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Effect of alpha lipoic acid on superoxide dismutase levels after surgical periodontal therapy in patients with diabetes and chronic periodontitis- A randomized clinical trial

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Abstract

Context: Periodontitis is exacerbated by the hosts immune response It has been interlinked with many systemic diseases, diabetes being the most prominent. Both, the diseases are immunoinflammatory in nature and agents which aid in resolution are beneficial.

Alpha lipoic acid (ALA) is a highly efficient scavenger of free radicals. Ample literature is available showing nonsurgical periodontal therapy improves the glycosylated haemoglobin levels in diabetic patients with periodontitis, nonetheless not much research is available on antioxidant therapy after surgical periodontal therapy (SPT).

Aims: This study evaluated the benefits of ALA administration on superoxide dismutase (SOD) and glycosylated hemoglobin levels (HbA1c) in well controlled diabetic patients with periodontitis.

Settings and Design: This study included 24 subjects who were uniformly split into Group A and Group B. Patients attending the outpatient ward of a referral care center and a reputed diabetic center in Hyderabad participated.

Methods and Material: Group A included 12 subjects who underwent open flap debridement followed by administration of ALA 600mg thrice a day for 3 months. Group B included 12 subjects who underwent flap surgery only. The clinical parameters were recorded

preoperatively, 3 months and 6 months after surgery. HbA1c and SOD levels were also examined at the same time intervals. Consent was taken and was approved by the institutional ethical committee (PERIO/DN/0171-17) and was registered. (CTRI 017346).

Statistical analysis used: Comparisons within and between the groups was made with IBM SPSS statistics 20.0. Descriptive statistics, Friedman's test, was used for intragroup comparison and Mann Whitney test for intergroup comparison.

Results: Clinical parameters markedly improved within the groups. Hb A1c and SOD levels reduced significantly in Group A, at the end of 3 months however, at 6 months reassessment, the results were insignificant.

Conclusions: Group A fared better than Group B at 3 months however, at 6 months did not yield significant results.

Keywords: Diabetes, Glycosylated haemoglobin, Periodontitis, Superoxide dismutase, Alpha lipoic acid

Key Messages: Antioxidant therapy could prove beneficial especially in well controlled diabetic patients undergoing surgical periodontal therapy.

Introduction

Periodontitis is initiated by plaque and progresses due to the interaction of microbes and the host response. It is proven that periodontitis could cause widespread systemic ramifications, amongst which diabetes is a key player. Periodontitis is more often seen in diabetic patients as both the diseases are interlinked.[1] Oxidative stress is an important etiological factor implied in many diseases like diabetes and periodontitis. It involves the excessive release of free radicals (ROS) which cause havoc to the body.[2] SOD is an enzymatic antioxidant present within the body which has a protective role to play during oxidative stress. Among the endogenous nonenzymatic antioxidants released to counteract the ROS, are Vitamins C, E, and reduced glutathione (GSH). ALA helps in GSH synthesis and hence has been employed in this study.[3] Though plaque control and removal are the cornerstone of periodontal therapy, surgical treatment is mandatory in very deep pockets which do not resolve after scaling. This study was done to understand if ALA has a beneficial role to play when administered after surgical periodontal therapy.

Subjects and Methods

With 95% confidence levels and P value <0.05, 24 patients were thought to be sufficient to partake of this study. Patients aged between 35 to 60 years, with well controlled Type II Diabetes (HbA1C levels 6 – 7%) and Chronic periodontitis (Having minimum of 15 teeth present with Probing pocket depth ≥5mm, Clinical attachment loss ≥3mm) were included and patients who had systemic ailments other than diabetes, who were on antibiotics or anti- inflammatory drugs, smokers and pregnant and lactating women were excluded. Investigator KRR screened and randomly allocated the patients in sealed envelopes into two test groups. Investigator CG performed the surgeries. (Fig 1). Subjects allocated to Group A were administered 600 mg ALA (Inlife Pharma Private Limited, Himayatnagar, Hyderabad, India) thrice daily for 3 months after flap surgery (Fig2) whereas only open flap debridement was performed in patients allocated under Group B. (Fig3) Clinical parameters assessed were the Sulcular bleeding index (SBI), Pocket probing depth (PPD) and Clinical attachment level (CAL) The clinical examination was done using a customized stent and University of Carolina (UNC-15) probe. The patients were examined at baseline, 3months and 6months after periodontal surgery. Both Hba1c and SOD levels were recorded similarly. The primary outcome for the study included the biochemical parameters (Hba1c and SOD) and the clinical parameters were the secondary outcomes

