Phenytoin-Induced Gingival Over Growth: A Review

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Context: Gingival overgrowth can be associated with pharmacotherapy. Among the offending medications of gingival overgrowth, phenytoin is the first reported and the most common agent.
Evidence Acquisition: A literature search was performed with the relevant key words in different databases such as Scopus, Medline, Embase, and Google scholar.
Results: About 50% of individuals receiving phenytoin may develop gingival overgrowth usually after 3-6 months of treatment. Poor oral hygiene and young age are two identified independent risk factors of phenytoin-induced gingival overgrowth. The possible relationship between this adverse drug reaction and dose, serum levels of phenytoin as well as other co-administered antiepileptic agents is equivocal. It may be associated with pain, tenderness, and bleeding of the gums. Phenytoin-induced gingival overgrowth can interfere with speech, mastication, nutrition, tooth eruption, and esthetics and may results in teeth shifting and malocclusion. Several cellular and molecular mechanisms have been suggested for phenytoin-induced gingival overgrowth including: 1) inducing local inflammatory responses; 2) stimulating angiogenesis, extracellular matrix, and collagen synthesis; 3) inhibiting extracellular matrix and collagen degradation; 4) inducing systemic as well as localized folate deficiency; and 5) development of bacterial biofilm. Avoiding local irritants, rigorous plaque control, chlorhexidine gluconate mouth rinse, and regular periodontal maintenance therapy at 3-month intervals are the suggested preventive measures against phenytoin-induced gingival overgrowth. Strategies for the management of phenytoin-induced gingival overgrowth can be categorized as surgical and non-surgical. Surgical approaches including gingivectomy, periodontal flap, electro surgery, and laser excision are generally reserved for severe and advanced stages of phenytoin-induced gingival overgrowth. In mild to moderate stages, non-surgical options such as oral hygiene measures, scaling and root surface instrumentation, discontinuing, dose de-escalation or the replacement of phenytoin with other antiepileptics (e.g. lamotrigine, gabapentin, sulthiame, and topiramate), and pharmacotherapy (e.g. oral folic acid supplementation) can be considered.
Conclusions: Both pharmacoprophylaxis and pharmacotherapy of phenytoin-induced gingival overgrowth with potentially effective agents such as tamoxifen, finasteride, levamisole, celecoxib, and azithromycin has been largely overlooked and should be taken into account in future clinical investigations.

Keywords: Phenytoin; Gingival Overgrowth; Epidemiology; Clinical manifestations; Mechanisms; Prevention; Treatment

1. Context

Gingival overgrowth (GO) is characterized by an inflammatory hyperplasia and/or hypertrophy of the soft tissue between the teeth. The enlarged gingival tissue develops a characteristic of thickened and lobulated appearance that gradually extends along the labial, lingual, and coronal aspects to cover the entire anatomic crowns of teeth. It may be associated with pain, tenderness, and bleeding of the gums; in advanced cases gingival overgrowth may interfere with speech, mastication, nutrition, tooth eruption, and esthetics. It may also increase the risk of oral infection caries and predispose the affected individuals to periodontal diseases (1, 2).

GO has been associated with multiple factors including congenital diseases, hormonal disturbances, long-term poor oral hygiene, inflammation, neoplastic conditions, and adverse drug reactions (3, 4). Up to now, about 20 drugs have been reported in the literature that may be associated with GO (5). The medication classes most commonly involved with GO are antiepileptics (primarily phenytoin), immunosuppressants (primarily cyclosporine), and calcium channel blockers (primarily nifedipine and verapamil) (4). Among the offending medications of GO, phenytoin is the first reported as well as the most common agent (6).

