Original Article

Does Gabapentin Have A Role in the Improvement of Feeding Resistance in Infants?

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Abstract

Background: Eating disorders in some infants can be due to the inability to reach a level of relaxation necessary to start the feeding process. Gabapentin (GB) has been proposed as a stabilizer of nerve function in improving this disorder. This study aimed to investigate the effect of GB on improving feeding resistance in infants aged 3–6 months.

Materials and Methods: This randomized, controlled, double-blind clinical trial was done on 64 infants aged 3-6 months with feeding resistance who were referred to the pediatric clinics and assigned to two groups of 32. The case group was given a dose of 5 mg/kg of GB in the first week, and if not too much sedation, it was increased to 10 mg/kg in the second week every 8 hours, whereas the control group received a placebo. The number of effective breastfeeding and the volume of formula in cc before and after 2 weeks of drug usage were recorded in both groups.

Results: The number of breastfeeding sessions significantly had a higher increase in the GB group compared with placebo (median [IQR]: 1 [0,1] vs. 0 [0,1], $P = 0.005$) as well as an increase in consumed formula volume (mean ± SD: 42.81 ± 24.49 vs. 18.67 ± 14.57, $P = 0.003$).

Conclusion: Considering the significant increase in formula consumption and the number of breastfeeding sessions in the GB group, it is possible to use this drug as a nerve-stabilizer and pain reducer to treat this disorder.

Keywords: Feeding resistance, gabapentin, infants

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Introduction

Visceral hyperalgesia refers to the increase in pain sensation in response to the sensory stimulus of the gastrointestinal tract.[1-3] In infants with neurological disorders, visceral hyperalgesia has been described as the primary source of neuropathic pain, which presents as irritability, poor weight gain, resistance to feeding, hypertonicity, and all common neurological and gastrointestinal signs of prematurity.[2-6] It is often misdiagnosed or not even considered as a cause.[7]

Despite treatment of common sources of disease such as gastroesophageal reflux disease (GERD) and constipation, one of the most common sources of pain in children with severe neurological disorders is the gastrointestinal tract.[2-6,8] Pain attributed to the gastrointestinal tract is defined as pain intensity greater than 7.5 (on a scale of 0-10), second to the pain of unknown etiology, with a significantly higher rate of pain in children previously treated for GERD or gastrointestinal motility disorders (2.5, 8). Many have recurrent symptoms

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despite targeted evaluation and treatment of these problems, and such children may need to undergo repeated tests to find the cause. These problems can lead to feeding resistance, which can be recurrent and persistent problem in some cases despite known resource management. It is one of the most common problems in children with untreated progressive genetic, metabolic or neurological conditions. Pain, sleep, and feeding problems are identified as the three most common complaints of the parents, and symptoms are often poorly controlled.[8]

Gabapentin (GB), a structural analog of c-aminobutyric acid, has antiepileptic and analgesic properties and targets multiple pathways involved in neuropathic pain and inflammation.[9] In adults, GB is commonly used to relieve pain from cancer and chemotherapy, pain from spinal cord injury, and peripheral neuropathic pain. In children, it has other uses, including postoperative and visceral pain management, dystonia, and irritability management in complex medical and neurological patients.[10-11] Information on the safety and efficacy of GB in infants is limited. There are several case series that reported the usage of GB for a range of indications with varying results in neonates and infants. Symptoms in this case series include visceral pain, poor oral feeding skills, withdrawal, and irritability.[12-13]

In a study of a premature newborn with myelomeningocele and persistent neuropathic pain with symptoms of irritability, resistance to feeding, poor weight gain, and hypertonicity, gabapentin was used as a successful treatment for visceral pain in this baby with neurological disorders. After excluding other causes, the diagnosis of visceral hyperalgesia was suspected and GB was used to treat the infant after appropriate GB titration to effect and careful monitoring of the side effects, subsequent improvement in tone, decreased irritability with feeding, and appropriate weight gain have been demonstrated.[14] In patients with chronic painful stimuli, there is a possible upregulation of $\alpha 2$-δ subunit receptors associated with tactile allodynia.[12] These channels probably activate the excitatory neurotransmitters' release and lead to pain or the processing of potentially painful stimuli. GB prevents the transmission of painful stimuli by binding and inhibiting these currents. It can be an attractive option for the management of refractory pain and restlessness in children because it is highly lipophilic and penetrates well across the blood-brain barrier and also contrasts with the sedative and addictive properties of opioids and benzodiazepines with a relatively mild adverse effect profile. Despite this, there is relatively limited clinical experience of doses and efficacy of GB in the treatment of neonates and infants' pain and agitation in.[10-13]

