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What is the Effect of Folic Acid Supplementation on the Incidence or Reduction of Phenytoin-Induced Gingival Overgrowth? A Systematic Review

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Abstract

Background: Several published studies have reported both positive and negative effects regarding the administration of folic acid (FA) on either prevention, or reduction of phenytoin (PHT)-induced gingival overgrowth (PIGO). Several other published studies have evaluated the effect of FA supplementation upon gingival health.

Objective: The primary objective is a systematic assessment review of studies evaluating the efficacy of FA therapy for the prevention or reduction of PIGO. Secondary objectives entail evaluation of the FA and seizure control, on the mechanism of Drug-IGO, and on FA supplementation and gingival health.

Materials and methods: Electronic databases (a Medline via PubMed database, and Cochrane Central Register of Controlled Trials) search was conducted; other sources were searched such as Google Scholar and clinicaltrials.gov. Reference lists of retrieved articles were searched. Randomized placebo-controlled trials (RCTs) assessing the effect of topical or systemic administration of folic acid on gingival enlargement in phenytoin patients were included. Two reviewers (HH, RB) performed the study search, data extraction, and risk of bias assessment. The literature was reviewed regarding PHT-FA interaction, and FA supplementation to promote gingival health.

Results: The main research was through Pubmed search, and done on February, 15, 2015. It resulted in eight items. Only five items were considered for screening. The other three items were not interventional. One extra title was found on Google Scholar website. The total RCTs included for the systematic review were six trials. Studies regarding FA and gingival health were also evaluated which produced another four items.

Conclusion: FA supplementation may improve the gingival health status, and may delay the onset of PICO, as there are only at present a limited number of studies with a limited number of subjects, further studies are necessary to confirm or deny the positive effects of FA therapy. In PHT-treated epileptic patients properly managed, FA supplementation has a very limited risk in interfering with seizure control. Due to very limited toxicity and the potential for promoting gingival health, future FA supplementation therapy studies should be considered,

Introduction

Phenytoin (PHT) was used for the first time to treat seizures in 1938 [1] and gingival overgrowth was recognized as a side effect just the following year [2]. According to community and hospital-based studies, the incidence of PH-induced gingival overgrowth (PIGO) was estimated as 25%–40% and 50%–60%, respectively [3-5] PHT and other anticonvulsant drugs are noted for causing Drug-IGO (DIGO) along with such other drug categories as Calcium Channel Blocking Agents, and Immuno-suppressive drugs such as Cyclosporine [6].

PIGO is cosmetically disfiguring and may impede the functions of mastication and articulation in severe cases. Additionally, the pseudo pockets formed as a consequence of this overgrowth act as plaque retentive areas which worsen the overgrowth [7]. Surgical resection of the enlarged gingiva has been the traditional intervention in cases of severe overgrowth, but the overgrowth recurs owing to its insidiously progressive nature [6].

Vogel [8] was the first to hypothesize that the involvement of bacterial plaque and folic acid deficiency caused by phenytoin [7] are plausible causes for PIGO. Based upon his hypothesis, different treatment and preventive regimes of plaque control and folic acid supplementation have been studied. There are several mechanisms proposed for the effect of systemic folic acid as follows i) The interference of folic acid of p- HPPH, a by-product of phenytoin metabolism , which is basically responsible for the gingival overgrowth ii) competitive antagonism exists between PHT and FA. FA is a vitamin which works with vitamin B12 as a co-factor. FA is necessary for protein synthesis and is particularly important with regard to blood formation, mucosal health, and the prevention of neural tube birth defects [9,10]. Furthermore, several studies were performed to evaluate FA therapy for the treatment of gingival health with varying results. In evaluating FA as a therapeutic, it is important to have an understanding of the scientific rationale and further discussion regarding possible mechanisms will be discussed.

Methods

A systematic review of the evidence available in the literature was performed following PRISMA statement [10].

Eligibility criteria

- Randomized clinical trials and controlled trials (quasi trials)

- Studies published in English
- Studies assess the effect of topical or systemic folic acid on the prevention or reduction of gingival hypoplasia in patients taking PHT.

