Dental Research Journal

Original Article

Efficacy and safety of premedication with single dose of oral pregabalin in children with dental anxiety: A randomized double-blind placebo-controlled crossover clinical trial

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ABSTRACT

Background: Dental anxiety is a relatively frequent problem that can lead to more serious problems such as a child entering a vicious cycle as he/she becomes reluctant to accept the required dental treatments. The aim of this randomized double-blind clinical trial study was to evaluate the anxiolytic and sedative effect of pregabalin in children.

Materials and Methods: Twenty-five children were randomized to a double-blind placebo-controlled crossover clinical trial. Two visits were scheduled for each patient. At the first visit, 75 mg pregabalin or placebo was given randomly, and the alternative was administered at the next visit. Anxiolytic and sedative effects were measured using the visual analogue scale. The child's behavior was rated with the Frankl behavioral rating scale and the sedation level during the dental procedure was scored using the Ramsay sedation scale. The unpaired, two-tailed Student's *t*-test was used to compare the mean changes of visual analog scale (VAS) for anxiety in the pregabalin group with that of the placebo group. A repeated measures MANOVA model was used to detect differences in sedation level in the pregabalin and placebo groups regarding the interaction of 3-time measurements; sub-group analysis was performed using Student's *t*-test. The Mann–Whitney U-test was used to analyze the nonparametric data of the Frankl and Ramsay scales. A $P < 0.05$ was considered significant.

Results: The reduction of the VAS-anxiety score from 2 h post-dose was statistically significant in the pregabalin group. From 2 h to 4 h post-dose, the VAS-sedation score increased significantly in the pregabalin group. The child's behavior rating was not significantly different between the groups. The number of "successful" treatment visits was higher in the pregabalin group compared to the placebo group.

Conclusion: Significant anxiolytic and sedative effects can be anticipated 2 h after oral administration of pregabalin without serious side effects.

Key Words: Anxieties, dental anxiety, sedatives

Received: August 2014
Accepted: December 2014

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INTRODUCTION

One of the most important problems in pediatric dentistry is how to manage the treatment needs of uncooperative and anxious children. Dental fear and anxiety is one of the most common causes of noncompliance during a dental visit. The prevalence of the dental fear/anxiety that causes behavior

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How to cite this article: Eskandarian T, Eftekharian H, Soleymanzade R. Efficacy and safety of premedication with single dose of oral pregabalin in children with dental anxiety: A randomized double-blind placebo-controlled crossover clinical trial. Dent Res J 2015;12:528-33.

management problems in children undergoing dental treatments was reported to be 5% to 20%.[1] The Children's Fear Survey Schedule-Dental Subscale (CFSS-DS) is a reliable scale for measuring dental fear and anxiety in children. This scale includes 15 dental and related medical situations scored from 1 to 5 (1 meaning "not at all afraid" and 5 "very afraid"). Total score is from 15 to 75, and a score of 38 or more indicates severe dental fear and anxiety.[2,3]

A proper behavior-guidance technique may lead to friendly communication and suitable dental management in an anxious child, but in cases of severe anxiety, pharmacological methods as an adjunct therapy can help a dentist to communicate more effectively with the child.[4] In-office, pharmacological techniques should provide sufficient efficacy and safety. Pharmacological agents that are administered by pediatric dentists should produce a mild depressed state in which the patient can respond to physical and verbal stimulations and retain his/her ability to maintain a patent airway independently.[5]

Although pregabalin was labeled as an agent for treating fibromyalgia and neuropathic pain, its anxiolytic effects have also been considered in numerous studies.[6] Using pregabalin as an anxiolytic drug has shown its acute anxiolytic effect,[7,8] as well as its chronic treatment effects in generalized anxiety and also in social anxiety disorders.[9-15]

It is stated that pregabalin binds to α2 δ-subunit of voltage-dependent calcium channels, which in turn leads to up-regulation of the inhibitory action of gamma-aminobutyric acid. Therefore, the neurotransmitters' release will be reduced.[6,16-18] Studies have shown faster anxiolytic effect of pregabalin when compared to the selective serotonin reuptake inhibitors and fewer side effects in comparison with the benzodiazepines.[6,10,12,13,19]

Despite various techniques and pharmacological agents which are available to be used as conscious sedation in pediatric dentistry, dentists always try to find more techniques and agents that are not only effective but also safe enough for in-office use without serious side-effects. This trial evaluated the safety and anxiolytic effect of a single dose of 75 mg pregabalin compared to a placebo given as a premedication in a pediatric dental anxiety model. As a secondary measure, its sedative effect was also evaluated.