Phenytoin, as a hydration, was first introduced by Merritt & Putnam in 1938 for the treatment of all forms of epilepsy, except the petit mal (7). Because of its ability to regulate cellular bioelectrical activity, phenytoin was also tried in a variety of other disorders including mood and behavior diseases, stuttering, migraine and other headaches, neuropathies (e.g. trigeminal neuralgia), neuromuscular pathologies, and cardiac problems

during the previous decades (8). In the UK and the USA, phenytoin is currently indicated for the control of generalized tonic-clonic seizures, partial seizures (including temporal lobe), or a combination of these, and also both the prevention and treatment of seizures caused by neurosurgery or traumatic brain injury (9). It has been estimated that over 3 million phenytoin prescriptions are filled annually in the United States (10). In 1939, just a year after its introduction as the treatment of epilepsy, Kimball reported that 57% of patients treated with phenytoin developed some degrees of GO (11). Since this report more than 7 decades ago, many studies have focused on various features of phenytoin-induced GO (PIGO). Although phenytoin has been mostly replaced by other second generation antiepileptic agents in many developed areas of the world, but PIGO has remained as a problem in developing countries where phenytoin is continued to be prescribed very commonly because of the relatively higher cost of other antiepileptic medications. The lack of acceptable dental hygiene in a considerable population of developing countries may also contribute in compromising PIGO (12).

In this review, different aspects of PIGO including the prevalence, risk factors, clinical manifestations, histopathology, suggested mechanisms, and preventive as well as treatment modalities were discussed briefly.

2. Evidence Acquisition

A literature search was performed in the following databases: Scopus, Medline, Embase, Google scholar, Cochrane Central Register of Controlled Trials, and Cochrane Database Systematic Reviews. The key words used for literature search included "gingival hyperplasia", "gingival overgrowth", "gingival enlargement", "phenytoin", and "diphenylhydantoin". All published English-language papers including original articles, reviews, and case reports with no time limitation were considered eligible. The reference lists of published articles were examined for identifying any additional relevant studies.

3. Results

3.1. Prevalence

Although PIGO occurs in about 50% of patients, but different studies have reported that its incidences varies from 3% to 84.5% (6). A review of relevant literature from 1939 to 1972 by Angelopoulos and Goaz found that 0% to 84.5% of patients taking phenytoin may develop GO during their course of treatment (13). A community-based cross-sectional study in 1997 reported 39% as the prevalence of PIGO in patients treated with phenytoin for more than 1 year (14). A preliminary observational study by Mousavi demonstrated that 46 out of 86 (53.5%) of Iranian epileptic individuals receiving phenytoin were involved with GO (15). These wide variations in the prevalence of

PIGO may be attributed to the different definition(s), detection method(s), study methodology as well as sample size, age of the study population, concomitant administration of other drugs, and dose along with the duration of phenytoin treatment (2, 12).

3.2. Risk Factors

Patient's oral hygiene is considered as a significant risk factor for the severity of PIGO (12). Indices of gingival inflammation and plaque accumulation have significant correlation with grades of PIGO (16, 17). Dental plaque can also act as a reservoir for the accumulation of phenytoin (18). "Plaque-induced gingival diseases modified by medications" as one of the categories of periodontal diseases classification highlights the important role of plaque in developing GO (2). Mousavi found that the rate of PIGO is higher in patients with a poor as compared to those with a good oral hygiene condition (55% *vs.* 30%, respectively) (15). Age is another identified risk factor for PIGO. Children and young adolescents are the most susceptible population to PIGO (2). It has been hypothesized that high levels of circulating androgens that have a stimulatory effect on gingival fibroblasts may account for the increased risk of GO in this age group (19). In contrast to nifedipine and cyclosporine, male gender appears not to be an independent risk factor for PIGO (20). An early study demonstrated that the co-administration of other antiepileptic agents, especially phenobarbitone and carbamazepine, increases the risk of PIGO probably through increasing the levels of certain phenytoin metabolites secondary to the induction of hepatic cytochrome P450 enzymes (21). However, at least one more recent study has questioned this concept in adult epileptic patients (22). The plausible relationship between dose as well as serum levels of phenytoin and PIGO remains unclear and controversial (12). Kamali et al. reported that the high serum concentrations of (4-hydroxyphenyl)-5-phenylhydantoin (4-HPPH), the major metabolite of phenytoin, were linked to GO in cats and rats experimental models (23). However, even the local levels of phenytoin or 4-HPPH in saliva (24) or gingival crevice fluid (25) have no clear correlation with the prevalence and severity of PIGO in clinical studies. Brunet et al. in a cross-sectional study also found no significant association between the total accumulated dose of phenytoin and PIGO (3).

