Prevalence of Gingival Hyperplasia Induced by Anticonvulsants: A Systematic Review

Prevalência da Hiperplasia Gengival Induzida pelo uso de anticonvulsivantes: Revisão sistemática

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ABSTRACT

Objective: Gingival hyperplasia (GH) is one of the side effects of anticonvulsant drugs. The aim of this study was to verify the prevalence of GH associated with the use of anticonvulsant, through a systematic review. Material and Methods: Systematic search was done at databases Pubmed and Embase between January 1984 and March of 2020 for identification of articles addressing the prevalence of GH associated with the use of anticonvulsant drugs. The methodological index for non-randomized studies (MINORS) was independently assessed for quality in the selected papers. Results: The search identified 4,471 references. Nine articles were selected and evaluated 632 participants. All of the studies included in the systematic review showed a low risk of bias. The anticonvulsants used by patients were carbamazepine, ethosuximide, phenytoin, primidone, phenobarbital, and sodium valproate. The studies showed a correlation between different types of anticonvulsants and GH prevalence, with a range from 0% to 73%. Among the anticonvulsants used, phenytoin showed the greatest incidence of GH, varying between 15.61% and 73% in patients. Conclusion: In the analysis of the results obtained in the literature, it is possible to notice that the great majority of studies presented incidence of GH associated with anticonvulsant use. However, further studies are necessary to understand the anticonvulsant action mechanism inducing GH, as well as the prevention forms, given that GH is a significant side effect.

KEYWORDS

Anticonvulsants; Gingival hyperplasia; Prevalence.

RESUMO

Objetivo: Hiperplasia gengival (HG) é um dos efeitos colaterais das drogas anticonvulsivantes. O objetivo deste estudo foi verificar a prevalência de HG associada ao uso de anticonvulsivantes, por meio de uma revisão sistemática. Material e Métodos: A busca sistemática foi realizada nas bases de dados Pubmed e Embase entre janeiro de 1984 e março de 2020 para identificação de artigos que abordassem a prevalência de HG associada ao uso de drogas anticonvulsivantes. Foi avaliado independentemente, o risco de viés através do “Methodological index for non-randomized studies” (MINORS), para análise da qualidade dos trabalhos selecionados. Resultados: A pesquisa identificou 4,471 referências. Nove artigos foram selecionados e avaliaram 632 participantes. Todos os estudos incluídos na revisão sistemática mostraram baixo risco de viés. Os anticonvulsivantes utilizados pelos pacientes foram carbamazepina, etosuximida, fenitoína, primidona, fenobarbital e valproato de sódio. Os estudos mostraram correlação entre os diferentes tipos de anticonvulsivantes e a prevalência de HG, com variação entre 0% a 73%. Entre os anticonvulsivantes utilizados, a fenitoína apresentou a maior incidência de HG, variando entre 15,61% e 73% em pacientes. Conclusão: Na análise dos resultados obtidos na literatura, é possível notar que a grande maioria dos estudos apresentou incidência de HG associada ao uso de anticonvulsivantes. No entanto, estudos adicionais são necessários para compreender o mecanismo de ação do anticonvulsivante para a indução da HG, bem como as formas de prevenção, dado que a HG é um efeito colateral significativo.

PALAVRAS-CHAVE

Anticonvulsivantes; Hiperplasia gengival; Prevalência.
INTRODUCTION

Gingival hyperplasia (GH) is a common condition to patients who take three different drug classes, anticonvulsants (phenytoin, phenobarbital, vigabatrin), immunosuppressors (cyclosporine A) and calcium channel blockers (nifedipine, amlodipine, diltiazem, verapamil) [1-5]. The pathogenesis of this condition is multifactorial, involving a number of factors, including the quality of plaque control, gingival inflammation, age, sex, duration of therapy, drug concentration, concomitant use of certain medications and genetic factors [4].