MATERIALS AND METHODS

This randomized double-blind placebo-controlled crossover clinical trial was designed to evaluate the early-onset anxiolytic and sedative effects of a single dose of pregabalin 75 mg (Lyrica, Pfizer Ltd., Germany) in anxious children needing dental treatment. With the approval of the Ethics Committee of the Vice-Chancellery of Research and Technology (Trial registration: IRCT201206131674n2), 25 healthy (ASA Physical Status I) male and female children in the age range of 4 to 6 years old were selected among patients attending the Pediatric Dentistry Department (Shiraz, Iran). Children were included in the study if they met all of the following criteria:

1. Age 4-6 years old;
2. The CFSS-DS score ≥38 in the screen visit and also at the beginning of the dental procedures in other visiting days;
3. Having at least two mandibular primary molars that needed pulpotomy treatment;
4. Signed written informed consent by the legally responsible parent or guardian.

Children were excluded from the study if they met any of the following criteria:

1. A history of seizure disorders;
2. A current diagnosis of neuropathic pain;
3. Any serious or uncontrolled systemic disease;
4. Known sensitivity to related drugs;
5. Having been on central nervous system-active drugs in the past 2 weeks;
6. Anytime if the child or the parents refused to continue their participation in the study procedure;
7. If the baseline CFSS-DS <38 at the second scheduled dental visit.

The screening visit was 4-8 weeks before the scheduled date of the dental treatment, and the dental anxiety level of the children was measured by the CFSS-DS questionnaire, which was filled out by the mothers.

Two separate dental visits were scheduled for each patient. We packed pregabalin and placebo capsules separately in two pockets with the same shape and color and then asked the patient to pick up one of them randomly for the premedication at the first visit; the alternative drug was given at the next visit. There was at least a 1-month interval between the first and the second dental visits. According to the manufacturer's instructions, the medication will take

effect earlier if it is taken on an empty stomach. Therefore, mothers were asked to keep their children N.P.O. for 6 h before taking the premedication. Premedication was performed with a pregabalin capsule (75 mg) or placebo 2 h before the beginning of the dental treatment.

Two efficacy measures were then completed by the mothers to record their satisfaction regarding the premedication's effect on their children's behavior at the dental visit. The first efficacy measure was the VAS-Anxiety, which was completed before the premedication as the baseline and then also 2 h post-dose. The VAS-Anxiety is a 100 mm-line, which is labeled by "not at all anxious" at the left end and "extremely anxious" at the right end. With this explanation, we asked mothers to report their child's anxiety level from a minimum to a maximum degree by marking on the scaled line. The second measure was the VAS-Sedation, a 100 mm-line, which is labeled with "not at all sedated" at the left end and "extremely sedated" at the right end, and was completed at the baseline (before premedication) and at 2 and 4 h post-dose.

The other two measures were the Frankl behavioral rating scale and the Ramsay sedation scale, which were completed by the dentist as measures of the child's cooperation during the dental procedure. The Frankl behavioral rating scale divides the child's behavior into four categories, ranging from "definitely positive" to "definitely negative".[20,21] The Ramsay sedation scale describes the patient's sedation in six levels, from "anxious and agitated" to "nonresponsive".[22]

In the current study, we classified the outcome of the dental visits into "successful" and "unsuccessful" groups. This classification was done according to the nonpharmacological techniques that are used to manage the children during the dental procedure. The "tell-show-do" technique was performed for all the patients. The "voice control" and "positive reinforcement" techniques were also acceptable. Treatments that were finished with the aid of these techniques were considered "successful," but when a treatment couldn't be finished without the aid of a more aggressive technique (e.g., HOM or physical restrains), it would be categorized as an "unsuccessful" treatment visit.

Vital signs including blood pressure, pulse, respiratory rate, and blood oxygen saturation were recorded before giving the premedication, and these signs were monitored continuously throughout the dental procedure until discharging time. The criteria for discharging the patient were having normal vital signs and being conscious enough to walk unaided and to communicate verbally. Postoperative instructions were also given at the end of the visit.