assessed. Random blood samples (2ml) were collected by venepuncture of antecubital vein. About 1 ml each was placed in two test tubes.1ml was used for estimating Hb A1c.10 minutes after collection 1ml of blood in the other test tube was centrifuged at 3000 rpm for 10 minutes.

The supernatant straw- colored fluid (plasma) was stored in two vials for SOD estimation. Glycated hemoglobin was assessed using spectrophotometer (Erbachem 5 plus v2Transasia Biomedicals Limited, Mumbai). Preop and three months postop.

Superoxide dismutase: was assessed pre and 3 months after SPT by commercial kit (Bioassay Technology Laboratories, Shanghai, China).

Reagents used

Standard Solution, Biotin-Conjugate Antibody, Streptavidin-HRP Stop Solution, Substrate Solution A, Substrate Solution B, Wash Buffer Concentrate (25x). The patients were instructed on both mechanical and chemical plaque control. They were examined 2 months after phase I therapy to finalize their participation in the surgical protocol.

The site to undergo surgery was anaesthetized using local anesthetic (2%Lignocaine HCL with 1:80,000 Adrenaline). A no 15 BP blade was used to give the crevicular and interdental incision. The muco-periosteal flap was then reflected using a periosteal elevator, and the necrotic tissue was debrided from the defect site using gracey curettes by investigator CG. After debridement, the area was thoroughly irrigated. The flap was then sutured and periodontal dressing was given. All the patients received antibiotics (Amoxicillin 500mg thrice a day for five days) and analgesics (Aceclofenac 100 mg thrice a day for five days) after post-operative instructions. The post-operative care included chlorhexidine gluconate rinses (0.12%) twice a day for 2 weeks. The sutures were removed after 2 weeks, and patients were motivated to maintain oral hygiene.

Results

Within the groups there was a marked improvement pertaining to all the variables at baseline and at 3 and 6 months. In Group A (Test Group) the PPD values were 5.42±0.67,2.92±0.79 and 2.33±0.49 (P<0.001) and in Group B (Control group) it was 6.00±0.95, 2.75±1.14 and 2.33±0.65 (P<0.001). The CAL values in the test group was 3.50±0.80,1.25±0.87, 0.58 ±0.67(P<0.001) and in the control group was 3.83±0.72, 0.92±1.00, 0.42 ±0.51, (P<0.001). The SBI values in the test group was 3.67±0.78, 0.17±0.39, 0.08±0.29, (P<0.001) and in the control group it was 3.67±0.78, 0.25±0.45, 0.17±0.39 (P<0.001). All the clinical parameters showed significant improvement at all the tested time intervals in both the groups. (Table 1). The HbA1c values in the test group was 6.63±0.29, 4.37±0.62 and 5.46±0.60 (P<0.001) and in the control group it was 6.73±0.25, 6.11±0.61and 5.87± 0.65 (P<0.001). Pertaining to the SOD values in Group A it was 328.80±56.83, 175.11±45.85 and 204.65±43.27 (P<0.01) and in Group B it was 250.83±47.29, 261.84±113.03 and 231.25±82.85 (P<0.01). The Biochemical parameters also showed significant improvement within the groups. (Table 1). Nevertheless, when a comparison between the groups was done, it was found that both the clinical and biochemical parameters did not show any statistically significant results, though in Group A there was a marked improvement in both the HbA1c and SOD levels at 3 months when compared to Group B (Table 2).

