ABENHA MEDICAL JOURNAL bmi
Print ISSN 1110-208X
Online ISSN 2357-0016

Original article

A New Clinical Approach to Manage the Increased Incidence of Dental Caries Associated With Diabetes Mellitus Using Pilocarpine Nanoparticles and an InsituGel as an Oral Drug Delivery System

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Received:

Accepted:

Abstract

Diabetes mellitus is one of the serious diseases with more prevalence in middle East and North Africa. The poor metabolic control associated with diabetes mellitus results in reduced salivary flow rates with remarkable increase in the incidence of dental caries. The aim of this study was to provide a new clinical approach for diabetic patients, during the initial periods of poor metabolic control, in order to decrease the incidence of demineralization and establishment of carious lesions. One hundred diagnosed type 2 diabetic patients were included in this study. They were divided into two groups of 50. Group B was the control group while group A represented the group of patients that underwent the clinical management using Pilocarpine and an insitu gel of carbapol and chitosan that acted as a local drug delivery system. DMFT scores , salivary flow rates and salivary pH measurements were obtained. The results showed that group A patients were significantly superior to those of group B in terms of the DMFT scores , salivary flow rates and salivary pH measurements.

Key words: Diabetes mellitus ; caries incidence ; salivary flow rates ; pilocarpine ; local drug delivery systems.

Introduction

Diabetes mellitus is one of the most prevalent diseases that was first reported in Egyptian manuscript about 3000 years ago [(1)] . The international federation (IDF) has reported that 425 million people worldwide , are affected with diabetes mellitus , with 35.4 million of them living in the middle east and north Africa [(2)] . It has been estimated that the number of

diabetics is likely to vastly increase and reach 592 millions by the year 2035 [3-5].The world health organization (WHO) has reported that the proportions of annual health budgets spent on diabetes mellitus related diseases reached 15% [3] . Diabetes mellitus occurs as a result of decreased insulin production by the pancreas body or body cells leading to impairment of the carbohydrates , lipids and protein metabolism and thus chronic hyperglycemia [1] .This hyperglycemia results in reduced salivary flow rates with subsequent reduction in the advantages of saliva as regards its washing ,buffering ,remineralization , antimicrobial and immunological roles .

Thus the diabetic patient suffers from an increased acidity in the oral cavity, less salivary minerals available for remineralization , presence of comparatively large number of microorganisms , especially streptococcus mutans and compromised immunity [1-5].More over during periods of poor metabolic control , glucose leakage into the oral cavity may occur , thus facilitating the growth and increase in number of aciduric and acidogenic bacteria [3,6] .A further complication is that diabetes mellitus affects the organs and tissues rich in capillary vessels . Similar changes in small vessels can be found in the oral tissues [3,6,7]. The impairment in the buffering capacity and the remineralization potential are not only due to the decrease in the amount of secreted saliva in diabetic patients but also due to the fact that the saliva its self becomes acidic in nature with fewer minerals content [8-12] .

The purpose of this study was to set up a method for the patients with type 2 uncontrolled diabetes to relatively increase the already impaired salivary secretion as well as to raise its pH . The method included the oral use of pilocarpine with an insitu gel of a local drug delivery system (composed of carbapol and chitosan) which is sensitive to changes in pH in order to produce a controlled , sustained and targeted release of the drug .

The method was intended to be used for those patients during the initial periods of poor metabolic control in order to decrease the incidence of demineralization and the establishment of carious lesions in those patients until they attain a more controllable status of diabetes.

Methods and Materials

This is a prospective study which was approved of by the ethical committee of Pharos University and had the ethical approval number PUA 02202002233011 .

Selection and grouping of subjects

A total of 100 diagnosed type 2 diabetic patients were included in this study . All patient suffered from poorly controlled type 2 diabetes mellitus .They were divided into two groups of 50 (males and females). Group (A) represented the group of patients that were intended to undergo the medical procedure aiming at increasing the salivary flow rate as well as raising its pH .Meanwhile group (B) represented the control group .The two groups matched for age and sex . The age range of patients was (40 – 60) years old . A signed informed consent was obtained from each patient included in this study . The consent form included the purpose and nature of the experimental work , the number of visits to the dentist and the use of medications and their possible adverse effects .The patients were asked to fill in a printed questionnaire for baseline data collection .It was made sure that all the patients included in this study demonstrated , almost , similar conditions of oral hygiene and salivary flow. Also , it was confirmed that the patients were not allergic to the medicaments necessary for the clinical procedure of the study (according to their past medical and dental history) .A preliminary medical examination was ordered from each patient to make sure the patients did not suffer any serious systemic diseases other than diabetes .