Information sources

The databases searched are Pubmed, Cochrane Central Register of Controlled Trials. The database search was supplemented by searching Google Scholar, clinicaltrial.gov and the reference lists of included studies.

Search strategy

The search strategy for the main electronic search (PubMed) is presented in Table 1 copied from PubMed page to eliminate the risk of typing error.

Study selection

Two independent reviewers (HH, RSB) used a predefined inclusion criteria form to screen the studies identified by the search and then obtained the full text of potentially relevant articles and screened them for inclusion. Discrepancies were resolved by discussion.

Data collection

A pilot data extraction form was developed by HH. Then, the two independent reviewers (HH, RSB) used data extraction form to extract relevant data. When multiple study publications reported data from the same population, the more elaborative publication report was considered.

Data items

Data items summarized in table 2

Risk of bias:

Table 3 illustrates evaluation of the risk of bias using Cochrane risk of bias tool.

Results

Study selection

The literature search yielded eight citations from PubMed and 310 from Google Scholar, and zero from Cochrane Central Register of Controlled Trials. Clinicaltrial.gov yielded only one citation. After screening of the titles, and abstracts, and elimination of the duplicates, six RCTs/controlled trials were selected to be included in the review.

Study and patient characteristics

All of the included studies were RCTs, or controlled trials.

Only two studies evaluated the preventive effect of phenytoin on PIGO.

Search	Add to builder	Query	Item Found
#8	Add	Search (((“Gingival enlargement”[ti/ab]) OR “Gingival overgrowth”[ti/ab]) OR “Gingival hyperplasia”[ti/ab])) AND ((“Folic acid”[ti/ab]) OR Folate[ti/ab]	8
#7	Add	Search (“Folic acid “[ti/ab]) OR Folate[ti/ab]	14489
#6	Add	Search Folate[ti/ab]	8031
#5	Add	Search “Folic acid”[ti/ab]	6794
#4	Add	Search ((“Gingival enlargement”[ti/ab]) OR “Gingival overgrowth”[ti/ab]) OR “Gingival hyperplasia”[ti/ab]	1140
#3	Add	Search “Gingival hyperplasia”[ti/ab]	528
#2	Add	Search “Gingival overgrowth”[ti/ab]	431
#1	Add	Search “Gingival enlargement”[ti/ab]	184

Table 1: search strategy of Pubmed

So, pre-existing gingival overgrowth was an exclusion criterion. The same two trials were also the only trials performed exclusively on children. Noticeably, one trial by Brown et al. [14] excluded pregnant women. The number of participants ranged from only eight to 120 participants. The duration of follow up varied from six months in three studies, 12 months in two studies, and four weeks in one study. Three studies used 5 mg folic acid/day.

Risk of bias

Only one of the included trials by Ayra et al. [12] adequately reported generating the random sequence using a printed random number table and adequately reported allocation concealment. Drew et al. [17] adequately reported blinding of participants, operators, and outcome measurement.

