (4.0)	0.46
Intervals from the last seizure to treatment, minutes*	63.1 (75.4)	53.0 (37.3)	0.62
Pathogens	Rotavirus 4, norovirus 1	Rotavirus 3, norovirus 1	0.97
Prior febrile seizure, n (%)	1 (14.3)	0 (0)	1.0
Prior CwG, n (%)	2 (28.6)	1 (16.7)	1.0

CwG, convulsions with mild gastroenteritis.
* Mean (standard deviation).

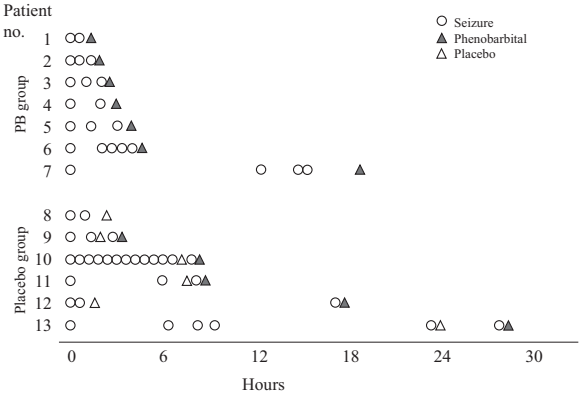

Fig. 2. Clinical course of the patients. The phenobarbital (PB) group comprised Patient Nos. 1–7, and the placebo group comprised Patient Nos. 8–13. A significant difference in efficacy was observed between the two groups (P = 0.005).

thereafter. Therefore, no patient was administered an additional 5 mg/kg of PB.

No significant differences in heart rate, blood pressure, or SpO_2 were found between the two groups after administration of PB or placebo (Table 2). The interictal electroencephalogram was normal after discharge in all patients.

4. Discussion

This is the first randomized controlled trial to evaluate the efficacy of an anticonvulsant for CwG. In this study, PB was significantly more effective for terminating seizure clusters with CwG than placebo. Kawano et al. [3] reported that 10 mg/kg of PB was effective in 8 of 15 (53.3%) patients. Okumura et al. [9] reported that 5–10 mg/kg of PB was effective in 25 of 38 (65.8%) patients. Intravenous PB was not available in Japan before December 2008. The lower efficacy of PB in the studies by Kawano et al. [3] and Okumura et al. [9] might have been due to the relatively low dose of PB or administration by suppository. Absorption of a suppository might be low and slow in patients with gastroenteritis. In contrast, we previously reported that 10 mg/kg of intravenous PB for CwG was effective in 70 of 73 (95.9%) patients [7]. We adopted 10 mg/kg of intravenous PB because oversedation is often observed after intravenous administration of 15 –20 mg/kg of PB, which is the dose for status epilepticus. However, our previous study was not a controlled study. The use of other anticonvulsants might affect cessation of seizure clusters. Therefore, we excluded patients in whom other anticonvulsants were used in this study.

Carbamazepine, fosphenytoin, and lidocaine seem to be effective for CwG, although no controlled studies have been conducted [2,3,8–10]. Although carbamazepine is a good option for CwG, patients might experience difficulty with oral administration immediately after the seizure or during sleeping; oral administration might also be difficult in patients who have been vomiting. Fosphenytoin is approved for patients aged >2 years in Japan, but it might have limited use because many patients with CwG are <2 years of age. Lidocaine is not approved for seizures in Japan. However, PB can be administered intravenously when the

Table 2
Changes in vital signs after administration of phenobarbital or placebo.

	Phenobarbital group (n = 7)		Placebo group (n = 6)		P value
	Before	After	Before	After	
Heart rate, bpm	112.0 (9.5)	109.9 (11.4)	108.3 (6.9)	111.5 (15.4)	0.94
Systolic blood pressure, mmHg	101.0 (13.1)	95.0 (9.0)	103.2 (4.9)	104.8 (9.2)	0.50
Diastolic blood pressure, mmHg	58.4 (8.3)	53.7 (8.6)	59.5 (9.8)	61.0 (11.2)	0.49
Saturation of percutaneous oxygen, %	97.9 (2.0)	97.6 (1.7)	97.8 (0.8)	97.5 (0.8)	0.49

Values are mean (standard deviation).

patient cannot take it orally, and PB is available for infants and toddlers.

The half-life of PB is 30–75 h [11]; thus, the effect of a single dose lasts throughout the period during which seizures readily occur in patients with CwG. In a previous study by the first author, the plasma concentrations of PB ranged from 7.6 to 14.4 μg/ml in 21 patients with CwG at 12–24 h after intravenous administration of 10 mg/kg of PB [6]. PB was effective at a low plasma concentration despite the fact that the therapeutic plasma concentration is 15–40 μg/ml [11].

Multiple seizures can occur in 56–75% patients with CwG [4,12–15]. In this study, 17 of 24 patients with CwG had a single seizure at the time of arrival at our hospital. None of these patients had used any anticonvulsant, and 11 (64.8%) patients had second seizures. Furthermore, 9 of 10 (90%) patients who had second seizures without the use of an anticonvulsant had third seizures. Patients who have a second seizure may tend to have more seizures than patients with a single seizure. CwG is known to have a good prognosis, even if the seizures are clustered [4,5]. No consensus has been reached regarding the optimal timing of treatment for seizure clusters with CwG. We planned to treat patients if they had two or more seizures because the seizures were brief and not necessarily clustered when the patients had a single seizure.

We found that PB was safe; no serious adverse events occurred. There were no significant cardiovascular or respiratory adverse events. Some patients developed transient mild somnolence or mild unsteadiness in both groups. Because these symptoms were also observed after placebo administration, they were caused not only by PB but also by the seizures and gastroenteritis. Comparison of somnolence and unsteadiness between the groups was difficult because five of six patients in the placebo group were administered PB thereafter.

Our study has some limitations. First, we performed a single-blind study because we wished to treat the patients immediately. Observer bias in perceiving seizures by medical staff was unlikely. No significant difference in the interval from the last seizure to treatment was found between the two groups. Second, we used the sealed envelope method, which is susceptible to selection bias. However, the numbers of patients in the PB and placebo groups were similar. Additionally, the remaining envelopes were checked at the end of the study, and the authors confirmed that the envelopes were opened appropriately. Third, the sample size was small. However, we showed a significant difference in efficacy between the PB and placebo groups.

In conclusion, PB is effective and safe for cessation of seizure clusters in patients with CwG. The authors recommend 10 mg/kg of intravenous administration of PB for patients with CwG and multiple seizures.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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