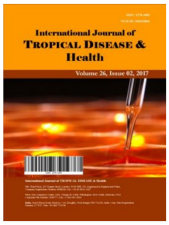

International Journal of TROPICAL DISEASE & Health

28(3): 1-12, 2017; Article no.IJTDH.39039
ISSN: 2278–1005, NLM ID: 101632866

The Influence of Antiepileptic Drugs Alteration as Adjunctive Therapy of Drug Induced Gingival Enlargement among Epileptic Patients in Aseer Region, Saudi Arabia

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MMAAA, SSMA and MJA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MMAAA and MJA managed the analyses of the study. Authors SSMA and MMAAA managed the literature searches. Author MMAAA critically revised the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2017/39039
Editor(s):
(1) Shankar Srinivasan, Department of Health Informatics, University of Medicine & Dentistry of New Jersey, USA.
Reviewers:
(1) Karthikeyan Ramalingam, Rajasthan University of Health Sciences, India.
(2) Mehmet Yaltirik, Istanbul Universty, Turkey.
(3) Dorina Lauritano, University of Milan-Bicocca, Italy.
Complete Peer review History: http://www.sciencedomain.org/review-history/22706

Original Research Article

Received 27th October 2017
Accepted 9th January 2018
Published 13th January 2018

ABSTRACT

Background: Drug induced gingival enlargement is a common clinical finding among epileptic patients who are under medical care. This gingival enlargement is generally managed by different methods as scaling and polishing, surgical or substitution of drugs etc. So this study was designed to evaluate the influence of antiepileptic drugs alteration as adjunctive therapy of drug induced gingival enlargement among epileptic patients in Aseer region, Saudi Arabia.
Materials and Methods: The present study was done on thirty epileptic patients (10 patients per group) between the ages of 15 and 52 years with gingival enlargement which were treated using

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scaling and polishing (SP) alone in group I addition chlorhexidine digluconate 0.2% in group II and alteration of drugs in group III. Plaque index (PLI), gingival index (GI) and gingival overgrowth (GO) scores were evaluated at baseline, 3 weeks and 6 weeks after therapy, then tabulated and compared statistically using SPSS and the various in proportions was calculated using Chi-square test. Statistical significance ($P < 0.05$) was detected in PLI, GI, GO score between baseline, 4 weeks, and 6 weeks. Friedman Test and Wilcoxon Signed Ranks Test were carried out to account the significant differences.

Results: There were improvement in all clinical findings among epileptic patients in all study groups in the 1st, 2nd and 3rd visit, but the improvement was most evident among the patients of group III that were treated by SP and alteration of anti epileptic drugs.

Conclusions: Professional and self-plaque control also the alteration of antiepileptic drugs might be a useful in the management of drug induced gingival enlargement, consequently diminishing the necessity of surgical therapy.

Keywords: Antiepileptic drugs alteration; drug induced gingival enlargement; scaling and polishing.

ABBREVIATIONS

SP : Scaling and polishing
G : Group
PLI : Plaque index
GI : Gingival index
GOI : Gingival overgrowth index
1st : First visit at baseline
2nd : Second visit at 4 weeks
3rd : Third visit at 6 weeks

1. INTRODUCTION

The enlargement of gingival tissues may occur as a response to different reactions of host to bacterial plaque [1], it may be caused by drugs as antiepileptic drugs [2-5], hereditary anomalies, such as hereditary gingival fibromatosis, [6] and proliferative lesions, etc. [7].

Epileptic disease is considered as one of the most common chronic neurological disorders, 50 million of the population of the world are affected, 85% in developing countries [8]. On the other hand epilepsy prevalence in Saudi Arabia is unknown exactly, but about three quarter million people epileptic patients live in the Arab world that is may be due to the shortage in the epidemiological studies in the Arabic region and the unwillingness of people to reveal epilepsy to avoid the social smirch [9]. The essential options of epileptic patient therapy depend on the antiepileptic drugs (AEDs), stimulation of vagus nerve or surgical treatment. There are more than 15 AEDs for the treatment of epilepsy in North America and Europe have been approved [10].

Phenytoin (Dilantin@), carbamazepine (Tegretol@), primidone (Mysoline@) or phenobarbital (Luminal@) is considered the essential drugs recommended for the management of partial seizure disorders [11] Although the availability of anticonvulsant drugs, phenobarbital and phenytoin stay the most commonly antiepileptic drugsall of these anticonvulsant agents (except for phenytoin) capable of inducing gingival overgrowth as clinical side effect [12,13]. The surgical periodontal therapy remains the preferred method for management of drug induced gingival enlargement, moreover substitution strategies to inhibit undesirable results and reduce its recurrence also regular periodontal therapy with scaling and polishing (SP) has been revealed some reduction in gingival overgrowth [14,15].