Folic Acid and Gingivitis Studies

The history of folate supplementation/gingival health is provided below. In 1970 Dreizen et al. [18] reported that folic acid deficiency in marmosets produced several deficiency-related negative changes within the periodontium, including interference with epithelial maturation, keratination impairment, and increased susceptibility to ulceration and infection. In 1976, Vogel et al. [19] utilizing a double-blind randomized format, reported a study evaluating the influence of folate supplementation upon gingivitis. They reported no differences with respect to plaque and gingival indices between the active and control groups. However, they reported a significant decrease ($P<0.05$) within the active treatment group compared to the control group with regard to gingival exudate flow. They concluded that folic acid supplementation appeared to increase the resistance of the gingiva to local irritants and decrease gingival inflammation. In 1978, Vogel and Deasy [20] published a study to evaluate folate supplementation on experimentally produced gingivitis. Healthy volunteers were randomly selected to either the active or control group. Both groups were instructed to refrain from oral hygiene procedures for two weeks and the gingiva was evaluated for plaque, bleeding, and exudate indices and evaluated at 14 days. At 14 days, both groups were advised to initiate regular oral hygiene procedures. On day 14, the plaque index comparison was not significant, while both the gingival inflammation and exudate flow demonstrated significance. At 28 days, there was not difference between groups with regard to any of the indices. They concluded that folic acid may increase gingival resistance to local etiologic factors. Also in 1978, Vogel et al. [21] evaluated the efficacy of topical folic acid upon gingival health with a randomized double-blind study. The subjects were instructed to rinse with a 5 ml measure for one minute and spit out and then rinse again with tap water. The active treatment group was provided a one mg per one ml of folic acid solution, and the control group a placebo solution. After sixty days, the co-investigators evaluated the subject’s gingival health, plaque, and bleeding indices. The co-investigators reported significant differences in the groups with respect to gingival and bleeding indices. They concluded that folic acid supplementation may increase host resistance to gingival inflammation due to a hypothesized local deficiency of folate within the gingiva. In 1980, Pack and Thomson [22] utilizing a randomized double-blind format for 14 days, investigated the effect of topical and systemic folate supplementation upon gingivitis within pregnant subjects. Three groups were compared consisting of an active topical drug (5 ml of 1mg/1ml - rinse and spit bid and placebo rinse bid, and placebo tablet qd), active systemic drug (5 mg tablet, and placebo rinse, bid and placebo tablet qd), and a placebo (placebo rinse bid and tablet qd) groups. Subjects were evaluated for gingival exudate flow, gingival index, and plaque index for 14 day periods during both the 4^{th} and 8^{th} months of pregnancy. They reported a significant improvement of gingival health in the topical active treatment group ($P<0.001$) when compared the placebo group, (while the systemic treatment group did not demonstrate a significant difference when compared to the placebo group) and noted that unrecognized cases

Study ID	Authors and year	Study Design	Participants		Intervention	Duration
			N	Age		
1	Arya et al. [12]	RCT	120	6-15	0.5 mg/day	6 m
2	Prasad et al.[13]	Controlled	60	8-13	5 mg/day	12 m
3	Brown et al. [14]	RCT	21	N/A	3 mg/day	16 week
4	Poppel et al. [15]	RCT	8	N/A	5 mg/day	Up to 6 m
5	Backman et al. [16]	RCT	31 9	Children Adults	5 mg/day	12 m
6	Drew et al. [17]	Double blind	15	11-29	4 mg/day or topical	6 m

Table 2: Data extraction from primary trials

Article	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome measurement	Incomplete outcome data	selective reporting	Other risk of bias
Arya [12]	Low	Low	Low	Low	Low	Low	Low
Prasad [13]	High	Unclear	Unclear	Low	High	Low	Low
Brown [14]	Unclear	Unclear	Low	Low	Low	Low	Low
Poppel [15]	Unclear	Unclear	Low	Low	Low	Low	Low
Backman [16]	Unclear	Unclear	Low	Low	Low	Low	Low
Drew [17]	Low	Unclear	Low	Low	Low	Low	Low

Table 3: risk of bias assessment

of B12 deficiency may be allayed by routine serum B12 assays. Thomson and Pack [23] in 1982 published a similar randomized double blind study in which the supplementation was for 28 days during only the 8th month of pregnancy utilizing the same evaluation groups and indices within their 1980 study. Their results confirmed the results of the previous study in that with no significant differences within the plaque index, and that the topical treatment group demonstrated a significant improvement ($P<0.001$) compared to the placebo group, and the systemic treatment group did not demonstrate significance when compared to the placebo group. In 1984 Pack [24] published a study evaluating the efficacy of folic acid on established gingivitis. She utilized a randomized double-blind format to evaluate subjects within an active drug group (5 ml of folate mouth rinse 1 mg/1 ml, bid) compared to a placebo mouth rinse (bid) with respect to color change sites, bleeding sites, and plaque scores. At four weeks, the active drug group demonstrated a significant reduction compared to the placebo group in both color change sites and bleeding sites ($P<0.001$) and concluded that topical folate appears to impact upon gingival health through local rather than systemic influence. In 1986, Pack [25] reported a study evaluating the efficacy of topical folate on experimental gingivitis. Within a randomized double-blind study format, she evaluated and compared subjects in two experimental groups; the active drug group rinsed twice daily with 5 ml of a 1 mg/1 ml folic acid, while the other group rinsed with a placebo rinse. To produce the experimental gingivitis, both groups wore a custom clear acrylic mouth guard from mandibular first bicuspid to first bicuspid which prevented oral hygiene procedures of the mandibular anterior dentition. At three weeks, the indices (the same as within the Pack [24] 1984 study) between the groups were compared and no significant differences were found. Pack [25] concluded that experimental cessation of plaque removal over a three week period may not represent an authentic representation of established gingivitis. Six out of these seven human subject studies demonstrated the efficacy of folate supplementation in regard to the promotion of gingival health, [19-26] and provided the impetus to consider folate supplementation for DIGO therapy (Table 4).