A blood glucose level test was carried out for all the patients included in this study to make sure they had approximately similar conditions regarding the metabolic control . The patients were provided a diet diary that included the time and average daily in take of food , beverages and snacks for two weeks . All patients were instructed to follow that common food diary .

The clinical procedure:-

The clinical procedure included three main investigations that were carried out before and after the clinical management procedure .

1) Assessment of the DMFT scores .
2) Determination of the flow rate of saliva
3) Measuring the salivary pH .

Oral dental lesions were examined visually and using a dental explorer in addition to transparency and percussion testing of all teeth. Bitewing radiographs were performed for the carious teeth to measure the extent of existing carious lesions . Carious lesions , restorations , secondary caries and missing teeth were registered by surface (mesial , distal , facial , vestibular , occlusal) . The (DMFT) scores were recorded after registering decayed , missing and filled (restored) teeth.

Determination of the salivary flow rate:

The patients were investigated under fasting conditions . An hour before testing the patients were directed not to brush their teeth , eat , drink or smoke . A basal (passive) and a stimulated accumulation of saliva was carried out as follows :each patient was allowed to sit comfortably in the dental chair with the head , slightly , tilted forward and the lips separated . The patient was then ,directed to retain the accumulated saliva with in the mouth for one minute .Afterwards, the patient was instructed to pour the accumulated saliva ,each minute into a glass funnel attached to a calibrated sterile test tube during a total of 5 minutes .The same method was used to measure the stimulated salivary flow with the exception that the patient was initially instructed to chew a paraffin tablet for 5 minutes .For both methods of measurement (basal and stimulated salivary output), the tubes containing the collected saliva were allowed to stand for a few minutes in order to get the foam cleared away and thus facilitate measurements . The amounts obtained were divided by 5 in order to indicate the basal unstimulated or the stimulated salivary flow rates in milliliters per minute.

Measuring the salivary pH:

The salivary pH was measured using a pH meter (Bench top pH/MV/temp. meter-jenway) by immersing the glass electrode inside the test tube containing the collected saliva and recording the device reading.

Rubber base impressions (Table 1), were taken for all patients belonging to group A and poured in cast stone. Provisional acrylic devices were formed on the casts using a heat / vacuum forming machine . The devices were tried in the patients mouths for further trimming and occlusal adjustment.The devices were perforated and had fine pores in order to allow the diffusion of the drug into the oral cavity. Pilocarpine drug (table 1) in an insitu gel was used in the form of a thin film perforated matrix that was placed into the area of each tooth. The material [pilocarpine / insitu gel (carbapol and chitosan)] is biodegradable ,thus a daily check was made and any remnants were removed then replaced by a new material in each tooth area by the operator. Pilocarpine was prepared as follows : its powder was dissolved in deionized water to produce a solution of 10 mg/ml Pilocarpine nanoparticles were prepared by an ionic gelation method. That method included the following; dispersion of 60 mg chitosan in 20 ml of 1% acetic acid using a magnetic stirrer with 200rpm, at 50ºC for 30 minutes. Then, adjusting the pH at 5 using 4% sodium hydroxide. Afterwards, STTP (15 mg) was

dissolved in 5 ml of deionized water and added stepwise with continuous stirring for an additional 30 minutes. Finally 6 ml of the prepared drug (pilocarpine solution 10 mg/ml) was added with continuous stirring for an additional one hour. In the end the nanoparticles were separated by cooling centrifugation at 10000 rpm for 10 minutes at of -4ºC. The resultant nanoparticles were then incorporated in the insitue gel to form a final concentration of 2% pilocarpine.