Epilepsy is a very frequent neurological disease, surpassed in number only by cerebrovascular accident. Its incidence significantly varies with age, affecting nearly 1% of the population worldwide. Epilepsy is a condition that requires the use of anticonvulsants, and phenytoin (PHE) is the most frequently prescribed drug, as it is clinically effective, powerful and inexpensive [2,6-7]. PHE was initially adopted in 1938 and the first case reported in the literature on GH associated with the use of PHE was in 1939, by Kimball [8]. Since then, there has been a growing number of studies on this subject [9].

GH may develop within 1 to 3 months after the beginning of an anticonvulsant treatment. Initially, this hyperplasia is present in the interdental papilla and shows a diffuse increase, extending to the free gingiva and attached gingiva, exhibiting a lobulated aspect [4,10-12]. It mainly affects the anterior region, both in the maxilla and mandible [2]. At times, this proliferative tissue may cover the teeth vestibular face, leading to dental displacement [10], besides unfavorable esthetics and difficult teeth cleaning. GH can reach occlusal and lingual faces, interfering in speech, mastication and occlusion. Finally, GH induces plaque accumulation, increasing the susceptibility to periodontal disease and cavities [1].

Although PHE is the main used and studied anticonvulsant, several others are also associated with GH during therapy, including carbamazepine (CBZ) [10,13-14], sodium valproate (VPT) [14-15], primidone (PMD) [10], phenobarbital (PB) [6,10], vigabatrin (VGB) [16]. This systematic review was performed aiming at verifying, in the literature, the prevalence of GH associated with anticonvulsant use, due to great data variability and the importance of awareness on this issue. These data are important in order to plan preventive actions and better kinds of treatment for GH, improving buccal health conditions and patient quality of life. Therefore, integrated knowledge on this side effect of the therapy with anticonvulsant is fundamental for dental practice.

MATERIAL AND METHODS

Focus issue

The present systematic review was carried out in agreement with the Cochrane Collaboration and followed the principles of Preferred Reporting Items for Systematic Reviews and Meta-analysis [17]. Questions raised in this study were developed using patient characteristics, type of intervention, control, and outcome (PICO). The focus questions analyzed in this review were the following: “What is the prevalence of gingival hyperplasia associated with anticonvulsant use?” and “Which anticonvulsant develops higher incidence of gingival hyperplasia?”

Search strategy

Two databases (PubMed and EMBASE) were systematically analyzed between January 1984 and March of 2020 for selection of articles. The keywords used in the searches were (“phenytoin” [MeSH Terms] or “phenytoin” [All Fields]) and (“gingival overgrowth” [MeSH Terms] or (“gingival” [All Fields] and “overgrowth” [All Fields]) or “gingival overgrowth” [All Fields]); (“phenytoin” [MeSH Terms] or “phenytoin” [All Fields]) and (“gingival hyperplasia” [MeSH Terms] or (“gingival” [All Fields] and “hyperplasia” [All Fields]) or “gingival hyperplasia” [All Fields]); (“anticonvulsants” [Pharmacological Action] or “anticonvulsants” [MeSH Terms] or “anticonvulsants” [All Fields]) and (“gingival overgrowth” [MeSH Terms] or (“gingival” [All Fields] and “overgrowth” [All Fields]) or “gingival overgrowth” [All Fields]); (“anticonvulsants” [Pharmacological Action] or “anticonvulsants” [MeSH Terms] or “anticonvulsants” [All Fields]) and (“gingival hyperplasia” [MeSH Terms] or (“gingival” [All Fields] and “hyperplasia” [All Fields]) or “gingival hyperplasia” [All Fields]).

Selection of articles

The selection criteria of articles were: a) controlled clinical studies; b) retrospective and prospective studies; c) studies evaluating the prevalence of gingival hyperplasia associated with anticonvulsant use. The exclusion criteria were the following: literature reviews, clinical case reports, case series and studies not published in the English language.
Prevalence of Gingival Hyperplasia Induced by Anticonvulsants: A Systematic Review

Cláudio MM et al.
Braz Dent Sci 2021 Jan/Mar;24(1)

Data collection
A reviewer (MC) collected the main data in the articles and two reviewers (MC and JVS) did the analysis of the studies. In case of doubt, a third reviewer (LT) was consulted. The following data were collected from the selected studies: year of publication, country, authors, study design, prevalence of GH, number of participants, and period of evaluation. Only data on the prevalence of GH presented by the authors as tables or in the text were considered.