The essential objective of nonsurgical periodontal therapy is to minimize the inflammatory changes in gingival tissues by reducing the numbers of periodontal pathogens [1] and due to the shortage in studies of their unwanted effects on a patient's oral hygiene, thus there is little knowledge about the side effects of the drugs.

Dental treatment of patients with special needs is a topic in dentistry today. Patients with epilepsy fall into this category. Thus the oral disease prevention protocols greatly improve the quality of life of these patients. Moreover, Health in Arab countries is very oriented in the care of patients with special needs. So we designed this study to discuss the influence of antiepileptic drugs alteration as adjunctive therapy of drug induced gingival enlargement among epileptic patients in Aseer region, Saudi Arabia.

2. SUBJECTS AND METHODS

2.1 The Study Samples

The present study was conducted on thirty epileptic patients with gingival enlargement were selected from the outpatient department of periodontics, college of dentistry, king Khalid university. Case history was recorded. The patient should be under medical care with an antiepileptic drug during three months later. Patients who had subjected to periodontal therapy during the last 3 months before starting our study, non smoker patients, patients with other systemic disease and pregnant patients were excluded.

2.2 Ethical Clearance

The written and oral agreement of patients was taken after clarifying the clinical procedures that was according to the protocol of the scientific research committee, college of dentistry, king Khalid University.

The patients were divided into three groups; group (I) as a control group, ten epileptic patients were treated by scaling and polishing (SP) alone, group II, ten epileptic patients were treated by SP and chlorhexidine digluconate 0.2% and group III, ten epileptic patients were treated with SP and substituted with other generation antiepileptic drugs. All patients in group III were sent to their physician for substitution of the drugs and all of them were substituted the antiepileptic drugs. All patients received SP in the first visit.

2.3 Clinical Examination

The clinical evaluation with plaque index (PLI) [15], gingival index (GI) [16] and gingival over overgrowth index (GOI) [17] were recorded at baseline, 4 weeks and 6 weeks. All indices were evaluated in 6 aspects around each tooth by the same examiner.

2.4 Statistical Analysis

All data were collected and analyzed by using SPSS version 13.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and the various in proportions was calculated using Chi-square test. Friedman Test and Wilcoxon Signed Ranks Test were carried out to account the significant differences.

3. RESULTS

The current study was done on a total of 30 epileptic patients (N = 10 in each group), they continued to the end of the study intervals. Table 1 and Fig. 1 summarizes the mean and standard deviation (±SD) of the age in the present study, the age of the group I was a range of 15-49 years with mean and standard deviation (±SD) of 25.8±9.920 years, whereas the age range of group II was 21-36 years with mean and standard deviation (±SD) of 29.3±4.8 years and the mean and standard deviation (±SD) age of group III was 38.3±8.76 years with an age range of 26-52 years. There was a significant difference in age distribution between the groups of the present study (P > 0.006). The patients in the present study were taking antiepileptic drugs, but these drugs were substituted in group III where an antiepileptic drug was altered to Sodium valproate in 40% of patients, carbamazepine in 30% of patients and Levetiracetam in 30% of patients (Table 2 and Fig. 2).

Table 1. Mean and standard deviation (±SD) of patient age groups

Groups		Mean (±SD)	P value
I	15-49	25.8±9.920	
II	21-36	29.3±4.8	0.006*
III	26-52	38.3±8.76	

3.1 Dental Plaque and Oral Hygiene Assessment

Table 3 and Fig. 3 show the clinical evaluation of dental plaque accumulation and oral hygiene status of the patents in all study groups at 1st, 2nd and 3rd visit. In group (I) that was included the epileptic patients with gingival enlargement who were treated by scaling and polishing (SP) only, there were 70% of patients had moderate plaque accumulation and moderate oral hygiene and 30% of patients had heavy plaque accumulation and poor oral hygiene in the 1st visit compared to 60% of patients had mild plaque accumulation and mild oral hygiene and 40% of patients had moderate plaque accumulation and moderate oral hygiene in the 2nd visit moreover, 90 % of patients had mild plaque accumulation and mild oral hygiene in the 3rd visit.

In group (II) that was included the patients who were managed by SP and chlorhexidine digluconate 0.2%, there were 30% of patients had moderate plaque accumulation and moderate oral hygiene and 70% of patients had

heavy plaque accumulation and poor oral hygiene in the 1st visit compared to10 % of patients had mild plaque accumulation and mild oral hygiene and 90% of patients had moderate plaque accumulation and moderate oral hygiene in 2nd visit, furthermore 70% of patients had mild plaque accumulation and mild oral hygiene and 30% of patients had moderate plaque accumulation and moderate oral hygiene in the 3rd visit.