Discussion

Periodontitis is an immunoinflammatory disorder initiated by the plaque biofilm and a predominantly gram -negative microflora.[4] It can potentiate the spread of infection via the blood stream and hence has been considered as a risk factor for many systemic diseases like diabetes, coronary

heart disease, rheumatoid arthritis etc. [5] The incidence of periodontitis is more in diabetic patients. It causes impaired glucose tolerance in prediabetics who as time progresses become diabetic if proper counselling and treatment is not initiated.[6] It is a proven fact that the diseases are interlaced, and many studies conducted assert the same. In a study conducted on 2273 Pima Indians aged above 15 years, it was observed on dental examination, that 60% of the samples with non- insulin dependent diabetes mellitus (NIDDM)had periodontitis and 36% who were not diabetic did not. Therefore, it was concluded that periodontitis could be associated with NIDDM.[7]

Another study assessed if the risk and progression of alveolar bone loss is greater in uncontrolled diabetics when compared to well controlled or nondiabetic subjects. The poorly controlled group had HbA1c greater than 9%; the better controlled group had HbA1c< 9%. Data from this longitudinal study pointed out odds ratio for the uncontrolled group was 5.3 and for subjects with better control was 2.2. These results suggested that poorer glycemic control led to an increased risk of bone loss and disease progression.[8]

HbA1c reflects average plasma glucose over previous 8 - 12 weeks. As it can be assessed at any time of the day and at 3month intervals it has become a more sought -after diagnostic and screening test for diabetes.

A study was done on 36 diabetic patients who received SRP to treat periodontitis during an 18-month period. 36 more diabetic patients were included in the control group wherein SRP was not performed. After a 9month observation period when HbA1c levels were assessed, there was an improvement of 17.1% in the SRP when compared to 6.7% in the control group.[9]

Another study was done to evaluate the role of NSPT on glycated hemoglobin levels in prediabetic patients with periodontitis. Sixty prediabetic patients were split uniformly. The case group underwent SRP whereas in the control group no treatment was given. The clinical parameters (OHI, PI, MGI, CAL, PPD) and the systemic variables HbA1c, fating blood glucose and lipid profile were assessed pre and 3 months post SRP. There was significant improvement in periodontal parameters in the case group, also HbA1c levels decreased significantly after SRP ($P < 0.05$).[10]

Well controlled diabetic patients show favorable response to surgical periodontal therapy pertaining to the clinical periodontal variables. But the effects of SPT on HbA1c levels have not been studied. In this study HbA1c levels were assessed pre and postoperatively. Within the groups (both the test and control) the HbA1c levels reduced significantly($p<0.001$). (Table1). However, an Intergroup comparison pointed out that the HbA1c levels after 3 months in Group A reduced significantly from baseline (6.63± 0.29 to 4.37±0.62) rather than Group B (6.73 ± 0.2 to 6.11 ± 0.61) which was statistically significant (P= 0.03). There was an increase in the HbA1c levels from 3 to 6 months in Group A (4.37±0.62 to 5.46±0.60), rather than in Group B (6.11 ± 0.61to 5.87 ± 0.65), however the values obtained at 6 months between the groups were not significant (P= 0.63) (Table 2)

Some researchers evaluated the response to SPT in both diabetic and nondiabetic patients. 20 diabetic and 20 nondiabetic patients participated. The clinical parameters (gingival status, probing pocket depth (PD), clinical attachment level (CAL), mobility, and position of the gingiva) were studied after 6 months. It was observed that both the groups showed an improvement in PD and CAL with no significant statistical difference between them, showing that well controlled diabetics respond well after surgery.[11]

Yet another study researched on 20 patients with diabetes, and 20 controls with the same amount of periodontal

destruction. All the samples underwent SRP. After 3 months sites with gingival bleeding and probing pocket depths >5mm were scheduled for periodontal surgery using modified Widman flap technique. Reassessment of the clinical parameters was done at 12,24 and 60 months. During the 5year study period, all the samples had good oral and periodontal health and the frequency of sites exhibiting recurrence was the same in both the groups.[12]

In this study both the groups underwent modified widman flap surgery. The clinical parameters PPD, CAL, SBI significantly reduced within both the groups, which was statistically significant ($p<0.001$) (Table 1) However, a comparison between the groups did not yield significant results. (Table2).