Determination of the nano particle size of pilocarpine

Particle size was determined utilizing the Particle Sizing Systems(ZPW388-V2.13), Santa Barbara, Calif., USA (Egyptian national research center)

Operation conditions

Run time	0 Hr 1min 10 sec	Wave length	632.8 nm
Count rate	312 Khz	Temperature	30 ºC
Channel #1	720 K	Viscosity	0.995 cp
Channel width	140 usecond	Index of refraction	1.333

INTENSITY-Weighted GAUSSIAN DISTRIBUTION Analysis (Solid Particle)

Gaussian summary

Mean diameter	**998.5 nm**	**Variance PI**	0.222
Standard deviation	**470.3 nm (47.1%)**	**Chi squared**	**47.555**
Norm Standard deviation	**0.471**	**Base line adjustment**	**0.000%**
Coefficient of variance		**Z-Avg. Diff. Coeff. =**	**4.47E-009 cm2/s**

Cumulative results:

25 % of distribution < 650.1 nm
50 % of distribution < 893.2 nm
75 % of distribution < 1227.2 nm
90 % of distribution < 1633.4 nm
99 % of distribution < 2671.8 nm
80 % of distribution < 1327.7 nm

The Gaussian analysis showed that 75% of particles were less than 1227.2 nm with average value of 998.5 ± 470.3 nm indicating that pilocarbine particle size was reduced to the nano range, which facilitated drug absorption through the oral mucosa upon drug release from the gel matrix.

The purpose of producing nanoparticles from the original prepared pilocarpine solution was to assist in the process of the controlled and targeted release of the drug (pilocarpine). The insitu gel prepared included a drug delivery system in order to produce a sustained, controlled and targeted release of pilocarpine. This drug delivery system [which acted as a base carrying pilocarpine], included two polymers, carbapol and chitosan (Table 1). Carbapol is a polyacrylic acid polymer that shows a sol to gel transition in moisture as the

pH is raised above 5.5[21] . Thus its gel consistency as a drug delivery system, provides sustained and controlled release of the drug and , in addition to that , the sensitivity of carbapol to pH changes provides further control on the drug release. Thus when the pH is lowered carbapol is converted from the gel state to the sol one, facilitating the diffusion of the drug (Pilocarpine) intra orally (Figures 1-3). Carbapol was prepared, (Table 2), by dissolving its powder in deionized water at pH 8. At such step the dissolution was incomplete and a suspension was ,rather, formed. Eventually the suspension was subjected to refrigeration (4ºC) for 24 hours; then a magnetic stirrer was used to complete the dissolution process ending up by a clear crystal gel. Chitosan is a naturally occurring amine-polysaccharide that is also a pH dependent cationic polymer. At a pH exceeding 6. 2 it forms a hydrated gel like precipitate[22],while when the pH is lowered it gradually turns into a solution thus facilitating the drug (pilocarpine) release and diffusion into the oral cavity when the situation demands. The combination of those two polymeric agents (carbapol and Chitosan) potentiates the effect of the local drug delivery system. Chitosan is prepared by dissolving its powder in 1% acetic acid using a magnetic stirrer at a temperature of 50ºC to produce a translucent creamy white homogenous gel.The fine pores of the acrylic provisional devices provided further controlled and extended release of the drug (Pilocarpine).The patients were recalled after two weeks and the same initially performed clinical investigations were carried out.

Table 1: Materials used in this study

Materials	Components	Batch number	Manufacturers
Zeta Plus	Silicone dental impression material	394658	Zhermack S.p.A via Bovazercchino, 10045021 Badia Polesine (Rovigo Italy)
Pilocarpine hydrochloride	Pilocarpine hydrochloride	N/A	Alexandria Co., for Pharmaceuticals & Chemical industries Alexandria-Egypt
Carbopol 971P NF	polyacrylic acid	SLGL1708	Sigma-Aldrich Co. Ltd
Chitosan	poly (D-glucosamine) medium molecular weigh 100-300 K Da (viscosity (20 oC): 287.6 cpsDeacetylated degree 77.4%	wwETU665rg	LANXess company.India
STPP	Sodium tripolyphosphate (purity 85%)	0000139573	Sigma-Aldrich Co. Ltd
Acetic acid (glacial 96%)	Acetic acid	N/A	Al Nasr Pharmaceutical Chemicals Co., Cairo, Egypt
Sodium hydroxide	Sodium hydroxide	N/A	Al Nasr Pharmaceutical Chemicals Co., Cairo, Egypt