In group (III) that was included the patients who were managed by SP and substituted with other antiepileptic drugs , there were 60.0% of patients had moderate plaque accumulation and moderate oral hygiene and 40% of patients had heavy plaque accumulation and poor oral hygiene in the 1st visit compared 50% of patients had mild plaque accumulation and fair oral hygiene and 50% of patients had moderate plaque accumulation and moderate oral hygiene in the 2nd visit and 90.0% of patients had mild plaque accumulation and fair oral hygiene and 10% of patients had moderate plaque accumulation and moderate oral hygiene in the 3rdvisit. There were differences in plaque accumulation and oral hygiene status among the patients in the present study in the 1st, 2nd and 3rd visit, but the differences were significantly in the 2nd visit of the present study (P <0.05).

Table 4 and Fig. 4 demonstrate the mean rank of plaque index (PLI) of the all patients' groups at the 1st, 2nd and 3rd visit. The statistical analysis was carried out using Friedman test and Wilcoxon Signed Ranks test and there were decreases in mean plaque index after therapy to be statistically high significant (P <0.05).

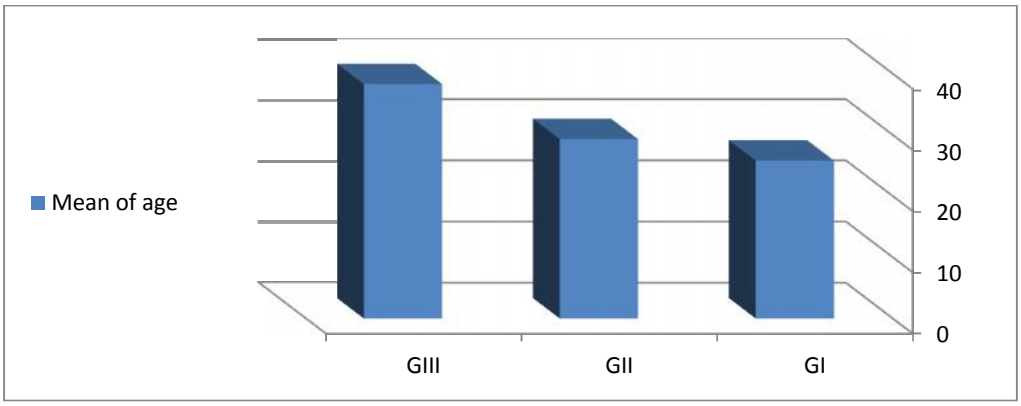

Fig. 1. Mean of patient age groups

Table 2. Distribution of patients, according to substituted antiepileptic drugs

Drugs	Sodium valproate	Carbamazepine	Levetiracetam	Total
N	4	3	3	10
%	40%	30%	30%	100%

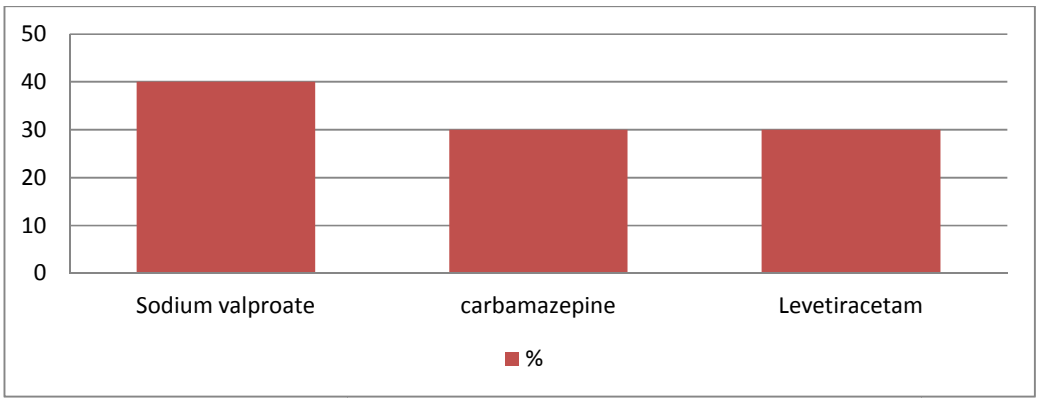

Fig. 2. Distribution of patients, according to substituted antiepileptic drugs

Table 3. Dental plaque evaluation of the patient groups

	1st visit			2nd visit			3rd visit		
	GI	GII	GIII	GI	GII	GIII	GI	GII	GIII
No plaque	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	10.0%	0.0%	0.0%
Mild	0.0%	0.0%	0.0%	60.0%	10.0%	50.0%	90.0%	70.0%	90.0%
Moderate	70.0%	30.0%	60.0%	40.0%	90.0%	50.0%	0.0%	30.0%	10.0%
Heavy	30.0%	70.0%	40.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%