FA and PHT Interaction

The usual dose of FA for patients with low serum FA and/or signs or symptoms of FA deficiency is 1 mg daily by mouth. The normal range for serum FA is between 6 and 20 ng/mL. Low serum FA is associated with heart disease, stroke, psychiatric disease, birth defects, and cancer. It is important for clinicians to evaluate patients for B12 deficiency as FA may mask the clinical signs of B12 deficiency which may lead to neurologic deterioration with time, in patients not properly evaluated for B12 deficiency and not provided B12 supplementation as necessary. However, the main concern with regard to the administration of FA for patients utilizing PHT for epileptic seizure control is the possibility of decreased serum concentrations of PHT leading to loss of seizure control [10,26]. Lewis et al. [10] reported that the PHT-FA interaction is a complex dual and interdependent interaction. There is a decrease in serum FA concentrations with the initiation of PHT anticonvulsant therapy. Conversely, serum PHT concentration decreases with FA administration to FA-depleted PHT treated epileptic patients [10,27].

PHT is an antiepileptic drug that decreases convulsions by stabilizing the neuronal membrane. The therapeutic dose is between 10 and 20 micrograms per mL. PHT has a several months half life, which makes this drug particularly difficult to titrate. Furthermore, PHT is highly protein bound, with a therapeutic free concentration range of between 1 and 2 micrograms per mL. PHT displays Michaelis-Menten kinetics demonstrating a saturation of the metabolic pathway of PHT, resulting in the potential of a small dosage increase to cause a large increase in serum concentration. PHT is primarily metabolized to 5-(p-hydroxyphenyl)-5 phenyhydantoin (p-HPPH), an inactive metabolite. PHT steady-state concentrations are clinically determined after one month of drug therapy. Part of the rationale for taking as long as it does to determine steady-state appears to be due to the FA-PHT relationship. FA is a co-factor in PHT metabolism, and serum FA needs to be stabilized before PHT can reach true steady-state concentrations. Decreased serum FA implies that there

Study ID	Authors	Study Design	Participants		Intervention	Duration
			N	Age		
1	Vogel et al. [19]	RCT	30	19-58	4 mg/day	30 d
2	Vogel and Deasy [20]	Controlled	16	22-33	4 mg/day	28 d
3	Vogel et al. [21]	RCT	30	21-32	5 mg rinse/day	60 d
4	Pack and Thomson [22]	RCT	30	Mean age 24.5	5 mg rinse bid/5 mg tab/day	14 d
5	Thomson and Pack [23]	RCT	30	Mean age 25.4	5 mg rinse bid/5 mg tab/day	28 d
6	Pack [24]	RCT	60	21-61	5 mg rinse bid	28 d
7	Pack [25]	RCT-Crossover	20	19-23	5 mg rinse bid	Two 21 d

Table 4: Folate Therapy for Gingivitis Studies

is less FA to act as a cofactor for the metabolism of PHT. Therefore, there is decreased metabolism and the concentration of PHT increases until FA comes into equilibrium. It is necessary for FA to establish steady-state (which may cause a PHT serum concentration deficiency) for PHT to reach true a true steady-state. PHT administration often requires dosage adjustment and superior patient compliance. The reality is that PHT-FA dynamics are complex and require physician experience and training for proper seizure management. Lewis et al. [10] concluded that initiation of PHT and FA together caused no change in serum FA concentration, and that FA, whether decreased or supplemented, does not affect the pharmacokinetics of PHT, and explains the dual and interdependent PHT-FA interaction [10,27,28].