Table 2: The components percentages of the ingredients of the insitu gel

Ingredients		%
Carbapol (mg)	40 mg/10 ml	0.4% solution (A)
Chitosan (mg)	100mg/10 ml	1% solution (B)
Percentages of carbapol and chitosan	5 g of solution A+5 g of solution B	0.2% carbapol and 0.5% of chitosan
pH	5.8	

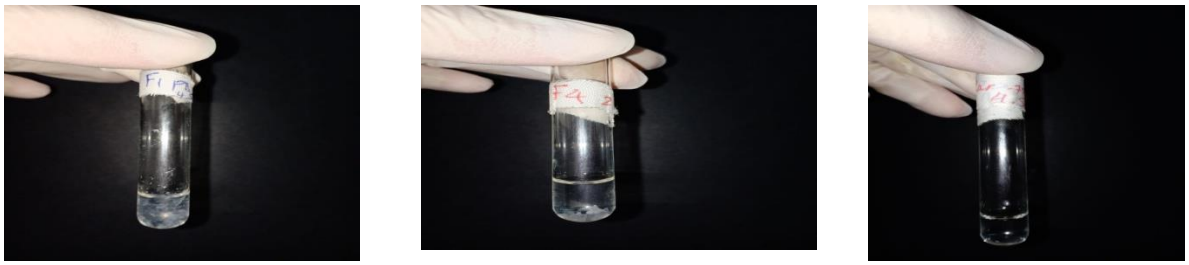

Figure (1-3) showing gel to sol transition of the insitu gel in response to pH changes

Statistical analyses

The paired - t- and confidence interval tests were used to assess the mean DMFT scores, salivary flow rates, and pH values within each group before and after the two weeks interval. The sample - t – and the confidence interval tests were used after the two weeks interval , to set up a comparison between the two groups as regards the mean DMFT scores, salivary flow rates, and pH values.(Tables 3 – 11, and figures 4 – 6).

Results

Regarding group (A): Comparison of the mean values of DMFT index before and after the two weeks of clinical management, showed that there was no significant difference between the mean values of DMFT score before and after two weeks (p>0.05),meaning that no new demineralization processes occurred and no new carious lesions were established. Therefore, after two weeks of clinical management using pilocarpine and an insitu gel of carbapol and chitosan as a local drug delivery system, the incidence of dental caries did not show significant changes i.e the deterioration (increased caries incidence as a result of the diabetic poor metabolic control) ; has stopped; meaning that the clinical management was successful.

- Also, after two of weeks of clinical management the salivary flow rates increased

significantly and the measured salivary pH levels ranged from 5.9-7.1. Regarding group (B):Comparison among the mean values of DMFT index before and after two weeks demonstrated a significant difference (p<0.01). After two weeks the incidence of dental caries significantly increased. The salivary flow rates significantly decreased and the measured pH levels ranged from 5 to 5.3 .

Comparison between group A and group B revealed that group A demonstrated significantly lower caries incidence than group B. Also group A was significantly superior to group B regarding the salivary flow rates and pH levels

Table 3: DMFT scores before and after treatment for group A(the group that received the treatment)

	N	Mean	Standard deviation	SE.Mean
DMFT before treatment	50	9.309	1.304	0.184
DMFT after treatment	-50	9.268	1.345	0.190
difference	50	0.0416	0.3184	0.0450

95% CI for mean difference: (-0.0489, 0.1321)
T-Test of mean difference = 0 (vs not = 0): T-Value = 0.92(NS) P-Value = 0.360(NS)
NS meaning non significant
SE meaning standard error of mean

Table 4: DMFT scores for group B(the control group) at the beginning of the study and two weeks later

	N	Mean	Standard deviation	SE.Mean
DMFT control	50	8.977	1.489	0.211
DMFT control two weeks later	50	10.692	1.070	0.151
difference	50	-1.715	0.932	0.132

95% CI for mean difference: (-1.979, -1.450)
T-Test of mean difference = 0 (vs not = 0): T-Value = -13.01 p-Value = 0.000(S)
S meaning significant differences
SE meaning standard error of mean