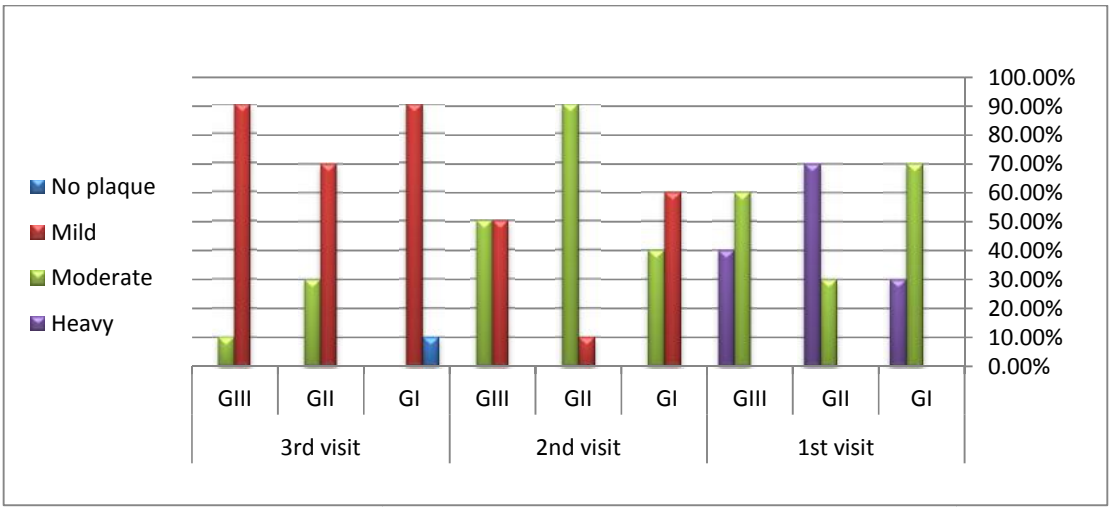

Fig. 3. Dental plaque evaluation of the patient groups

Table 4. Mean of plaque index

		GI	GII	GIII
1st visit		2.900	2.850	2.900
2nd visit		1.850	1.900	1.800
3rd visit		1.250	1.250	1.300
Friedman test P-value		<0.001*	<0.001*	<0.001*
Wilcoxon Signed Ranks Test P-value	1st-2nd	0.007*	0.005*	0.007*
	1st-3rd	0.004*	0.006*	0.004*
	2nd -3rd	0.025*	0.014*	0.046*

3.2 Gingival Inflammation Assessment

The gingival status of the patients in the present study is revealed in the Table 5 and Fig. 5, There were differences in the inflammation of the gingival tissue among the patient groups at the 1st, 2nd and 3rd visit. In group I patients that were treated with SP only there were 10% of patients had mild gingival inflammation, 60% of patients had moderate gingival inflammation and 30% of patients had severe gingival inflammation in the 1st visit but in the 2nd visit there were 40% of patients had mild gingival inflammation and 60% of patients had moderate gingival inflammation compared to 80% of patients had mild gingival inflammation and 20.0% had moderate gingival inflammation in the 3rd visit and there were no patients with severe gingival inflammation in 2nd and 3rd visit.

In group II, there were differences in the severity of gingival inflammation among the patient who were treated with SP and chlorhexidine digluconate 0.2% at all intervals where there were 80% of patients had moderate gingival inflammation and 20% of patients had severe gingival inflammation in the 1st visit these findings changed in 2nd visit to 70% of patients had mild gingival inflammation and 30% of patients had moderate gingival inflammation and there were no patients with severe gingival inflammation while the gingival inflammation reduced to mild gingival inflammation in the 3rd visit in all patients of group II.

On the other hand all the patients of group III had moderate gingival inflammation in the 1st visit this percentage reduced to 80% moderate gingival inflammation and 20% mild gingival inflammation in the 2nd visit while in the 3rd visit 10% of