This study was double-blinded, neither the patients nor the dentist or a dental assistant was aware of the placebo or pregabalin groups. At the time of the first dental visit, each participant was coded as "A" or "B" according to the medicine received. Those who received pregabalin at the first visit and placebo at the second were coded as the "A" group and vice versa were coded as "B" group. Medication and randomization were done by an educated isolated nurse.

Power analysis was performed using a power of 80% and $\alpha = 0.05$. For detecting a 33% reduction of the mean VAS-anxiety score after premedication with pregabalin, a sample size of at least 15 patients per group was required. Data were analyzed using SPSS Statistics for Windows, Version 18.0. (Chicago: SPSS Inc). The unpaired, two-tailed Student's *t*-test was used to compare the mean changes of VAS-anxiety score in the pregabalin group with that of the placebo group. A repeated measures MANOVA model was used to detect differences in sedation level in the pregabalin and placebo groups regarding the interaction of 3-time measurements; sub-group analysis was performed using Student's *t*-test. The Mann–Whitney U-test was used to analyze the nonparametric data of the Frankl and Ramsay scales. The comparison of the number of "successful" treatment visits was done with the Chi-square test. A $P < 0.05$ was considered significant.

RESULTS

Twenty-five patients were included in this clinical trial. Twenty-one patients completed the study procedure, and the results are based on this number of subjects. Of the four participants who were excluded from the study, two patients refused to take the medication, and the other two patients had a baseline CFSS-DS of <38 at the second visit. Each patient participated in two dental visits with at least 1-month between them; therefore, physical status and the baseline anxiety level of both groups (experimental and control) were comparable [Table 1].

The mean changes of the VAS-Anxiety score from baseline to 2 h post-dose were 10.52 ± 6.29 in the pregabalin group and 3.52 ± 4.33 in the placebo group [Table 2]. The two-tailed Student's *t*-test shows a significant change in the mean anxiety score in the pregabalin group compared to the placebo group ($P < 0.001$).

The VAS-sedation was measured at three times: at the baseline, 2 h post-dose, and 4 h post-dose [Table 2]. According to the results of the repeated measures MANOVA test, interaction effects between time and groups were significant ($P < 0.001$). The Student's *t*-test was used as subgroup analysis and showed that the sedation level at the baseline was comparable between the groups without significant difference and that there was a significantly higher sedation level in the pregabalin group than in the placebo group at 2 and 4 h post-dose ($P < 0.001$).

Using the Mann-Whitney test analysis showed that the Ramsay sedation score was significantly higher in the pregabalin group than in the placebo group ($P = 0.007$). The Frankl behavioral rating score was not significantly different between the groups ($P = 0.067$). The number of "successful" treatment visits was significantly higher in the pregabalin group ($P = 0.013$).

Table 1: Baseline demographic and clinical characteristics of study sample

Criteria	Range of amounts	
Gender (female/male)	10/11	
Age	5.28±1.10	
Weight (kg)	15.76±1.30	
Height (cm)	101.61±12.18	
	Pregabalin (*n*=21)	**Placebo (*n*=21)**
CFSS-DS score	50.33±6.390	49.71±6.649
VAS-anxiety	85.47±15.35	85.09±14.43
VAS-sedation	13.19±7.53	12.47±6.22

CFSS-DS: Children's Fear Survey Schedule-Dental Subscale; VAS: Visual Analogue Scale.

Table 2: VAS anxiety and sedation

VAS Scale	Prergabalin	Placebo	*P*
VAS-anxiety			
Baseline	85.47±15.35	85.09±14.43	NS
2 h postdose	66.14±16.55	81.43±14.79	0.003
VAS-sedation			
Baseline	13.19±7.53	12.47±6.22	NS
2 h postdose	27.90±14.79	13.67±6.12	<0.001
4 h postdose	40.14±15.18	16.33±8.33	<0.001

Data are presented as mean ± SD. SD: Standard deviation; VAS: Visual Analogue Scale; NS: Not significant.

Adverse effects and complications during the treatment procedure were recorded in the pregabalin and the placebo groups respectively as: Fatigue (n = 0,0); dizziness (n = 4,0); somnolence (n = 9,1); nausea and vomiting (n = 0,0); dry mouth or visual disturbances (n = 0,0). In the follow-up visits, no problems were reported by the parents in the placebo group. However, in the pregabalin group, two cases of nausea and vomiting and four cases of somnolence (continued up to 4 h after discharge) were reported. The severity of all complications was reported as mild.