Table 5: DMFT scores after two weeks comparing group A and group B

	N	Mean	Standard deviation	**SE mean**
DMFT after treatment (group A)	50	9.27	1.35	0.19
DMFT control two weeks later (group B)	50	10.69	1.07	0.15

Difference = mu (DMFT after treatment) - mu (DMFT control two weeks later)
Estimate for difference: -1.424
95% CI for difference: (-1.907, -0.941)
T-Test of difference = 0 (vs not =): T-Value = -5.86 P-Value = 0.000(S) DF = 93
S meaning significant difference
SE meaning standard error of mean

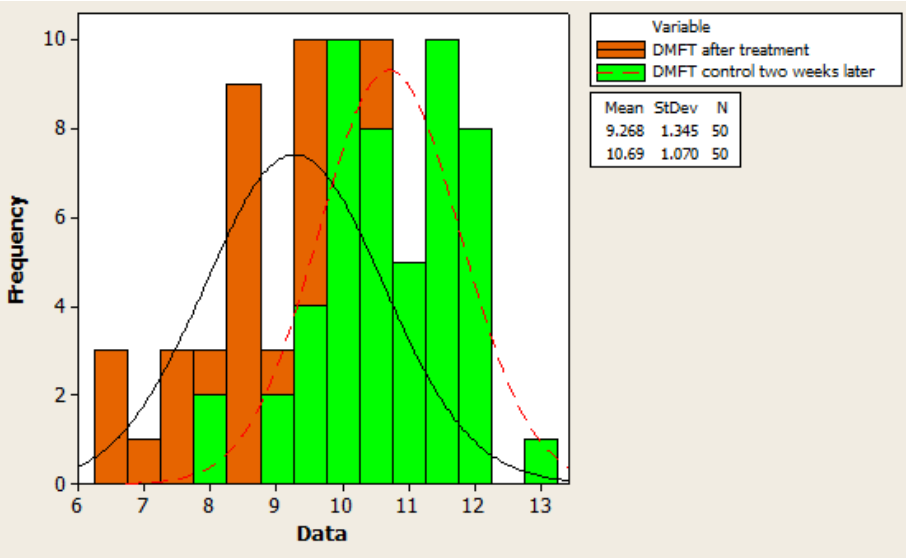

Figure (4) Histogram for the DMFT scores after two weeks comparing group A and group B

Table 6: Salivary flow rate (ml/min) before and after treatment for group A (the group that received the treatment)

	N	Mean	Standard deviation	SE.Mean
Salivary flow before treatment (ml/min)	50	1.1932	0.1713	0.0242
Salivary flow after treatment	50	1.9100	0.1542	0.0218
Difference	50	0.7168	0.2350	0.0332

95% CI for mean difference: (0.6500, 0.7836)
T-Test of mean difference = 0 (vs not = 0): T-Value = 21.57 P-Value = 0.000(S)
S meaning significant differences
SE meaning standard error of mean

Table 7: Salivary flow rate (ml/min) for group B (the control group) at the beginning of the study and two weeks later

	N	Mean	Standard deviation	SE.Mean
Salivary flow control (ml/min)	50	1.1986	0.1778	0.0251
Salivary flow control two weeks later	50	1.1796	0.1474	0.0209
Difference	50	0.0190	0.1090	0.0154

95% CI for mean difference: (-0.0120, 0.0500)
T-Test of mean difference = 0 (vs not = 0): T-Value = 1.23 P-Value = 0.224(NS)
NS meaning non significant differences
SE meaning standard error of mean

Table 8: Salivary flow rate (ml/min) after two weeks comparing group A and group B

	N	Mean	Standard deviation	SE mean
Salivary flow rate after treatment (group A)	50	1.910	0.154	0.022
Salivary flow rate of control two weeks later (group B)	50	1.180	0.147	0.021
Difference = mu (S.Flow control two weeks later) - mu (S. Flow after treatment)				
Estimate for difference: -0.7304				
95% CI for difference: (-0.7903, -0.6705)				
T-Test of difference = 0 (vs not =): T-Value = -24.21 P-Value = 0.000 (S) DF = 97				
S meaning significant differences				
SE meaning standard error of mean				