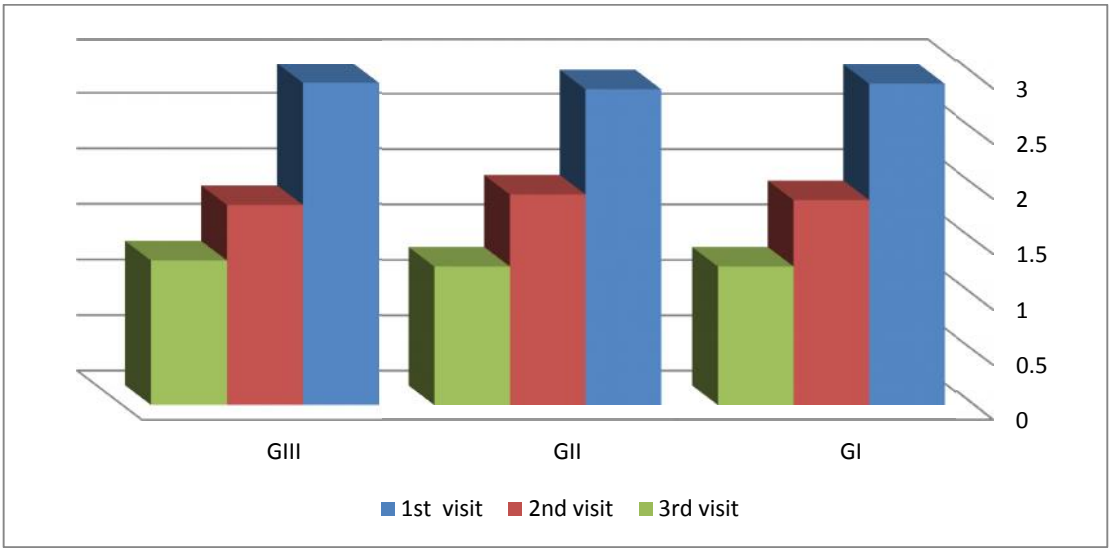

Fig. 4. Mean of plaque index

Table 5. Gingival inflammation evaluation of the patient groups

	1st visit			2nd visit			3rd visit		
	GI	GII	GIII	GI	GII	GIII	GI	GII	GIII
Normal	00%	00%	00%	00%	00%	00%	00%	00%	10%
Mild	10%	00%	00%	40%	70%	80 %	80%	100%	90%
Moderate	60%	80%	100%	60%	30%	20%	20%	00%	00%
Severe	30%	20%	00%	00%	00%	00%	00%	00%	00%

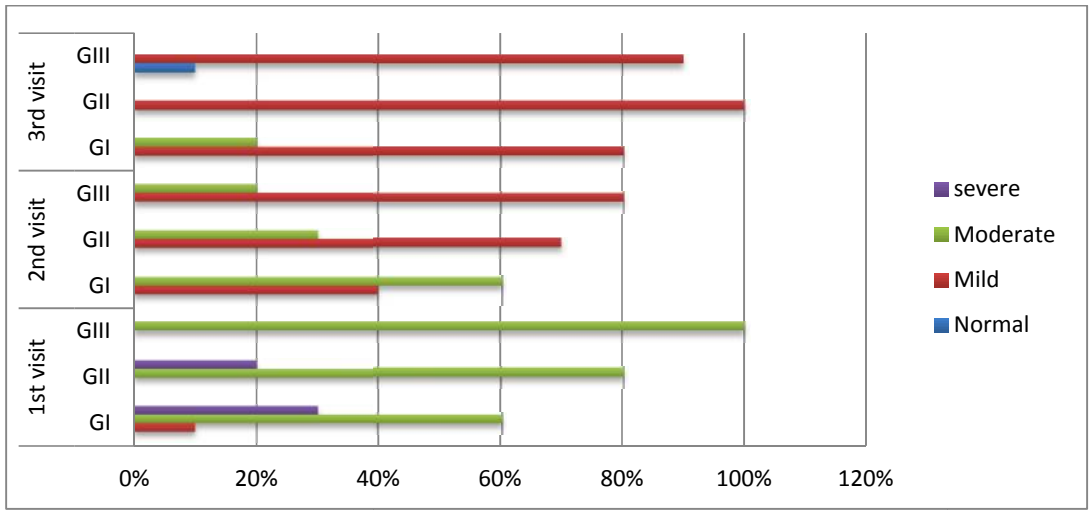

Fig. 5. Gingival inflammation status of the patient groups

patients became healthy and 90% of patients had mild gingival inflammation.

The differences in gingival inflammation severity were statistically not significant for group I, II and III but the difference was found to be statistically highly significant in the comparison between the 1st, 2nd and 3rd visit of all the present study groups. In Table 6 and Fig. 6 according to statistical analysis of Friedman test and Wilcoxon Signed Ranks test, there were decreases in the mean gingival index after therapy to be

statistically highly significant in the comparison between the patient groups at all intervals (P <0.05).

3.3 Gingival Enlargement Assessment

Table 7 and Fig. 7, gingival enlargement percentages are displayed. In the 1st visit of group I, 50% of the patients had grade I gingival enlargement and 50% of patients had grade II gingival enlargement whereas while in the 2ndvisit grade I was revealed in 40% of patients and grade II was affected 40% of patients furthermore, 20% of patients become healthy after SP which increased to 60% in the 3rd visit and 40% of patients had grade I gingival enlargement, there were significances differences in clinical findings of gingival enlargement that was treated by SP alone at all intervals of the present study.