This study aimed to investigate the effect of GB on the improvement of feeding resistance in infants aged 3–6 months. By reducing the pain of these infants, excessive anxiety of parents, frequent visits to multiple doctors, ineffective and costly treatments such as continuous replacement of formula, and use of antireflux drugs would be prevented.

Materials and Methods

This double-blind, randomized, controlled clinical trial study was conducted on 64 infants 3–6 months old with feeding resistance disorder who had been referred to specialized pediatric and subspecialized pediatric gastroenterology clinics in Isfahan city. The study has been approved by the Ethical Committee of Isfahan University of Medical Sciences (code: 399496) and has been registered in IRCT (code: IRCT 0190410043224N4). Considering the significance level of 0.05, the power of 0.8 to find a standardized effect size of 0.7 (14,27), and 15% of the sample missing, the required sample volume was obtained as 32 in each group [Figure 1].

The inclusion criteria were the term delivered infants of 3–6 months old who had breast or formula feeding with no problems in the general examination, having normal weight gain, and not suffering from GERD according to the standard gastrointestinal reflux questionnaire. The infants who had reflux or were on complementary foods and infants with acute or chronic diseases were excluded from the study.

To calculate the sample size, the formula for comparing the two means of the two independent groups was used.[12]

Patients who were not suffering from GERD based on the standard reflux questionnaire and did not have any other acute or chronic disease based on the examinations were assigned to case and control groups in equal numbers by using the randomized block method of size 4 and classified according to gender. People allocating children to groups and mothers were unaware of the process and sequence of allocation. Random allocation, concealment of the random allocation method, and significant sample size in this study made it possible to balance the two groups in terms of confounding variables.

The case group was given a dose of 5 mg/kg of GB in the first week, and if not too much sedation, it was increased to 10 mg/kg in the second week every 8 hours, whereas the control group received a placebo. The number of effective breastfeeding sessions, at least 10 minutes of feeding, or the mother's feeling of empty breasts after feeding an infant, the volume of formula in cc, and the weight of the infant before and after 2 weeks of drug usage were recorded in both groups and analyzed. GB with the mentioned dose was continued for 1 month, and at the end of the month, the times of effective breastfeeding, the amount of formula consumed, and the weight of the infants was recorded.

Descriptive data are expressed as mean ± standard deviation (SD) (Median [interquartile range (IQR)]) for quantitative and number (percentage) for qualitative variables. The normal departure of the outcomes was assessed using the Kolmogorov–Smirnov test. Within-group changes were assessed by paired samples *t*-test (or Wilcoxon test when normality was not met). The changes from baseline were calculated for all primary study outcomes, and an independent samples *t*-test (or Mann-Whitney test) was used to compare mean differences between the two groups. A *P* value of less