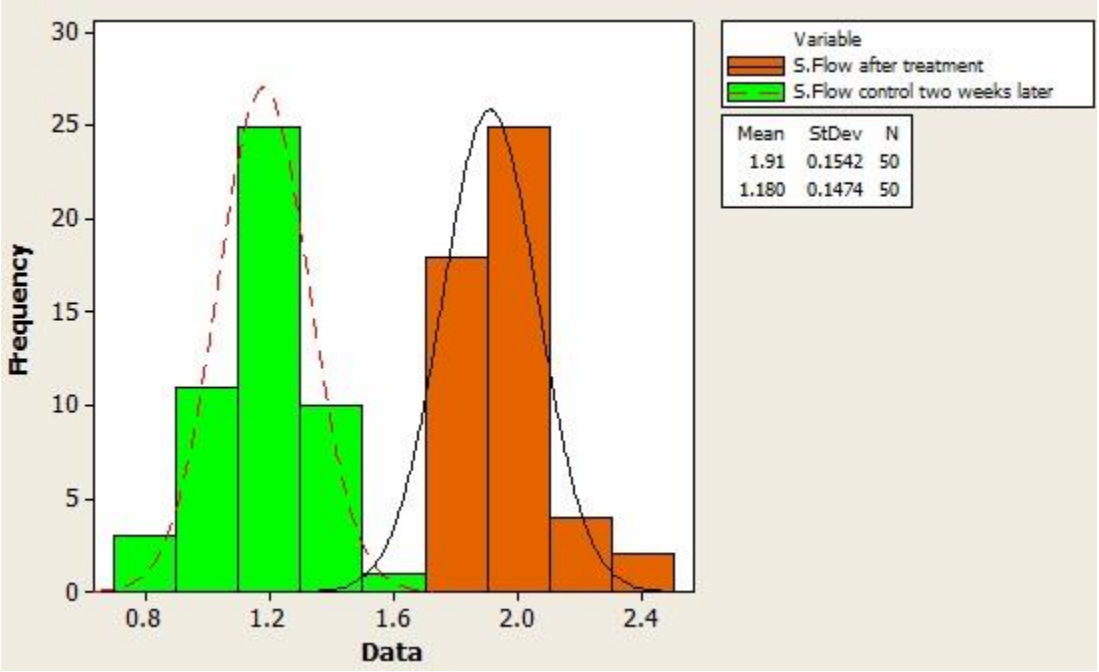

Figure (5) Histogram for the salivary flow rate (ml/min) after two weeks comparing group A and group B

Table 9: PH values before and after treatment for group A (the group that received the treatment)

	N	Mean	Standard deviation	SE.Mean
Salivary pH before treatment	50	5.1890	0.1353	0.0191
Salivary pH after treatment	50	6.3204	0.3226	0.0456
difference	50	-1.1314	0.3788	0.0536
95% CI for mean difference: (-1.2390, -1.0238)				
T-Test of mean difference = 0 (vs not = 0): T-Value = -21.12 P-Value = 0.000 (S)				
S meaning significant differences				
SE meaning standard error of mean				

Table 10: PH values for group B (the control group) at the beginning of the study and two weeks later

	N	Mean	Standard deviation	SE.Mean
Salivary pH of control	50	5.2792	0.1495	0.0211
Salivary pH control two weeks later	50	5.3296	0.1919	0.0271
Difference	50	-0.0504	0.1852	0.0262

95% CI for mean difference: (-0.1030, 0.0022)
T-Test of mean difference = 0 (vs not = 0): T-Value = -1. 92 P-Value = 0.060 (NS)
NS meaning Non significant difference)
SE meaning standard error of mean

Table 11: PH values after two weeks comparing group A and group B

	N	Mean	Standard deviation	SE mean
Salivary pH after treatment (group A)	50	6.320	0.323	0.046
Salivary pH control two weeks later (group B)	50	5.330	0.192	0.027

Difference = mu (pH treated after) - mu (pH control after)
Estimate for difference: 0.9908
95% CI for difference: (0.8851, 1.0965)
T-Test of difference = 0 (vs not =): T-Value = 18.67 P-Value = 0.000 (S) DF = 79
S meaning significant difference
SE meaning standard error of mean