Regarding group II of the present study that was included the epileptic patients with gingival enlargement who was treated by SP and chlorhexidine digluconate 0.2%.The grade of gingival enlargement percentage of patients in the 1st visit was appeared 40%, 40% and 20% of patients as grade I, II and III respectively, while in the 2nd visit there were 40.0% of patients had grade I and 60% of patients grade II, these percentage was not changed in the 3rd visit. There were differences in clinical finding among the patients in this group at all intervals of the present study but there were no significance differences.

These results changed in group III that were treated with SP and substituted with other generation antiepileptic drugs where there were 20% of patients with grade I and 40% of patients with grade II additional to 40% of patients with grade III in the 1st visit.

On the other hand in the 2nd visit these findings altered to 40% grade I and 60% grade II compared to 40% grade I and 40% grade II in the end of the 3rd visit additionally 20% of patients become healthy. There were significant differences in the clinical finding of gingival enlargement management among the patients of group III at all intervals of the present study.

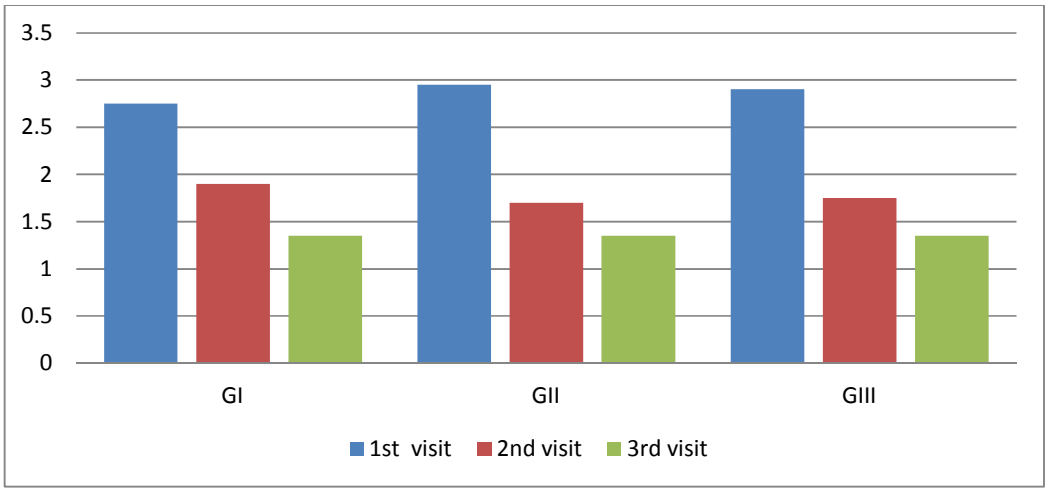

Fig. 6. Mean of gingival index

Table 6. Mean of gingival index

		GI	GII	GIII
1st visit		2.750	2.950	2.900
2nd visit		1.900	1.700	1.750
3rd visit		1.350	1.350	1.350
Friedman Test P-value		<0.001*	<0.001*	<0.001*
Wilcoxon Signed Ranks Test P-value	1st-2nd	0.014*	0.003*	0.005*
	1st-3rd	0.004*	0.003*	0.002*
	2nd -3rd	0.046*	0.083	0.083

Table 7. Gingival enlargement evaluation of the patient groups

	1st visit			2nd visit			3rd visit		
	GI	GII	GIII	GI	GII	GIII	GI	GII	GIII
Normal	00%	00%	00%	20%	00%	10%	60%	00%	20%
Grade I	50%	40%	20%	40%	40%	30%	40%	40%	40%
Grade II	50%	40%	40%	40%	60%	60%	00%	60%	40%
Grade III	00%	20%	40%	00%	00%	00%	00%	00%	00%