Oxidative stress is very commonly associated with serious ailments of the human body. It is a state associated with excessive free radicals which cause deleterious effects on the host. The free radicals like superoxide anion, peroxide and hydroxyl radicals accentuate tissue damage by causing undesirable changes in the DNA, the protein and lipid moieties, leading to severe tissue damage and cell apoptosis. [13-15]

Superoxide dismutase levels (SOD) are often observed to be increased in diabetic individuals rather than in healthy subjects. In a study including 17diabetic patients with periodontitis (DMCP),17 patients with periodontitis only (CP),18patients with diabetes only (DMPH) and 17 healthy controls (PH) the gingival SOD levels and serum glucose and lipid levels were assessed. The SOD levels in the gingiva were more in the DMCP and DMPH groups when compared to the CP and PH groups. Thus, it was inferred that there was a correlation between SOD levels, and Diabetic and periodontal status. The authors concluded that the higher SOD levels in diabetics could be an adaptive function of the tissues.

Another study was done to assess the SOD and total antioxidant capacity (TAOC) in the serum of diabetic patients, and heathy subjects with and without periodontitis. Each group comprised of 50 subjects. The results showed that the TAOC levels were more in the healthy group without periodontitis rather than the other two groups. However, the SOD levels were found to be higher in the diabetic patients which could be a protective mechanism of the tissues against oxidative stress.[16]

In this study, within the groups the SOD levels decreased, nevertheless, the results were more significant in Group A ($p<0.001$) when compared to Group B ($p=0.06$). When an intergroup comparison was made, the SOD values in Group A reduced significantly from baseline to 3 months post-surgery (328.80± 58.63 to 175.11± 45.85) when compared to Group B wherein there was a slight increase in SOD levels (250.83 ± 47.29 to 261.84±113.03) which was statistically significant (P= 0.02). The SOD levels increased slightly from 3 months to 6 months in Group A (175.11± 45.85 to 204.65±43.27), rather than in Group B (261.84±113.03 to 231.25±82.85), however the values obtained at 6 months between the groups were insignificant (P= 0.53) (Table 2).

ALA is minimally available through dietary sources. However, its administration exogenously has been observed to improve the glucose metabolism in diabetics.[17] In a study thirty-six male rats were divided into control (C), experimental periodontitis (PED), periodontitis treated with ALA (P-ALA), and periodontitis treated with ALA and VitC (P-ALA/VitC) groups. To induce periodontitis the first mandibular molars of the rats were sutured submarginally for 5 weeks. After the 5week period the ligatures were removed, and the rats were fed on ALA and Vit C (5omg/Kg each) for 15 days. Then they were ethuanised and the tissues obtained were sent for biochemical and histological analysis. It was observed that Malondialdehyde (MDA) and 8-hydroxydeoxyguanosine

(8-OHdG) levels were lower in both P-ALA and P-ALA/VitC groups compared to the PED group. Also, the reduced glutathione (GSH) levels were more in the P-ALA and P-ALA/VitC groups compared to the PED group. The histological analysis showed that in the P-ALA and P-Ala/Vit C groups the periodontal tissue destruction was inhibited in comparison to the PED group.[18]

Another study evaluated the benefit of systemic administration of ALA after SRP on serum resistin levels and Glycated Haemoglobin (HbA1c) in patients with diabetes and periodontitis. 40 patients were equally split into two groups A and B. Patients in group A received 600 milligrams of ALA thrice a day for 3months post SRP, and the patients allocated to Group B underwent SRP only. The serum resistin and HbA1c levels as well as the GI, PPD and CAL were assessed at baseline and 3 months post SRP. It was concluded that test group A subjects showed improvements in all the parameters after 3 months, when compared to Group B. (38) In this study also in Group A the patients received 1800 mg/day of ALA in 3 divided doses for 3 months after surgery.[19]

Yet another study determined the effect of 600 mg/day of ALA on the markers of oxidative stress (OxS), inflammation and RAGE in 135 elderly diabetic patients. The patients were divided into experimental group (EG) comprising of 50 subjects, Control group (CG)comprising 35 subjects and Placebo group (PG) having 50 subjects.