3.3. Clinical Manifestations

PIGO is firstly noticed usually after 3-6 months of phenytoin therapy (12). As mentioned previously in the introduction section, the early sign of painless enlargement is noticed in the inter-dental papilla region that gradually, gingival lobulations extend along the labial, lingual, and coronal aspects to cover the entire anatomic crowns of teeth by 9-18 months (12). This may interfere with mastication, speech, and esthetics which can eventually lead to shifting of teeth and malocclusion (2). PIGO is mostly

apparent in the anterior part of the mouth (26). Uncomplicated lesions are characterized by mulberry shaped, firm, pale pink, resilient, little lobulated surface, with no bleeding tendency. In contrast, secondary inflammatory changes are associated with an increase in the size of the lesion along with a red or bluish-red discoloration and bleeding diathesis (6).

3.4. Histopathology

The histopathological features of PIGO include a thick stratified squamous epithelium with proliferation and elongated rete pegs extending deep into the connective tissue, which suggests an increased proliferation of fibroblasts, accumulation of extracellular matrix components (pro-collagen as well as collagen fibers and non-collagen proteins, especially glycosaminoglycan) along with an increase in new blood vessels (27-30).

3.5. Mechanisms

Although the exact mechanisms of PIGO have not been elucidated yet, but several cellular and molecular mechanisms have been suggested (Table 1):

1) Phenytoin may stimulate the immune system through mechanisms including the induction of lymphoid overgrowth, lymphomas and cell-mediated immunological reaction via interleukin-1β (IL-1β) and tumor necrosis factor alpha (TNF-α), pro-inflammatory cytokines, and up-regulating the production of inflammatory mediators (e.g. interleukin-6 [IL-6] and interleukin-8 [IL-8]) (31) and also medullasin (32). This latter mediator is a neutrophil elestase-like serine proteinase, distributed mainly in neutrophils, and partly in monocyte/macrophage. It has been suggested that medullasin participates in the activation of inflammatory response through modulating cytokines (32).

2) Phenytoin may stimulate the gingival mast cells to release heparin (33) and fibroblasts to release three growth factors including transforming growth factor-β (TGF-β), connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF) (31). The first growth factor, TGF-β, is found in high concentrations in platelets, macrophages, neutrophils, and fibroblasts. It acts mainly on fibroblasts and endothelial cells and results in collagen and matrix synthesis (34). The second growth factor, CTGF, synthesized from endothelial cells and fibroblasts and has mitogenic as well as angiogenic activities in an autocrine manner. In response to TGF-β, it acts as an autocrine growth factor (35). The last one, PDGF, is primarily produced by platelets, macrophages, endothelial cells, and fibroblasts. It is believed to enhance mitogenic activity and chemotaxis (36).

3) Phenytoin may suppress extracellular matrix-degradation ability by both inhibiting lysosomal enzymes (e.g. cathepsin L, matrix-metalloproteinase-1 [MMP-1]) and inducing tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) (31). Cathepsin L is a lysosomal cysteine pro-

teinase and responsible for degradation of structural proteins such as type I collagen, laminin, and proteoglycans (37). MMPs are a family of extracellular matrix degrading enzymes called Ca^{+2}- and Zn^{+2}-dependent endopeptidase. They regulate many developmental processes including branching, morphogenesis, angiogenesis, wound healing, and extracellular matrix remodeling. There are now more than 20 members of MMP family. MMP-1, also called collagenase-1, is active against fibrillar collagen (38, 39). On the other hand, TIMP-1 is a representative of the natural MMP inhibitor family, encompassing at least four members. MMP-1-mediated collagenolysis can be inhibited by TIMP-1. Furthermore, it has been shown that TIMP-1 has growth-promoting activity for a wide variety of cell types such as dermal fibroblasts (37, 40).