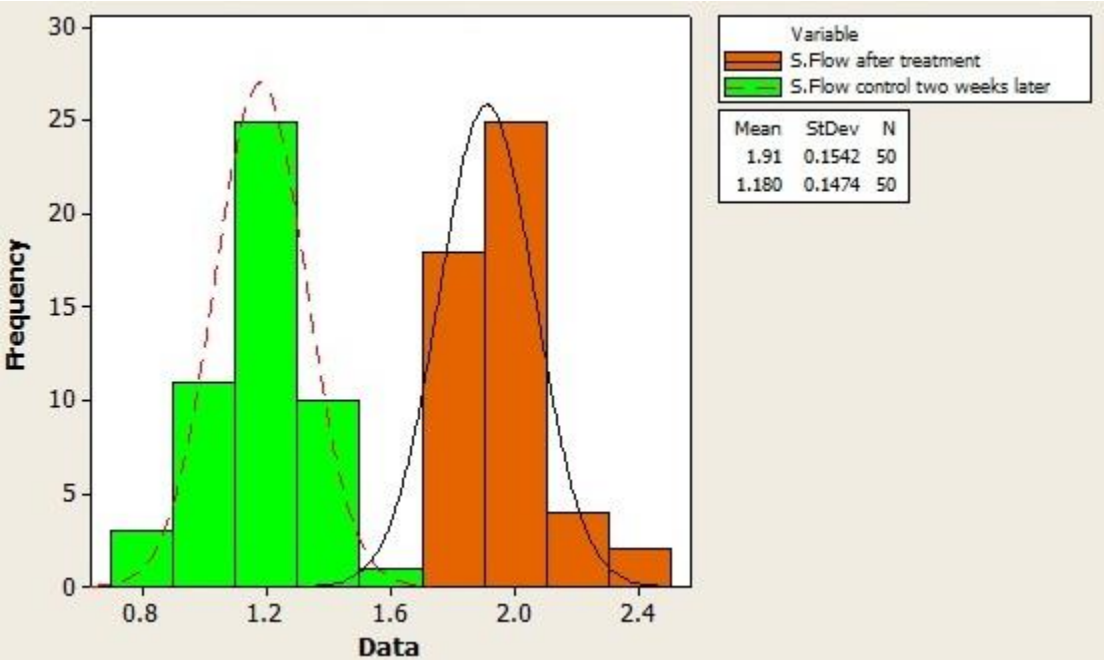

Figure (6): Histogram for pH values after two weeks comparing group A and group B

Discussion

Dental caries is an infectious disorder including multiple factors that coincide at a given point and at a given time [(13)]. Diabetes mellitus is an extreme disturbance in glucose metabolism accompanied with severe hyperglycemia and insulin deficiency. Several oral disorders have been associated with diabetes mellitus as dental caries, salivary dysfunction, periodontitis, gingivitis and oral mucosal diseases and infections [(14-16)]. The relationship between dental caries and Diabetes Mellitus is very complex. The decrease in insulin production by the pancreas results in impaired metabolism of carbohydrates, lipids and proteins ending up by chronic hyperglycemia (1). Hyperglycemia leads to decreased salivary flow rates. This leads to depriving the oral cavity of the advantages of saliva regarding the incidence of caries. Saliva has a washing capacity so its decrease causes more plaque accumulation with increased caries incidence. Saliva has a buffering capacity thus counteracting the increased oral acidity. Unfortunately this is impaired with the decrease in salivary flow rate leading to increased caries incidence due to the prevalence of aciduric and acidogenic bacteria. On the other hand, it has to be pointed out to the fact that in diabetic patients the decreased buffering capacity is bimodal. Its occurrence is not only related to the decreased salivary flow rate but also to the consistency of the remaining saliva as well. The relatively decreased, saliva its self suffers a decrease in the availability of calcium and phosphate ions which play a considerable role regarding the salivary buffering capacity. Meanwhile the decrease in calcium and phosphate ions partly due to the reduced salivary flow rate and partly due to the change in saliva consistency itself results in a significant reduction, in the remineralization potential of saliva thus the demineralization process of teeth progresses with the risk of developing new carious lesions and progression of old ones [(1, 17,16)].Because saliva demonstrates an antimicrobial effect due to the presence of mucins ,lycines, and salivary peroxidases, the decrease in salivary flow rate leads to the multiplication, growth and flourish of cariogenic bacteria especially streptococcus mutans which, in turn, increases the caries incidence[(1-5)]. Also, saliva contains the immuno- globulins IgG IgM which play an important role in immunity. Moreover, regarding diabetic patients and during periods