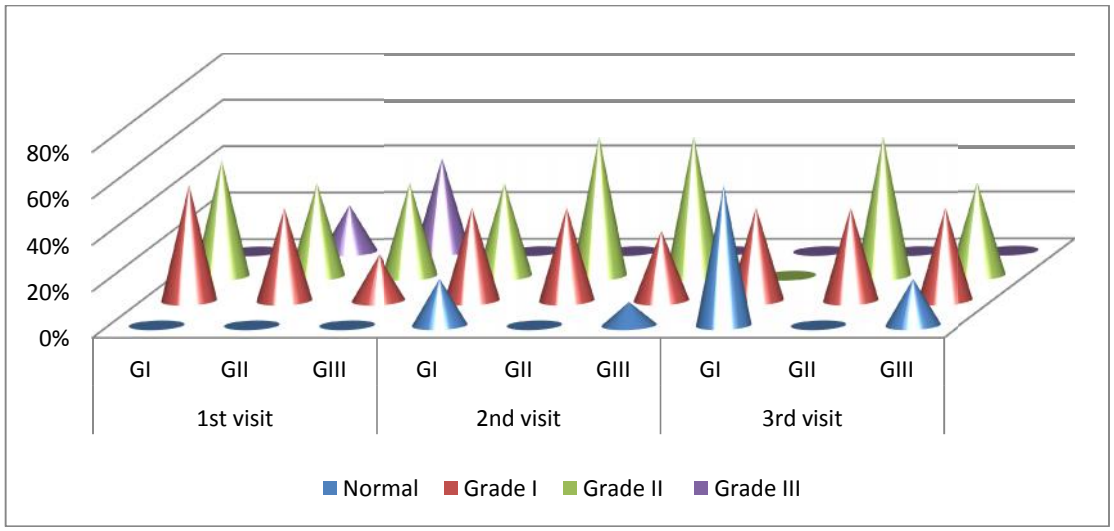

Fig. 7. Gingival enlargment evaluation of the patient groups

Table 8. Mean of gingival overgrowth index

		GI	GII	GIII
1st visit		2.650	2.200	2.800
2nd visit		2.250	1.900	1.800
3rd visit		1.100	1.900	1.400
Friedman Test P-value		0.000	0.135	0.001
Wilcoxon Signed Ranks	1st-2nd	0.083	0.157	0.008*
Test	1st-3rd	0.002*	0.157	0.004*
P-value	2nd -3rd	0.005*	1.000	0.083

Table 8 and Fig. 8 show the mean rank of the gingival enlargement at all study intervals where there were decreases in mean gingival enlargement after therapy and there was significances highly differences at all intervals that was according to statistical analysis of Friedman test and Wilcoxon Signed Ranks Test ($P < 0.05$).

4. DISCUSSION

The current study was designed to evaluate the clinical effect of antiepileptic drugs alteration as adjunctive therapy in the management of drug induced gingival enlargement that is complicated due to the overlap of gingival inflammatory reaction with hyperplasic reaction of gingival tissues. It is known that conventional periodontal treatment can contribute to eliminating of inflammatory reaction that is associated with gingival enlargement by scaling and polishing (SP) then surgical removal of the enlarged gingival and there were many studies that displayed a reduction of drug-induced gingival enlargement after self and professional plaque control [18,19].

It should be noted that the substitution or withdrawal of antiepileptic drugs is considered as from the most effective methods in treatment of drug induced gingival enlargement to reduce gingival overgrowth after 1-8 weeks, but this

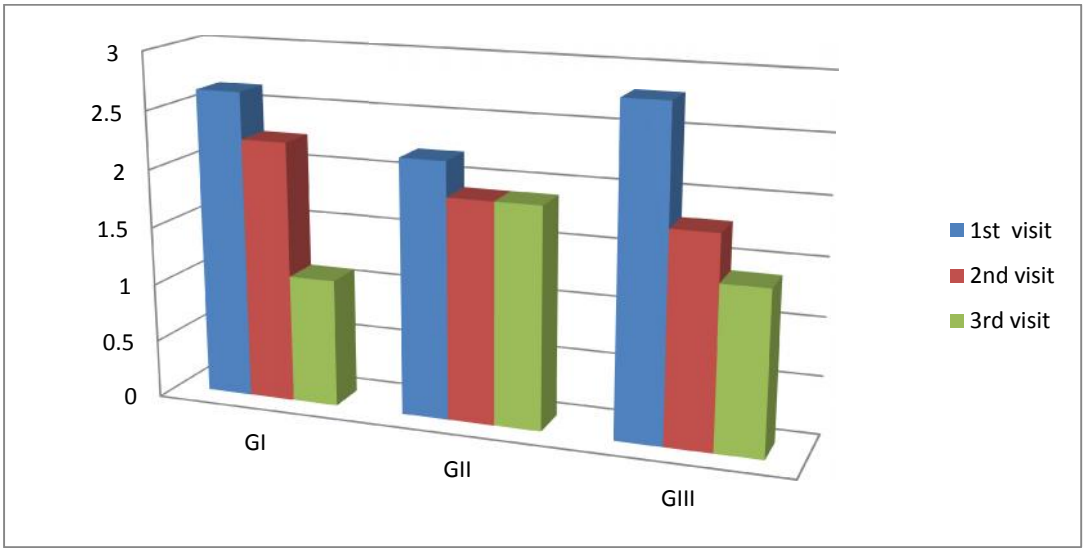

Fig. 8. Gingival overgrowth index

method of management is not effective in all cases, particularly in the longstanding gingival enlargement [20,21] thus, the surgical periodontal therapy remains the main methods in management of drug induced gingival enlargement by gingivectomy [22,23]. Nevertheless, there is proof that nonsurgical periodontal treatment decreases the inflammation with gingival enlargement therefore minimizes the requirement of surgical procedure [24]. In addition,professional plaque control and self plaque control can be done to reduce gingival enlargement with time [25].