DISCUSSION

In this clinical trial, an anxiolytic effect was seen 2 h after administration of the pregabalin 75 mg in 4- to 6-year-old children. The mean changes of the VAS-anxiety score from baseline to 2 h post-dose in the pregabalin group was 33% more than that of the placebo group, which is statistically and clinically significant (10 ± 6-3 ± 4, $P < 0.001$). Early anxiolytic effect of pregabalin within a few hours has also been reported in some studies.[7,8] In the current study, as well as the study of Gonano *et al*.[8] patients were asked to be N.P.O. before the procedure. Gonano *et al*.[8] found an anxiolytic effect 1-h after oral administration of 300 mg pregabalin in adult outpatients. They found a 40% reduction in the anxiety score, which is comparable with the results of the current study. Nutt *et al*.[7] found a clinically meaningful anxiolytic effect of pregabalin within the first 3-4 h after a single-dose administration of 150 mg pregabalin. The participants were not N.P.O. in their study, which may have led to the delayed onset of pregabalin when compared to the study of Gonano *et al*.[8] and also with the current study.

In this study, the VAS-sedation score yielded at the beginning of the dental visit was considered the baseline sedation level. The VAS-sedation score was recorded again in 2 h and then again 4 h after administering the medication. A significant increase in the sedation level was seen from 2 to 4 h post-dose, which was comparable with the results of the study of Nutt *et al*.[7] They had found a significant increase in the VAS-sedation score from 2.5 h post-dose. In another study, White *et al*.[23] evaluated the sedative effect of pregabalin in a dose-ranging study of adult participants. They found a higher sedation score in the group that received pregabalin 300 mg compared to the control group.

In the current study, although the increased sedation level in the pregabalin group was confirmed by the dentist's evaluation, the children's behavior rating scale did not show any significant difference between the groups. This may be the result of some shortcomings of the Frankl behavioral rating scale. Wright and Stigers believe that this scale does not provide distinct clinical information, especially in uncooperative patients,[20] and a wide range of clinical behaviors are categorized together in the same classification, such as "rating 2." Therefore, another analysis was performed in the current study to compare the number of "successful" treatment visits between the groups. The result showed that the number of "successful" treatment visits was significantly more in the pregabalin group than in the placebo group. It seems that this finding is related to the decreased anxiety and increased sedation level in the pregabalin group, which in turn caused the nonpharmacological techniques (such as Tell-Show-Do, voice control, and positive reinforcement) to be more effective. This effect was not visible in the placebo group, and disruptive behaviors were significantly more in this group than in the pregabalin group, which in turn resulted in the rejection of the treatment by participants.

The results of the current study show that pregabalin was a safe and tolerable drug in children, which was previously reported in the study of Vondracek *et al*.[24] They concluded, from their open-label study, that the pregabalin was safe, effective, and well-tolerated in children, though with temporary and uncommon adverse effects. Further controlled clinical trials are necessary to establish pregabalin as an early-onset anxiolytic drug for administration in anxious pediatric dental patients.

CONCLUSION

Premedication with pregabalin 75 mg seems to be safe and effective in anxious children requiring dental treatment. The results of this study suggest that a rapid anxiolytic and sedative effect can be seen from 2 h after oral administration of pregabalin 75 mg. However, the children's behavior rating did not improve significantly, but behavior-guidance techniques were more effective in the pregabalin group. The number of "successful" treatment visits was higher in the pregabalin group.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