of poor metabolic control and with the increase in hyperglycemia, glucose leakage into the oral cavity may occur thus leading to more growth and increase in the number of aciduric and acido genic bacteria[3,6]. A further complication occurs due to the fact that diabetes mellitus affects the tissues and organs rich in blood vessels. Similar changes, can be found in small vessels of the oral tissues[3,6,7]. Also the gingival recession accompanying periodontitis, which is an important manifestation of diabetes mellitus, leads to root caries [19]. In this study we tried to manage the diabetic patients‘ cases during the initial periods of the disease that showed poor metabolic control so as to decrease the incidence of demineralization and thus the establishment of carious lesions. Regarding the salivary secretion and flow, afferent and efferent stimuli modulate the neural control of salivation.

The parasympathetic efferent pathways of the sublingual and submandibular glands come from the facial nerve via the submandibular ganglion. Meanwhile, the para sympathetic efferent pathways of the parotid gland are from the glossopharygeal nerve via the otic ganglion. The para sympathetic nervous system, through the liberation of acetylcholine, acts on the M3 muscarinic receptors to produce an abundant secretion of saliva[20]. Pilocarpine was used ,in this study, as a therapeutic drug in order to increase the salivary secretion and flow. Pilocarpine is a direct muscarinic agonist. Direct muscarinic agonists are parasympathomimetic drugs that increase the cholinergic tone and thus the liberation of acetylcholine which, in turn, increases the salivary secretion[20, 23-26]. The para sympathetic action of pilocarpine induces both water and electrolyte flow in saliva. Also, there is evidence that pilocarpine stimulates the production of mucin as well as other several salivary constituents [21]. Mucins demonstrate powerful anti-bacterial effects and, also, prevent chemical and mechanical trauma to the oral structures[27]. Saliva is rich in mucins, therefore, any increase in salivary flow may induce symptomatic improvement for those patients. In this study pilocarpine was used in conjunction with a local drug delivery system composed of two polymers (carbapol and chitosan) .

The local drug delivery systems have been described as targeted drug delivery carriers. That, in turn, would result in increased efficacy as well as local concentration of drugs. The local drug delivery systems are polymers with a hydrogel state. This gel consistency could incorporate a high content of the drug (pilocarpine) molecules and, in

the mean time, due to their high swelling, would limit the possibility, of a burst release of the drug. That resulted in sustained, controlled and targeted release of the drug (Pilocarpine). In addition to that, regarding the local drug delivery system used in this study (carbapol and chitosan) ; both polymers, and carbapol and chitosan demonstrate a gel to sol transition in aqueous saliva as the pH is lowered than [5.5-6] ; thus providing further control on drug release by facilitating and increasing the drug (pilocarpine) release and diffusion into the oral cavity when the situation demands (at periods of lowered pH). That potentiated the efficacy of that local drug delivery system. Also the use of a combination of those two polymeric agents (carbapol and chitosan) further potentiated the effect of the local drug delivery system .The local drug delivery system used in this study took the form of an insitu gel which demonstrated appropriate viscosity and superior adhesiveness. This increased the contact time which imparted to the efficacy. The results of this study showed group [A] to be significantly superior the control group [B] in terms of the salivary flow rates, and the measured salivary pH levels. That indicated the success of the use of pilocarpine with an insitu gel local drug delivery system in decreasing the incidence of dental caries in patients with uncontrolled diabetes mellitus.

Conclusion

Diabetic patients should be managed during the initial stages of the disease especially those with poor metabolic control . Clinical procedures aim to increase the salivary flow rate in order to restrict the caries progression.

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To cite this article: Hala M. Fare , Enas El Zahaby. A New Clinical Approach to Manage the Increased Incidence of Dental Caries Associated With Diabetes Mellitus Using Pilocarpine Nanoparticles and an InsituGel as an Oral Drug Delivery System. BMFJ 2023;40 (surgical issue):384-399.