Pre and post treatment glycosylated hemoglobin (HbA1c), RAGE, 8-isoprostane, superoxide dismutase (SOD), glutathione peroxidase (GPx), total antioxidant status (TAS), and inflammatory (CRP, TNF-a, IL6, IL-8, and IL-10) markers were obtained. There was a decrease observed in HbA1c levels in the experimental and placebo groups when compared to the control group, though the results were insignificant ($p < 0.05$). It was concluded that ALA administered 600 mg/day for 6 months did not show superior results to placebo group pertaining to the biochemical variables in older adults with diabetes. The authors thus concluded that ALA should be administered in higher doses to elicit a more beneficial effect.[20]

As per our understanding no studies have been undertaken on the role of ALA as an adjunct after flap surgery on superoxide dismutase levels in diabetic patients. In this study patients on systemic ALA for 3 months (Group A) showed improvement in HbA1c levels and SOD levels 3 months post-surgery rather than in Group B. Further there was an increase in both HbA1c and SOD levels in Group A from 3 months to 6 months. This could be because patients had stopped taking ALA systemically at 3 months. Hence 6 months post-surgery no significant results were seen, pertaining to all the parameters between both test groups. (Table2).

Limitations of the study: The study could have been for 9 months, and ALA could have been administered for a longer time to achieve significant outcome.

Conclusion

It was observed in this study that test group A showed significant improvements in SOD and HbA1c levels,3 months after surgery, rather than in Group B. However, at 6 months though the SOD and HbA1c values increased slightly in Group A over Group B, intergroup comparison yielded insignificant results. Perhaps administering ALA for 6 months would have validated the study better.

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Legend Table and Figure

Table1: Intragroup comparison of clinical and biochemical parameters at various time intervals in Group A and Group B using Friedman's test

Group	Variable	Baseline		3 months		6 months		Chi square	P value	Post hoc analysis
		Mean	SD	Mean	SD	Mean	SD			
Group A (Test Group)	PPD	5.42	0.67	2.92	0.79	2.33	0.49	22.29	<0.001**	1>2,3
	CAL	3.50	0.80	1.25	0.87	0.58	0.67	22.37	<0.001**	1>2>3
	SBI	3.67	0.78	0.17	0.39	0.08	0.29	22.40	<0.001**	1>2,3
	HbA1c	6.63	0.29	4.37	0.62	5.46	0.60	18.42	<0.001**	1>2,3
	SOD	328.80	58.63	175.11	45.85	204.65	43.27	20.67	<0.001**	1>2,3
Group B (Control Group)	PPD	6.00	0.95	2.75	1.14	2.33	0.65	21.33	<0.001**	1>2,3
	CAL	3.83	0.72	0.92	1.00	0.42	0.51	22.29	<0.001**	1>2,3
	SBI	3.67	0.78	0.25	0.45	0.17	0.39	23.40	<0.001**	1>2,3
	HbA1c%	6.73	0.25	6.11	0.61	5.87	0.65	21.57	<0.001**	1>2>3
	SOD U/ml	250.83	47.29	261.84	113.03	231.25	82.85	7.17	0.06 NS	-

**P<0.05 statistically significant,NS-Not significant;SD-Standard deviation; PPD-Probing pocket depth;CAL- Clinical Attachment Level; SBI-Sulcular Bleeding Index;HbA1c%- Glycosylated Haemoglobin Percentage, SOD U/ml - Superoxide Dismutase.units/millilitre