REFERENCES

1. Klingberg G, Broberg AG. Dental fear/anxiety and dental behaviour management problems in children and adolescents: A review of prevalence and concomitant psychological factors. Int J Paediatr Dent 2007;17:391-406.
2. Cuthbert MI, Melamed BG. A screening device: Children at risk for dental fears and management problems. ASDC J Dent Child 1982;49:432-6.
3. Baier K, Milgrom P, Russell S, Mancl L, Yoshida T. Children's fear and behavior in private pediatric dentistry practices. Pediatr Dent 2004;26:316-21.
4. Klingberg G, Raadal M, Anrup K. Dental fear and behavior management problems. In: Koch G, Poulsen S, editors. Pediatric Dentistry: A Clinical Approach. 2nd ed.Singapore, Blackwell; 2009. p. 41.
5. Murray D. Pharmacologic management of patient behavior. In: Dean JA, Avery DR, Mc-Donald RE, editors. McDonald and Avery's Dentistry for the Child and Adolescent. 9th ed. Maryland Heights, Mo: Mosby-Elsevier; 2011. p. 253.
6. Aupperle RL, Tankersley D, Ravindran LN, Flagan T, Stein NR, Stein MB, *et al*. Pregabalin effects on neural response to emotional faces. Front Hum Neurosci 2012;6:42.
7. Nutt D, Mandel F, Baldinetti F. Early onset anxiolytic efficacy after a single dose of pregabalin: Double-blind, placebo-and active-comparator controlled evaluation using a dental anxiety model. J Psychopharmacol 2009;23:867-73.
8. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B. The anxiolytic effect of pregabalin in outpatients undergoing minor orthopaedic surgery. J Psychopharmacol 2011;25:249-53.
9. Pande AC, Feltner DE, Jefferson JW, Davidson JR, Pollack M, Stein MB, *et al*. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: A placebo-controlled, multicenter study. J Clin Psychopharmacol 2004;24:141-9.
10. Rickels K, Pollack MH, Feltner DE, Lydiard RB, Zimbroff DL, Bielski RJ, *et al*. Pregabalin for treatment of generalized anxiety disorder: A 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry 2005;62:1022-30.
11. Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: A novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther 2007;29:26-48.
12. Pohl RB, Feltner DE, Fieve RR, Pande AC. Efficacy of pregabalin in the treatment of generalized anxiety disorder: Double-blind, placebo-controlled comparison of BID versus TID dosing. J Clin Psychopharmacol 2005;25:151-8.
13. Montgomery SA, Tobias K, Zornberg GL, Kasper S, Pande AC. Efficacy and safety of pregabalin in the treatment of generalized anxiety disorder: A 6-week, multicenter, randomized, double-

blind, placebo-controlled comparison of pregabalin and venlafaxine. J Clin Psychiatry 2006;67:771-82.
14. Montgomery SA. Pregabalin for the treatment of generalized anxiety disorder. Expert Opin Pharmacother 2006;7:2139-54.
15. Mula M, Pini S, Cassano GB. The role of anticonvulsant drugs in anxiety disorders: A critical review of the evidence. J Clin Psychopharmacol 2007;27:263-72.
16. Fink K, Dooley DJ, Meder WP, Suman-Chauhan N, Duffy S, Clusmann H, *et al.* Inhibition of neuronal Ca (2+) influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 2002;42:229-36.
17. Dooley DJ, Taylor CP, Donevan S, Feltner D. Ca2+ channel alpha2delta ligands: Novel modulators of neurotransmission. Trends Pharmacol Sci 2007;28:75-82.
18. Brawek B, Löffler M, Dooley DJ, Weyerbrock A, Feuerstein TJ. Differential modulation of K(+)−evoked (3)H-neurotransmitter release from human neocortex by gabapentin and pregabalin. Naunyn Schmiedebergs Arch Pharmacol 2008;376:301-7.
19. Lydiard RB, Rickels K, Herman B, Feltner DE. Comparative efficacy of pregabalin and benzodiazepines in treating the psychic and somatic symptoms of generalized anxiety disorder. Int J Neuropsychopharmacol 2010;13:229-41.
20. Wright GZ, Stigers JI. Nonpharmacologic management of children's behaviors. In: Dean JA, Avery DR, Mc-Donald RE, editors. McDonald and Avery's Dentistry for the Child and Adolescent. 9th ed. Maryland Heights, Mo: Mosby-Elsevier; 2011. p. 27-40.
21. Klinberg G. Dental anxiety and behaviour management problems in paediatric dentistry — A review of background factors and diagnostics. Eur Arch Paediatr Dent 2007;9 Suppl 1:11-5.
22. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656-9.
23. White PF, Tufanogullari B, Taylor J, Klein K. The effect of pregabalin on preoperative anxiety and sedation levels: A dose-ranging study. Anesth Analg 2009;108:1140-5.
24. Vondracek P, Oslejskova H, Kepak T, Mazanek P, Sterba J, Rysava M, *et al.* Efficacy of pregabalin in neuropathic pain in paediatric oncological patients. Eur J Paediatr Neurol 2009;13:332-6.