The present study reveals that scaling and polishing method is the first option in treatment of drug induced gingival enlargement. These results are identical to the results of a previous study that was done by of Aimetti et al, who displayed additional proof that plaque is necessary in the pathogenesis of drug induced gingival overgrowth. The investigators explained that appropriate self-plaque control with scaling and polishing is efficient in management of drug induced gingival enlargement. In the end of the study of the one-year period, they found that there were a reduction in gingival size from 2.38 mm at baseline to 1.82 mm in the anterior teeth and from 1.29 mm at baseline to 0.84 mm in posterior teeth [26].

The current study displayed the mean value of plaque index where there was significant higher in epileptic patients in group I, II and III in 1st, 2nd and 3rd visit of gingival enlargement therapy. These results were agreed with some studies [27]. Besides, these results were in dispute with other study [28]. In the present study there were decreased in mean plaque index after SP with improvement of oral hygiene in the 1st, 2nd and 3rd visit among the patients of group I that was treated by SP only and among the patients of group II that was treated by SP and chlorhexidine digluconate 0.2% moreover, the patients of group III that was treated by SP and substituted with other antiepileptic drugs. Bad oral hygiene of epileptic patients has previously been present [29-31].

It is worth noting that spread and aggregate intensity of periodontal destruction associated with intensity of seizures in epileptic patients were not clear in previous studies where some investigators detected that scaling and polishing was enough in management of drug induced gingival enlargement [32] these clinical findings consensus had demonstrated the results of our study in group I that included the patients who were treated by SP only where there were improvement in the patients oral hygiene, gingival inflammation and gingival size in the 2nd and 3rd visit comparison to 1st visit.

Gingival inflammation is considered another cause for progression of drug induced gingival enlargement. the significance of plaque as a contributing factor in the etiology of drug induced gingival overgrowth has been included in the recent of periodontal disease classification. In this situation, severe gingival inflammatory reaction also existed [33].

Fig. 9. First visit of SP and antiepileptic drug alteration

Fig. 10. Second visit of SP and antiepileptic drug alteration

Fig. 11. Third visit of SP and antiepileptic drug alteration

Another study was carried out in Serbia where there was a high gingival index among the epileptic patients before periodontal treatment, but gingival index reduced at the end of periodontal therapy this is identical to what has been detected in the present study where it was detected that there was an increase in gingival mean values of the gingival index among the epileptic patients in group I, II and III in the 1st visit compared to 2nd and 3rd visit, This difference in the total mean values of gingival index were found to be statistically significant and these findings were in agreement with other studies [34-36].

In the previous studies that were carried out on the gingival status among epileptic patients there were increased in gingival size after 1 month of antiepileptic drugs use despite overgrowth happened gradually through the period of these studies, but it's persistent at a diminish rate during the second year of almost of these studies and to reach minimum 12-18 after periodontal treatment [37].

In the study of Marshall RI et al1993, they found not increased in gingival size when carbamazepine and sodium valproate were used as alternatives to phenytoin sodium [38].

In the present study, in group III, who were treated by SP and alteration of antiepileptic drugs, the patients received valproate in 40% of patients, carbamazepine in 30% of patients and Levetiracetam in 30% of patients, there were reduced in gingival enlargement in the 3rd visit compared to 2nd and 1st visit, the comparison of these results with the results of group I and group III, where the outcome was satisfactory at 2nd and 3rd visit.

In the study that was done by Nissal ZU et al, 2017 there were differences in periodontal status according to the type of anti-epileptic drugs where the gingival index was the highest among the group of patients that were using sodium valproate compared to the other groups [39].

According to these results sodium valproate may be considered a safe alternative, as regard to gingival and periodontal aspects to anther antiepileptic drugs. All studies, nearly that were carried out to evaluate the effect of anticonvulsants on gingival and periodontal status displayed that sodium valproate is rarely associated with gingival overgrowth [40].

Consequently, the epileptic patients are considered as special needs patients where the oral hygiene and gingival status are significantly bad compared to other population [41]. It is important to mention that we could not to evaluate the effect of genetic and the possible effects of antiepileptic drugs on gingival tissues in long duration.

5. CONCLUSION

In conclusion, the current study revealed the clinical information relating to the effective methods in management of drug induced gingival enlargement among epileptic patients. This study

has demonstrated the necessity of the consultation with epileptic patient's physician during the treatment of gingival overgrowth to, alteration of antiepileptic drugs (if feasible). Moreover, professional plaques control system and Chlorhexidine digluconate solution 0. 2% irrigation can be stated as essential for preventing the progression of gingival overgrowth among epileptic patients.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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