Analysis of bias
The methodological index for non-randomized studies (MINORS) was independently assessed for quality in the selected papers (Table I) [18]. The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate), being the global ideal score 16 for non-comparative studies and 24 for comparative studies.

RESULTS
Result of the search and excluded studies
The electronic database searches using EMBASE and PubMed are shown in the flowchart (Figure 1). Nine articles were selected after abstract analysis by two reviewers (MC and JVS), considering the prevalence of GH in patients under anticonvulsant treatment.

Description of studies
Among the nine analyzed studies (Table II), Suneja et al. (2016) [14] evaluated anticonvulsant effects on GH and the factors that influence its development by analyzing 30 children divided in three groups, according to the monotherapy in use, which could include PHE, VPT and CBZ. During a 6-month follow-up period, 53.6% prevalence of GH was observed in patients using PHE in the first 3 months of evaluation. VPT also presented GH, but at a mild level, showing no statistical relevance; while CBZ showed no signs of GH.

In a prospective observational study, Prasad et al. (2002) [7] also verified the prevalence of GH associated with PHE, during a six-month follow-up period in children. Thirty children were evaluated, and 57% presented GH in the mesiodistal area, reaching up to 82.35% in the vestibular area after 6 months of anticonvulsant use.

In a cross-sectional study, Brunet et al. (2001) [5] evaluated the prevalence of GH with two indices and the risk factors for its development. In that study, PHE action was evaluated in association or not with PB. Higher GH index was noticed in patients taking PHE (73%) compared with PB (31.8%) and control (1%) groups. In addition, when severity was evaluated, PHE presented 16.2% of cases, while PB was associated with 4.5%.

Majola et al. (2000) [19] analyzed the prevalence and severity of GH associated with PHE and its relationship with the risk factors. One hundred and thirty-four patients (average age: 32 years) making exclusive use of PHE or its association with another anticonvulsant were selected. Among those patients, 62% presented GH. Additional laboratorial tests showed that PHE and serum folate concentrations were 0.03mg/l to 3.89mg/l and 1.2ng/ml to 14.7ng/ml, respectively. A great number of patients (77%) reported brushing teeth regularly, while 3% admitted to not brushing.

Kamali et al. (1999) [10] evaluated the incidence of GH and the effects of co-medication of other anticonvulsants associated with PHE, monitoring anticonvulsant levels in the saliva and plasma. Thirty-six patients making use of PHE for at least 6 months without dosage alteration were selected. Out of these, 13 patients also made use of another medication such as CBZ (9), PB (3) and PMD (1). The age average of the patients was approximately 39.5 years for those taking only PHE and 38.8 for those associating...
PHE. The prevalence of GH was 57% for patients under monotherapy with PHE and 31% in patients associating PHE with CBZ, PB or PMD.

Perlík et al. (1995) [20] studied PHE concentration in the plasma of adult patients (average age: 36.55 ± 10.24 years), taking the drug for at least 1 year. This study evaluated 54 patients (27 women; 27 men) with epilepsy under anticonvulsant treatment, out of which 22 were under PHE monotherapy and 32 under polytherapy using VPT, CBZ, PMD, PB, ethosuximide or clonazepam. Among the analyzed patients, 24% presented mild to severe GH. In women, at least 55.5% discrete alterations or no hyperplasia were found, whereas approximately 77.7% of the men presented mild and/or severe GH. The obtained data demonstrated that the higher the dosage and the longer the use of PHE therapy, associated or not with another drug, the higher the incidence of GH.

Dahllof et al. (1993) [13] compared the periodontal condition of adult patients treated long-term with PHE or CBZ. Forty adult patients were selected (average age: 51 years) and treated with anticonvulsant therapy for 18 years on average (10-31 years). Regarding the drug type, 18 individuals were under PHE monotherapy, 11 were receiving an association between PHE and another type of anticonvulsant, 10 were receiving CBZ monotherapy and one was under CBZ associated with PB treatment. It was observed that 35% of patients taking PHE developed GH grade 1, while only 10% of patients using CBZ showed GH grade 1.