4) Phenytoin may enhance the matrix synthesis through its stimulatory effect on the activity of type 2 isoenzyme of 5α-reductase. This action can be driven in either ligand-dependent manner, by the stimulation of their own receptors, or ligand-independent manner, through the direct stimulation of androgen receptor. Type 2 reductase of 5α-reeducates has an anabolic role in gingiva, a target tissue for androgen metabolism, via the production of 5α-dihydrotestosterone (41). Furthermore, it has been suggested that some of the matrix stimulatory actions of androgen metabolites may be mediated by triggering alkaline phosphatase (42). On the other hand, estrogens alone also have anabolic functions by increasing the local level of dihydrotestosterone and stimulating collagen formation via enhancing the incorporation of proline in collagen molecules being synthesized in the gingival fibroblasts (43).

5) Phenytoin may stimulate the production of IL-1β. IL-1β activates the transcription of cyclooxygenase 2 (COX-2), an inducible enzyme which converts arachidonic acid into prostaglandins such as PGE2, via a prominent transcription factor (nuclear factor-kappaB [NF-κB]). PGE2 is an important mediator of inflammation process and may also stimulate the synthesis of TGF-β and its receptors (44). Furthermore, PDGF which can be induced by phenytoin increases the intracellular calcium and provokes arachidonic acid release probably through the activation of cytosolic phospholipase A2. This enzyme has a substantial role in the conversion of membrane phospholipids to arachidonic acid (45). In addition to the indirect effect of PDGF on the elevation of COX-2 substrate, arachidonic acid can directly contribute to the expression of COX-2 mRNA (46).

6) Phenytoin may inhibit the collagen phagocytosis by reducing α2 integrin expression or decreasing its binding affinity in the gingival fibroblasts. The latter mechanism has been attributed to disturbing the intracellular calcium flux secondary to the calcium channel antagonistic activity of phenytoin (31). Integrins are a large family of heterodimeric transmembrane receptors for extracellular matrix molecules. Each heterodimer consists of

α and β subunits. Studies have been indicated that α2β1 integrins serve as specific receptors of type I collagen in fibroblasts. It has been also shown that α2 integrin plays a critical role in the phagocytic regulation of collagen internalization (1).

7) Phenytoin may cause a decrease in sodium along with calcium flux and in cellular folic acid uptake. This can produce a systemic as well as localized folate deficiency

in the gingival tissue. The folate deficiency induced by phenytoin can cause degenerative changes in succular epithelium and also exacerbate inflammation (31).

8) Phenytoin may encourage the growth of bacteroides, actinomyces, fusiform bacteria, *Prevotella intermedia*, type II *Porphyromonas gingivalis*, and *Treponema denticola*. These microorganisms may contribute to GO through developing bacterial biofilm and aggravating inflammation (31).

Table 1. Summary of Molecular and Cellular Mechanisms of Phenytoin-Induced Gingival Overgrowth [a]

Pathway	Mediator(s)
Inducing local inflammatory responses	Medullasin, TNF-α, IL-1β, IL-6, IL-8, PGE2, NF-κB
Stimulating angiogenesis and synthesis of extracellular matrix components (e.g. pro-collagen, collagen, and glycosaminoglycans)	TGF-ß, CTGF, PDGF, Type 2 isoenzyme of 5α-reductase
Suppressing extracellular matrix and collagen degradation	TIMP-1, MMPs, α2 integrin
Inducing systemic and localized folate deficiency	Competitive inhibition of folate uptake
Development of bacterial biofilm	Overgrowth of *bacteroides*, *actinomyces*, fusiform bacteria, *Prevotella intermedia*, type II *Porphyromonas gingivalis*, and *Treponema denticola*

[a] Abbreviations: CTGF, connective tissue growth factor; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; MMP-1, matrix-metalloproteinase-1; NF-κB, nuclear factor-kappaB; PGE2, prostaglandins E2; PDGF, platelet-derived growth factor; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor-β; TIMP-1, tissue inhibitor of matrix metalloproteinase-1.

3.6. Prevention

Regarding the undeniable role of plaque as well as poor periodontal hygiene in development of GO in patients receiving phenytoin, the following preventive measures against PIGO can be considered: 1) avoiding local irritants; 2) meticulous plaque control; 3) chlorhexidine gluconate 0.12% mouth rinse (rather than chlorhexidine toothpaste); and 4) regular periodontal maintenance therapy (6). The regular periodontal maintenance therapy should be done regularly at 3-month interval visits. Each visit includes updating medical history, re-evaluating the clinical periodontal parameters, the detailed instruction of the oral hygiene principles (e.g. intra-sulcular brushing and inter-dental cleansing), and supra- and sub-gingival calculus removal as needed (47). However, these modalities are only effective in attenuating, but not complete prevention of PIGO (6).