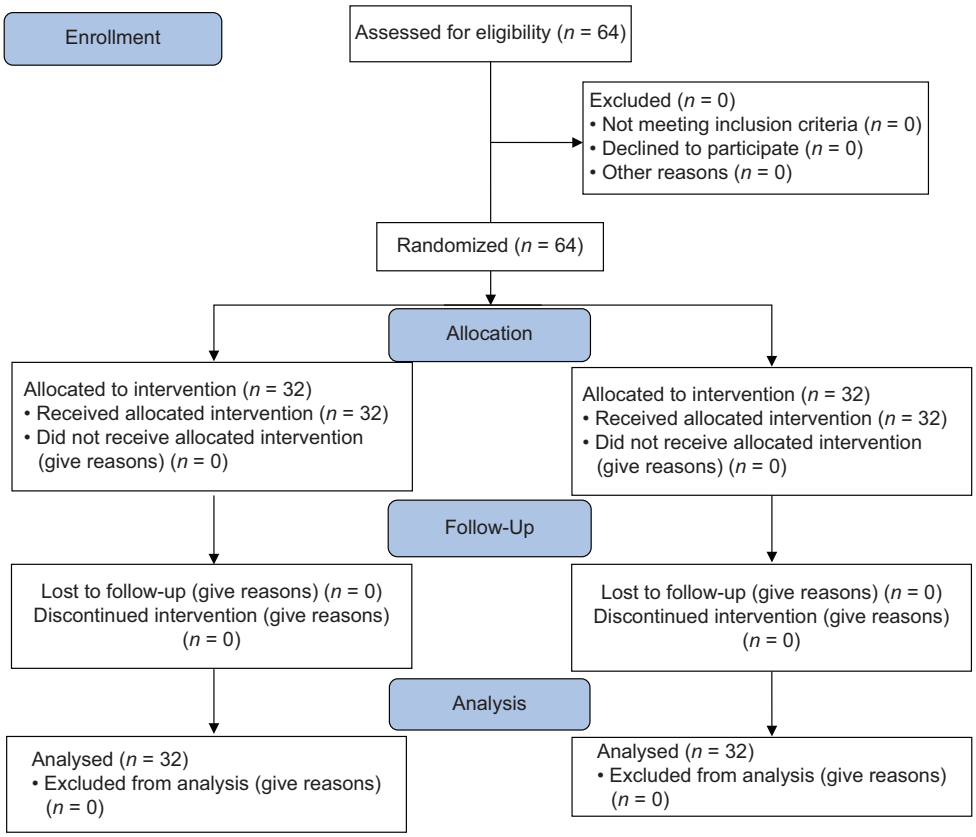

Figure 1: CONSORT flowchart

than 0.05 was considered statistically significant. We used the SPSS for Windows software (version 20; SPSS, Chicago, IL) for statistical analysis.

Results

The mean (SD) age of participating infants was 4.81 ± 0.86 and 4.92 ± 0.76 months in the GB and placebo groups, respectively ($P = 0.592$).

Table 1 shows descriptive statistics of study outcomes on the different occasions of the current clinical trial. There was no significant difference between the baseline number of breastfeeding ($P = 0.109$) and formula volume ($P = 0.245$) across groups. However, the change from baseline was statistically different between groups. The number of breastfeeding sessions had a significantly higher increase in the GB group compared with placebo (Median [IQR]: 1[0,1] vs. 0[0,1], $P = 0.005$) [Table 1]. Similarly, increased consumed formula volume was higher in the GB group (Mean ± SD: 42.81 ± 24.49 vs. 18.67 ± 14.57, $P = 0.003$) [Figures 2 and 3].

Discussion

This clinical trial study investigated the effect of GB on feeding resistance in infants. This disorder is likely caused by hyperalgesia and chronic pain in the mouth, oropharynx, esophagus, and stomach. The results of this study showed that the number of breastfeeding sessions had a significant increase as well as the volume of formula consumption in the GB group.

GB is used for neurologic pain in adults and children. GB is thought to reduce pain perception by reducing central sensitization.[15] Despite the lack of a prospective study to evaluate the dose, efficacy, and safety of this drug in infants, the use of GB in the neonatal period is increasing.[16,17] In neonatal intensive care units, GB is used to manage neonatal abstinence syndrome, chronic pain and irritability, visceral hyperalgesia (which is a neuropathic pain that results from the upregulation of gastrointestinal sensory input caused by pain), and irritability and feeding resistance in infants with neurological disorders and other comorbidities. In the gastrointestinal tract, non-painful stimuli such as abdominal distension caused by feeding or gas may lead to irritability, hypertonicity, inadequate oral feeding, and/or resistance to feeding.[18-21] Our data were in accordance with previous studies suggesting the use of GB in medically complex infants. The range of indications for GB treatment in this population includes feeding resistance/visceral hyperalgesia,[8,9] pain and irritability, and inadequate oral nutrition.[22,23] The use of GB to improve oral feeding in medically complex infants or infants in the postoperative period is based on the hypothesis that visceral pain may, at least in part, underlie poor oral feeding skills in these infants. There are reports about the improvement of oral nutrition and its volume after starting treatment with GB.[24] Other cases have focused on the use of GB for the treatment