Thomason et al. (1992) [21] compared the incidence of GH associated with the use of PHE in epileptic patients with gingival alterations typical of healthy patients. The percentage of GH found in these patients was 13%, which is considered low compared with other studies. In this study, a correlation between bacterial plaque and GH indices was also demonstrated, however, it was not possible to associate GH with drug concentration in the saliva.

Seymour et al. (1985) [15] analyzed the periodontal health of 45 adult epileptic patients, under PHE (average age: 34.2 years) or SV (average age: 31.3 years) monotherapies, besides control patients (average age: 35 years) who were not making use of anticonvulsant. These patients were under anticonvulsant treatment for no less than 2 years and 4 years maximum. GH was more significant in patients making use of PHE (34.5%), compared with SV and control groups (18%).

**Risk of Bias**

All of the studies [5,7,10,13-15,19-21] included in the systematic review showed a low risk of bias, with score varying from 16 to 24 (good quality; Table I). There was no disagreement between the reviewers assessing and evaluating the quality of studies.

### Table I - Quality assessment of the selected studies (MINORS)

| Quality criteria | Seymour et al.1985 | Thomason et al.1992 | Dahllof et al.1993 | Perlík et al.1995 | Kamali et al.1999 | Majola et al.2000 | Brunet et al.2001 | Prasad et al.2002 | Suneja et al.2016 |
|------------------|-------------------|--------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| 1. A clearly stated aim | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 2. Inclusion of consecutive patients | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 3. Prospective collection of data | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 4. Endpoints appropriate to the aim of the study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 5. Unbiased assessment of the study endpoint | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 6. Follow-up period appropriate to the aim of the study | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 7. Loss to follow up less than 5% | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 8. Prospective calculation of the study size | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 9. An adequate control group | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 10. Contemporary groups | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 11. Baseline equivalence of groups | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 12. Adequate statistical analyses | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Total Score** | 22 | 24 | 21 | 16 | 22 | 20 | 23 | 20 | 19 |
| **Quality of study** | Good | Good | Good | Good | Good | Good | Good | Good | Good |

Braz Dent Sci 2021 Jan/Mar 24(1)
Table II - Main demographic characteristics and results of selected articles

| Authors          | Study type                      | Drug in use | Drug concentration | Time of use | Plaque Index | Number of patients | Female | Male | Age | Prevalence of hyperplasia | Evaluation time | Location | Probing Depth | Index used to evaluate hyperplasia |
|------------------|---------------------------------|-------------|--------------------|-------------|--------------|-------------------|--------|------|-----|--------------------------|----------------|----------|---------------|----------------------------------|
| Seymour et al., 1985 | Cross-sectional study | PHE and VPT | PHE: 300 mg/day | not assessed | 16.7 mg/ml saliva | 45 patients | 22 | 23 | 34.2 years; VTP 31.3 years; control 35 years | Cross-sectional study | Newcastle, England | Pockets bigger than 3 mm: PHE 4.5% VS 3.16%, Control 2.1% | Seymour 1985 |
| Thomason et al., 1992 | Cross-sectional study | PHE | PHE, CBZ association PHE + ATC; CBZ + PBT | not assessed | average of 18 years; PHE: 19.2 years of use; CBZ 14.5 years | 46 patients | 27 | 19 | 34.5% | Cross-sectional study | Newcastle, England | CBZ: 8.19 mm, PD > 3 mm; Control 12.57 mm | Seymour 1985 |
| Dahlöf et al., 1993 | Cross-sectional study | PHE | PHE or association PHE + ATC (CBZ, VPT, PRM, PB, ETX) | Mean PHE dosage: 5.18 mg/kg/day mild GH; 5.73 mg/kg/day severe GH | PHE: 302.6 mg/day; PHE + ATC: 360 mg/day | 54 patients | 21 | 19 | 34.6% | Cross-sectional study | Huddinge, Sweden | PD > 4 mm in PHE; 176% > 3 mm in PHE in 1 AED | Seymour 1985 |
| Perik et al., 1995 | Cross-sectional study | PHE, PB, PRM, CBZ | PHE: PHE and CBZ; PHE and PB | not assessed data | 11.3 mg/ml in total PHE concentration level | 54 patients | 27 | 17 | 34.5% | Cross-sectional study | Prague, Czech Republic | PD > 3 mm: PHE 30%, non PHE 16%, control 5% | Seymour 1985 |
| Kamali et al., 1999 | Cross-sectional study | PHE, PB | PHE: PHE and CBZ; PHE and PB | not assessed data | not assessed data | 134 patients | 23 | 17 | 34.5% | Retrospective cross-sectional study and retrospective prospective study | Newcastle, England | PD > 3 mm in PHE: Seymour 1985 | Seymour 1985 |
| Majola et al., 2000 | Retrospective cross-sectional study | PHE, PB | PHE, PB | not assessed data | not assessed data | 90 patients | 23 | 17 | 34.5% | Cross-sectional study | Durban, South Africa | PD > 3 mm; VPT 2.62 mm; CBZ 2.52 mm | Seymour 1985 |
| Brunet et al., 2001 | Cross-sectional study | PHE | PHE, VPT, CBZ | not assessed data | not assessed data | 90 patients | 27 | 19 | 34.5% | Cross-sectional study | Chandigarh, India | PD > 3 mm; VPT 2.62 mm; CBZ 2.52 mm | Seymour 1985 |
| Prasad et al., 2002 | Prospective observational study | PHE | 3% | not assessed data | not assessed data | 90 patients | 27 | 19 | 34.5% | Cross-sectional study | Ludhiana, India | PD > 3 mm; VPT 2.62 mm; CBZ 2.52 mm | Seymour 1985 |