A number of clinical studies have evaluated the probable effectiveness of folic acid supplementation in the prevention of PIGO. The results of an early double-blind study by Drew et al. implicated that the topical application of 1 mg/mL folic acid solution for 6 months significantly prevented PIGO to a greater extent than either systemic folate or placebo (48). Another study in pediatrics reported that the oral supplementation with folic acid (5 mg/day) for one year in combination with the oral hygiene measures delays the onset and reduces the incidence as well as the severity of PIGO in comparison to oral hygiene measures alone (49). Recently, the results of a double-blind, randomized clinical trial demonstrated that 0.5 mg/day of folic acid oral supplementation for 6 months in children

with epilepsy aged 6-15 years is associated with absolute and relative risk reduction of PIGO by 67% and 0.76, respectively (50). According to these findings, Arya et al. in their literature review recommended folic acid co-prescription as a preventive approach over PIGO in any patient being started on phenytoin therapy (12).

3.7. Treatment

Despite our greater understanding of the pathogenesis of PIGO, its treatment still remains a challenge. This problem is compromised by the high recurrence rate arising from the chronic usage of phenytoin and the persistence of other risk factors (51). The management strategies for PIGO can be categorized as either surgical or non-surgical (52).

Despite some benefits of the non-surgical approaches, surgical correction is still the most frequent treatment. Such treatments are only advocated when GO is severe (grade 3 overgrowth) (12). Usually, the favorable results of surgery can be maintained for at least 12 months after operation (53). Currently, the surgical management modalities of PIGO include gingivectomy, periodontal flap, electrosurgery, and laser excision (54). Choosing any of the above surgical techniques by either a general dentist or a periodontist must be made on a case-by-case basis, and several factors such as extent of the area to be treated and the presence of osseous defects combined with the gingival enlargement lesions should be taken into account (54, 55).

Gingivectomy is an extensively used and straight-forward technique that causes minimal damage to the surrounding tissue. Post-operative hemorrhage is the main

disadvantage of this procedure. In gingivectomy unlike periodontal flap, the osseous recontouring is not feasible and sacrificing the keratinized tissue is possible (6). It is generally indicated in cases where, small areas (< 6 teeth) presenting with GO, there is no evidence of attachment loss and therefore, no anticipated need for performing osseous surgery. But ideally after gingivectomy, an at least 3 mm of the keratinized tissue in the apico-coronal direction should be remained. The periodontal flap is indicated in cases where larger areas of gingival enlargement (> 6 teeth) involved, or areas where the attachment loss along with the osseous defects are presented (54).

Electro surgery techniques have been used for the past 70 years (56). Despite its disadvantages such as causing a surrounding zone of thermal necrosis which may impede wound healing, in situations where conventional means are technically difficult and/or impractical (e.g. children, mentally handicapped individuals or those suffering from impaired haemostasis), the use of electrosurgery may be advantageous (57).

Dental laser excision can be considered as another alternative treatment to conventional gingivectomy techniques. Carbon dioxide or argon laser has a remarkable cutting ability and also generates a coagulated tissue layer along the wall of laser incision which promotes healing (58). Other advantages of laser excision are as follows: 1) decreased surgical time; 2) a relative bloodless operative and post-operative field; 3) greater accuracy in making incisions; 4) sterilization of the operating field; 5) minimal swelling and scarring; and 6) vaporization and cutting with minimal pain and discomfort both during and after the procedure. The laser gingivectomy may be particularly useful in patients on anticoagulant therapy or for whom, problems with haemostasis are anticipated. The only disadvantage of this procedure is its high cost (6, 54, 59-61).