Table 1: Number of breastfeeding sessions and used formula volume among the intervention and placebo groups

Outcome (n1/n2)	Gabapentin		Placebo		*P***
	Mean±SD	Median [IQR]	Mean±SD	Median [IQR]	
Age (32/32)	4.81±0.86	5 [4,5.5]	4.92±0.76	5 [4.5,5.5]	0.592[a]
No. Breastfeeding (19/19)					
Before	6.32±1.38	7 [6,7]	7.05±0.91	7 [6,8]	0.109[a]
After	7.37±1.57	8 [7,9]	7.32±0.95	7 [7,8]	0.544[a]
Difference	1.05±0.97	1 [0,1]	0.26±0.45	0 [0,1]	0.005[a]
*P**	0.001[c]		0.025[c]		
Formula volume (cc) (16/15)					
Before	510.00±87.25	505 [420,587.5]	550.67±03.40	600 [490,620]	0.245[b]
After	552.81±92.16	545 [465,620]	569.33±02.71	610 [500,630]	0.640[b]
Difference	42.81±24.49	42.5 [30,60]	18.67±14.57	20 [0,30]	0.003[b]
*P**	<0.001[d]		<0.001[d]		

*P** within-group comparison. *P*** between-group comparison. [a]Mann-Whitney test, [b]Independent *t*-test *t*, [c]Wilcoxon test, [d]paired *t*-test. SD=Standard deviation, IQR=Interquartile range

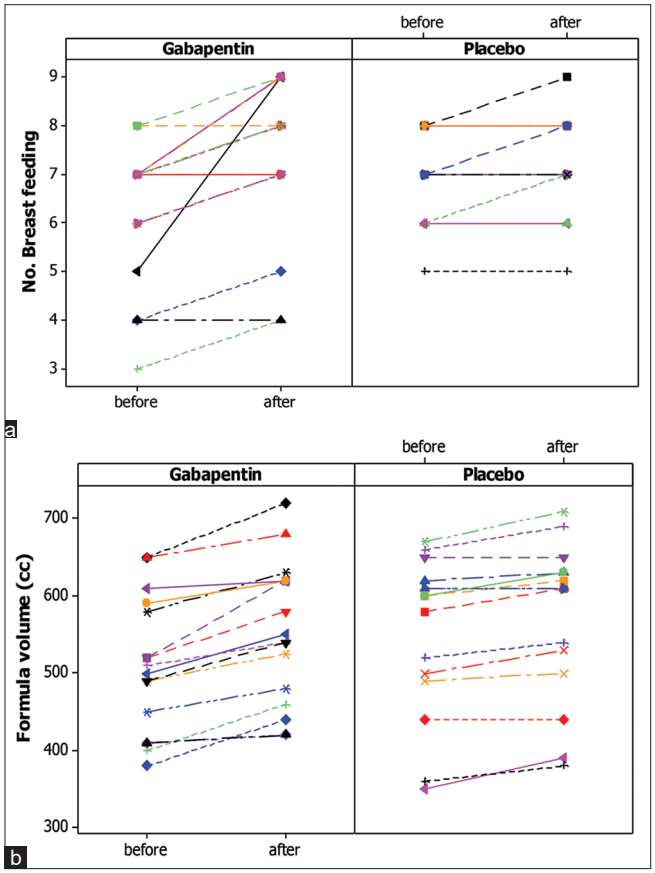

Figure 2: (a and b) Infant's number of breastfeeding sessions (a) and consumed formula volume (b) before and after the intervention