Legend: ATC: anticonvulsants, CBZ: carbamazepine, ETX: ethosuximide, GH: gingival hyperplasia, PD: probing depth, PHE: phenytoin, PMO: primidone, PB: phenobarbital, VPT: sodium valproate.
DISCUSSION

Anticonvulsants were first used in 1938, with the discovery of PHE. This drug has been used in the treatment of epilepsy, bipolar disorder, cerebral palsy, neuropathic pain, among other neurological alterations, as well as for the treatment of ventricular arrhythmias [22]. GH is one of the side effects of anticonvulsant drugs. Studies show the incidence of this gingival alteration, which can cause esthetic and functional issues in patients [2-5,10-12, 23].

In the analysis of the results obtained in the literature, it is possible to notice that the great majority of studies presented incidence of GH associated with anticonvulsant use. Nevertheless, there is a report on the non-incidence of this undesirable effect in children using CBZ [14]. The greatest incidence (varying from 15.61% to 73%) of GH was associated with the use of PHE. Regarding the methodological quality of the studies, the results showed that all the included studies (comparative and non-comparative) presented a low risk of bias (good quality).

GH associated with PHE presents a clearly fibrotic clinical characteristic. On the other hand, GH caused by other classes of drugs, such as cyclosporine, is associated with a discrete fibrosis aspect and intense inflammation [24]. The anticonvulsant action mechanism associated with GH is still unknown. Studies point to a multifactorial character for the development of this gingival alteration, where genetic susceptibility is a determining factor. It is likely that there is stimulation in the proliferation of some populations of gingival fibroblasts, which somehow would justify individual susceptibility to these drugs [21]. In addition, some studies show that due to an imbalance between synthesis and degradation of extracellular matrix (ECM), an accumulation of collagen fibers may occur, when reduction of the collagen degradation is more likely than its production increase [25-27]. This gingival increase can be related to an increased production of the transforming growth factor beta (TGF-β) and connective tissue growth factor (CCN2 growth factor), which leads to greater synthesis and deposition of extracellular matrix. Besides overexpression of these molecules, there is an increase in the proliferation of mesenchymal cells and decreased apoptosis [24].