Discussion

It is estimated that about half of the patients taking PHT demonstrate PIGO [29]. The side effect of PHT therapy causing cosmetic disfiguring and contributes to periodontal disease and dental caries [7]. Under a WHO protocol, in 2002, Sridharan reported the prevalence of epilepsy in India was 0.53% and the prevalence data for epilepsy worldwide range from 4 to 10 per thousand [30].

The conclusion of the included PIGO-Folate studies was as follows: First, regarding the gingival overgrowth as a primary outcome, Arya et al. [10] showed statistical and clinical significance ($p<0.001$) for folic acid as a preventive measure of PIGO. Prasad et al. [5] showed clinical but not statistical significance for the folic acid use. Prasad et al. [5] concluded that systemic folic acid prescribed along with phenytoin not only reduces the incidence and severity of gingival hyperplasia induced by phenytoin, but also delays its onset. Brown et al. [12] concluded that there were no differences between folic acid group and placebo treatment groups in the hyperplasia and plaque index scores. (However, the Brown et al. [12] study evaluated severely mentally compromised institutionalized subjects with relatively high plaque index scores). Backman et al. [14] concluded that the size of the gingival hyperplasia was significantly reduced. Drew et al. [15] showed that topical folic acid was statistically significant compared to the systemic folic acid and placebo.

These conclusions based on outcome measures included mainly indices of hyperplasia, gingival health, and plaque index of Loe and Sillness, probing depth. Only Drew et al. [15] used Kodachrome slides and study casts to assess the outcomes. We believe that Kodachrome and study casts provide more objective assessment. Poppell et al. [13] also utilized study casts. However, we can conclude that it is particularly difficult to obtain photographs or casts if the epileptic patients are severely ill. Another explanation may be the lack of resources

The possible reason for some of the non-significant effects of systemic supplementation of folic acid on gingival overgrowth may be that folic acid was initiated after commencement of phenytoin therapy. Another reason may be lack of strict concurrent oral hygiene measures or difficulty in its application due to severely ill, hospitalized epileptic patients as in the Brown et al. trial [12]. Topical folate in the form of a solution may have provided a greater folic acid concentration adjacent to the affected gingival fibroblasts and that is why it was statistically significant as opposed to systemic folic acid. Furthermore, studies investigating folate efficacy in reference to the treatment of gingivitis also tend to show greater efficacy of topical versus systemic therapy. Brown and Arany [6] proposed a unifying hypothesis which incorporated a rationale for folic acid within the mechanism of DIGO.

Secondly, regarding seizure control, it was unchanged in Backman et al. trial [14]. Drew et al. [15] reported no increases in frequency of seizures in any of the patients. This is unlike Arya et al. trial [10]. In Arya et al. [10] trial, 41.9% of the folic acid arm and 39.7% in the placebo arm required increasing the dose of PHT to achieve seizure control during the course of the study. PHT has a relatively long half-life and is not easily titrated and it is possible that folate may influence PHT serum values [10,13,26,27]. Therefore, we support that folate levels and PHT levels should be checked before and during supplementation with folic acid [4-6].

In conclusion, folic acid therapy is a relatively safe therapy with minimal problematic side-effects when managed responsibly. Folic acid therapy for PIGO/DIGO, provides a potential viable therapy for the treatment of Phenytoin/Drug-induced gingival overgrowth. Six studies evaluated folate therapy to treat PIGO. Of these six studies, three evaluated folate with regard to prevention of Phenytoin-induced gingival overgrowth, and three evaluated folate with regard to reversal of Phenytoin-induced gingival overgrowth. All of these studies demonstrated efficacy with the exception of one study which evaluated subjects with relatively high plaque index scores. The only reversal study to evaluate topical folate therapy demonstrated the most successful results. Successful topical folate therapy for gingivitis also appears to be evident. Therefore, future topical folate efficacy studies are strongly suggested for the treatment of Drug-induced gingival overgrowth.

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