In surgically-treated individuals who continued phenytoin treatment, the recurrence of PIGO is not an unusual phenomenon. It can occur as early as 3-6 months post-operation (6). The likelihood as well as the extent of PIGO recurrence is correlated with controlling the gingival inflammation, patient adherence to oral hygiene, the periodic supportive periodontal measures, and the stability of underlying systemic condition (62). The rate and degree of PIGO recurrence after surgery can be minimized by implementing rigorous dental hygiene program at home, chlorhexidine gluconate mouth rinse, and plaque control. Wearing a hard, natural rubber, and fitted bite guard at night may also be helpful in attenuating the recurrence (6). Poppell et al. showed that the oral supplementation of 5 mg of folic acid daily following gingivectomy is associated with a significant reduction in the rate of PIGO recurrence in comparison to the control group (63).

The mild to moderate stages of PIGO can be treated by non-surgical approaches. These modalities include: 1) oral hygiene measures; 2) professional tooth cleaning; 3) scaling and root surface instrumentation; and 4) interruption, modification of the dosage or the replacement

of phenytoin. The primary aim of non-surgical approaches is to reduce the inflammatory component in gingival tissue and thereby avoid the need for surgery (2, 6, 12, 54). In humans, chlorhexidine gluconate mouth rinse has been successfully exploited in the management of PIGO (6, 59). However, the rare unwanted effects of chlorhexidine gluconate such as teeth and tongue discoloration, taste disturbance (dysgeusia), desquamative gingivitis, and contact dermatitis may limit its long-term use (64).

The introduction of the second generation antiepileptic agents with actually no-reported gingival overgrowth such as lamotrigine, gabapentin, sulthiame, and topiramate in recent decades increases the feasibility of phenytoin substitution by the physicians. The possible resolution of GO usually occurs within 1-6 months after discontinuing or substituting phenytoin. However, not all patients may respond to this treatment approach, especially those with either severe or long-standing gingival lesions. Furthermore, dose reduction or phenytoin substitution may not be clinically possible due to the underlying disease(s) and condition(s) of the affected patients or the unresponsiveness of seizures to antiepileptic medications other than phenytoin (6, 54, 59).

Pharmacotherapy of PGIO is another choice of the non-surgical management approaches which has not been extensively considered yet. Besides prevention, plausible effects of folic acid in the treatment of PGIO have been also investigated in a number of clinical studies. Based on an early and pilot report published by Inoue and Harrison in 1981, seven out of nine individuals with PIGO had sub-normal folate levels. They demonstrated that folic acid supplementation (5 mg/week) for 6 months was associated with complete resolution of PIGO in six subjects (65). In line with this study, Backman et al. implicated that supplementation with 5 mg folic acid daily in children for one year significantly reduced the size of PIGO without altering seizure control (66). In contrast, a double-blind randomized controlled trial comparing 3 mg/day folic acid for 16 weeks versus placebo failed to show its efficacy as the sole therapeutic agent in the reduction of PGIO (67). These controversial findings can be partially justified by the different folic acid treatment regimen (the time of initiating with respect to phenytoin, dose, and duration) and methodological issues. Suggested mechanisms for justifying the beneficial effects of folic acid supplementation in preventing and treatment of PIGO are: 1) the competitive inhibition of phenytoin intake into the gingival tissue; 2) interfering with the production of 4-HPPH; and 3) binding to plaque-derived endotoxin and subsequently, reducing the gingival inflammation (49). Apart from unproven efficacy, the safety of folic acid administration in epileptic patients receiving phenytoin has been questioned. Folic acid in doses as low as 1 mg/day can decrease phenytoin level by 15% to 50%, within the first 10 days (68). However, the aforementioned clinical studies have found no exacerbation of seizure activity or altering seizure control following folic acid treatment (66, 67).

The first and the only case report published by Norris and Cunliffe in 1987 demonstrated the beneficial effects of oral isotretinoin in improving PIGO. This action of isotretinoin has been attributed to both increasing the level of cyclic adenosine monophosphate, a second messenger with inhibitory effects on fibroblast growth, and inhibiting ornithine decarboxylase activity, a rate limiting enzyme for the biosynthesis of polyamines (69).