GH induced by anticonvulsant use impairs oral hygiene. This condition, associated with the fact that a great number of these patients are incapable of carrying out their oral hygiene, due to muscle weakness, aggravates bacterial buildup and plaque formation. Taken together, it is plausible to affirm that anticonvulsant use exacerbates inflammation and gingival hyperplasia [23,24]. Studies point to a controversy regarding the role of bacterial buildup and plaque as a contributing factor for the development of GH or a consequence of it [28], being classified by some authors as a risk factor [19,21] or not [14].

Despite not causing significant damage to the health of a patient, this fibrotic increase directly affects quality of life, and may indirectly lead to systemic negative effects [29-31].

One option for GH treatment is to change the medication according to prescription from a neurologist and adopt a conservative periodontal treatment, emphasizing daily oral hygiene. In cases of no GH improvement within 6 to 12 months, periodontal surgery can be carried out to increase the clinical crown, using gingivectomy/gingivoplasty, the most frequently employed technique, which can be performed by laser or conventionally. Many times, further surgeries are necessary to control recurrent GH [3,4,32,33].

The use of folic acid has been associated with the use of anticonvulsant as an adjuvant to reduce GH development. However, studies point that the association between folic acid and PHE use does not inhibit GH development, but delays it [34,35].
The prevalence of GH varied widely between studies, mainly regarding the anticonvulsants used. Several studies evaluated the prevalence of GH associated with PHE and its association with other anticonvulsants [6,10,13-15,20]. When PHE is associated with another anticonvulsant, a reduction varying from 18% to 26% can be observed in GH incidence [10,15].

CBZ is considered the safest anticonvulsant for children, given that its use has not been associated with GH development [14,36]. However, PHE treatment is also used in children who present GH development after 6 months of therapy with this medication [7]. Studies show a correlation between the presence of dental plaque, as a risk factor and aggravating circumstance for GH [19,21]. Conversely, another study demonstrated that gingival inflammation is a risk factor for GH development [5]. Probing depth greater than 3 mm is considered statistically significant for evaluation of the correlation with GH [14,21]. This probing depth increase can be associated with the fact that GH leads gingival edge to more coronary levels, which tends to increase probing depth, even when there is no clinical attachment loss.

Regarding sex and race characteristics, anticonvulsants present similar GH development tendencies [10,13,15]. However, a study pointed to a 33.4% higher incidence of severe GH in men than in women [20]. GH can be severe due to the age factor, since PHE is used in a wide age group and very often the individual initiates its use during childhood, extending it throughout life. Thus, the incidence among age groups is varied.

It is possible to notice a greater severity of GH associated with PHE use, when drug concentration did not present itself as a risk factor for its development and severity [5]. The associated use of PHE with other anticonvulsants tends to reduce the extension of GH; however, it does not hinder its development [10]. In addition, severe GH associated with anticonvulsants was found in children [20,34]. Recent studies revealed higher production of prostaglandin E2 (PGE2), transforming growth factor-beta (TGF-β) and interleukin-6 (IL-6) in the gingival fibroblasts of children exposed to PHE, when compared with that of adults [37,38], while there was a reduction in interleukin-8 (IL-8) production [38].

The limitations of this review were only related to the implementation of qualitative analysis, due to the lack of standardization in the presentation of the results. Given the fact that several methods were used to evaluate gingival growth and plaque index, there is a considerable reduction in the comparative data available about epidemiological information on the actual severity of the disease [21]. The studies selected were not in most randomized clinical trials (RCT), due to the absence in the literature on the subject [18]. Thus, it is suggested that RCT studies should be made with the standardization of data collection.

CONCLUSION

It was concluded that among commonly used anticonvulsants, PHE is the drug with higher incidence of GH, varying from 15.61% to 73%. However, further studies aiming at understanding the action mechanism of anticonvulsants that induce GH are needed. In addition, GH prevention methods are necessary, since this gingival alteration is a significant side effect, which is aggravated by poor oral hygiene in patients with motor deficits.

Conflict of interest

The authors have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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Prevalence of Gingival Hyperplasia Induced by Anticonvulsants:
A Systematic Review

Cláudio MM et al.
Braz Dent Sci 2021 Jan/Mar;24(1)

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Prevalence of Gingival Hyperplasia Induced by Anticonvulsants: 
A Systematic Review

Cláudio MM et al.

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