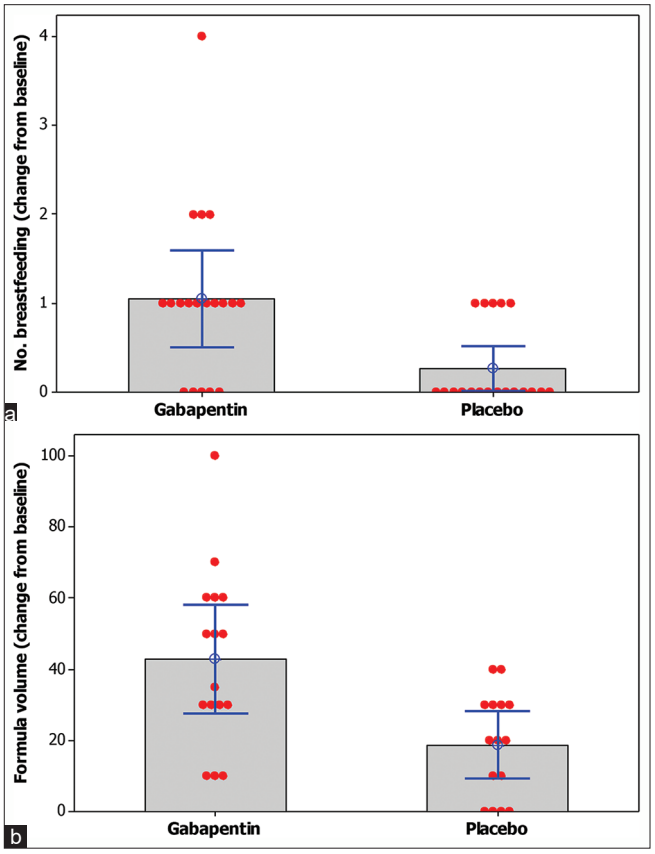

Figure 3: Mean (95% CI) change from baseline for the number of breastfeeding sessions (a) and formula volume (b)

of visceral hyperalgesia, reducing irritability and improving feeding tolerance.

A retrospective case series of 11 infants with complex medical conditions and neurological and gastrointestinal diseases was reported in which GB was used after unsuccessful treatment with multiple sedatives and analgesics. The starting dose in most of them was 5 mg/kg 2–3 times a day. In eight cases out of 11 patients, there was a decrease in irritability or an improvement in food resistance and oral nutrition.[15] Three neurological healthy infants with enteral feeding resistance and gastrointestinal complications alone (congenital diaphragmatic hernia, gastroschisis) were reported in a case series. Delays associated with enteral feeding resolved within 3 days after the initiation of GB in these infants. Infants started with minimal or no oral feeding and achieved full oral feeding within 120 days

of starting GB.[16] Another case series study reported 15 infants with complex congenital heart disease with a mean age of 2.4 months who had difficulty feeding after cardiac surgery. Children were initially treated with GB 10 mg/kg twice daily, with the frequency increased to 3 times daily if not sedated after the first doses. The majority experienced improved oral intake after the initiation of GB. Before GB initiation, infants received a voluntary oral intake of 401 ± 451 mL/day on average, and after GB, it was changed to 781 ± 586 mL/day with no acute safety issues or sedation effects.[19]

GB has been successfully used to treat visceral hyperalgesia in infants with gastrointestinal and neurological comorbidities. There are some cases of neuropathic pain treated with GB. GB was well tolerated, and very few short-term side effects were reported.[25-27]

One of the limitations of this study was its limited age range, which was chosen for ease of evaluation and quantitative measurement of the amount of milk consumed. In addition, it is better to conduct a study in the future with a plan to evaluate the "change in the amount of supplementary food" in older infants.

Conclusion: Considering the significant increase in formula consumption and the number of breastfeeding sessions in the GB group, it is possible to use this drug as a nerve-stabilizer and pain reducer in the treatment of this disorder. As a result, the patient and the family can be saved from the trouble of ineffective interventions and other costly procedures such as changing different formulas and using various antireflux and colic drugs.

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Conflicts of interest

There are no conflicts of interest.

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