A number of clinical studies have shown the effectiveness of short course systemic (500 mg/day orally for 3 consecutive days (70) or 500 mg/day orally on day 1, followed by 250 mg/day on days 2 to 5 (71)) or topical azithromycin (85 mg per gram of toothpaste twice a day for 1 month) (72) in the treatment of cyclosporine-induced GO in solid organ transplant recipients. It has been suggested that azithro-mycin may exert this action via several pathways such as inhibiting oral bacteria overgrowth, decreasing the inflammatory cytokines (e.g. IL-1a and TNF-α), increasing the anti-inflammatory cytokines (IL-10), and interfering with TGF-β functions (73, 74). Considering similarities between the mechanisms of PIGO and cyclosporine-induced GO, we previously hypothesized that azithromycin may be effective in improving both clinical and histological features of PIGO (75). Recently, Arya et al. also noticed this issue in their review article about PIGO (12). However, the plausible role of azithromycin in the treatment of PIGO has not been considered in either experimental or clinical studies so far. Table 2 summarizes the suggested surgical and non-surgical approaches for prevention and treatment of PIGO based on the current data in the literature.

Table 2. Surgical and Non-Surgical Approaches for Prevention and Treatment of Phenytoin-Induced Gingival Overgrowth

Surgical Approaches
Gingivectomy
Periodontal flap
Electrosurgery
Laser excision
Non-Surgical Approaches
Prevention
Avoiding local irritants
Rigorous plaque control
Using mouthwashes (e.g. chlorhexidine gluconate 0.12%)
Periodontal maintenance therapy at regular 3-month intervals
Topical (e.g. 1 mg/mL) or oral (e.g. 0.5 or 5 mg/day) folic acid supplementation
Treatment
Oral hygiene measures
Tooth cleaning
Scaling and root surface instrumentation
Discontinuing or decreasing the dose of phenytoin (if possible)
Substituting phenytoin with other antiepileptics (e.g. lamotrigine, gabapentin, topiramate), if possible
Oral folic acid supplementation (e.g. 5 mg/week or 5 mg/day)
Oral isotretinoin [a]

[a] Based on a single case report.

3.8. Future Perspectives

Two in vitro studies conducted by Soory et al. demonstrated the role of anti-androgens (finasteride), anti-estrogens (tamoxifen), and alkaline phosphatase inhibitors (levamisole) in attenuating PIGO (43, 76). Considering the pathogenesis and mechanisms of PIGO discussed above, these medications along with the selective COX-2 inhibitors (e.g. celecoxib) and macrolides (e.g. azithromycin) may be beneficial for both the pharmacoprophylaxis and pharmacotherapy of PIGO in humans. Apart from the clinical effectiveness, it is necessary to take into account the safety profile and cost-effectiveness aspects of the suggested medication classes including their adverse reactions, possible contraindications, serious interactions with other co-administered agents, availability, and cost. To our knowledge, the potential effectiveness of none of the aforementioned agents has not yet been evaluated in clinical settings.

4. Conclusions

Phenytoin is the first reported as well as the most common medication that can cause GO. PIGO can occur in about 50% of chronic users of phenytoin within 3-6

months of its initiation. It may interfere with speech, mastication, nutrition, tooth eruption, and esthetics of the affected individuals. The poor oral hygiene and young age are two identified risk factors of PIGO. Several cellular and molecular mechanisms with the centrality of altering connective tissue turnover and inflammation have been proposed for PIGO. The regular periodontal maintenance therapy and plaque control can be considered as preventive measures against PIGO. The surgical approaches such as gingivectomy and periodontal flap are only reserved for severe and advanced stages of PIGO. The non-surgical approaches such as the oral hygiene measures and discontinuing, reducing the dose or replacement of phenytoin with other antiepileptics can be considered for the mild to moderate stages of PIGO. The clinical effectiveness of topical as well as systemic folic acid supplementation in both prevention and treatment of PIGO has been demonstrated in a number of studies without compromising seizure control. Both pharmacoprophylaxis and pharmacotherapy of PIGO with potentially effective agents such as azithromycin has been largely overlooked and deserve more attention and investigation.

Authors' Contributions

Iman Karimzadeh contributed to literature review, data collection, and manuscript drafting. Soha Namazi contributed to study design and manuscript review. Afshin Borhani-Haghighi contributed to manuscript review. Hengameh Khosropanah contributed to manuscript review.

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