Table 2: Intergroup comparison of clinical and biochemical parameters in Group A and Group B using Mann Whitney Test

Time interval	Variable	Test group (Group A)		Control group (Group B)		U	P value
		Mean	SD	Mean	SD		
Base line	PPD	5.42	0.67	6.00	0.95	49.00	.15NS
	CAL	3.50	0.80	3.83	0.72	56.00	.32NS
	SBI	3.67	0.78	3.67	0.78	72.00	1.00NS
	HbA1c%	6.63	0.29	6.73	0.25	57.00	.38NS
	SOD U/ml	328.80	58.63	250.83	47.29	55.50	.31NS
3 months	PPD	2.92	0.79	2.75	1.14	62.50	.56NS
	CAL	1.25	0.87	0.92	1.00	55.50	.31NS
	SBI	0.17	0.39	0.25	0.45	66.00	.62NS
	HbA1c%	4.37	0.62	6.11	0.61	32.00	.03**
	SOD U/ml	175.11	45.85	261.84	113.03	33.00	.02**
6 months	PD	2.33	0.49	2.33	0.65	70.00	.89NS
	CAL	0.58	0.67	0.42	0.51	63.50	.58NS
	SBI	0.08	0.29	0.17	0.39	66.00	.55NS
	HbA1c%	5.46	0.60	5.87	0.65	26.00	.63NS
	SOD U/ml	204.65	43.27	231.25	82.85	61.00	.53NS

**P<0.05 statistically significant,NS-Not significant;SD-Standard deviation; PPD-Probing pocket depth;CAL- Clinical Attachment Level; SBI-Sulcular Bleeding Index;HbA1c%- Glycosylated Haemoglobin Percentage,;SOD U/ml-Superoxide Dismutase.Units/millilitre.

Fig 1: CONSORT Flow Diagram

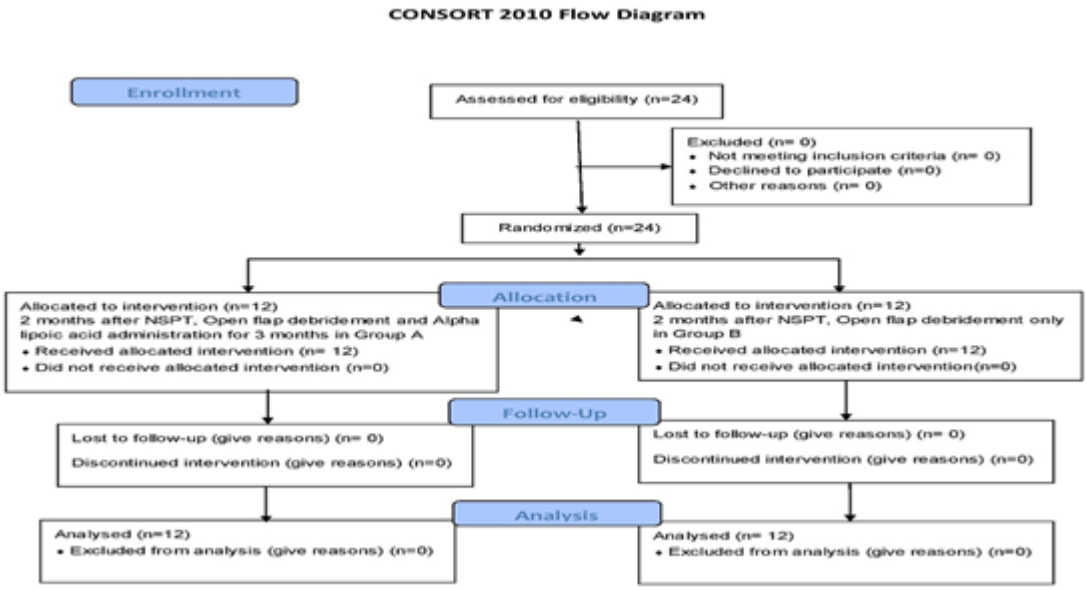

Fig 2: Alpha Lipoic acid supplement

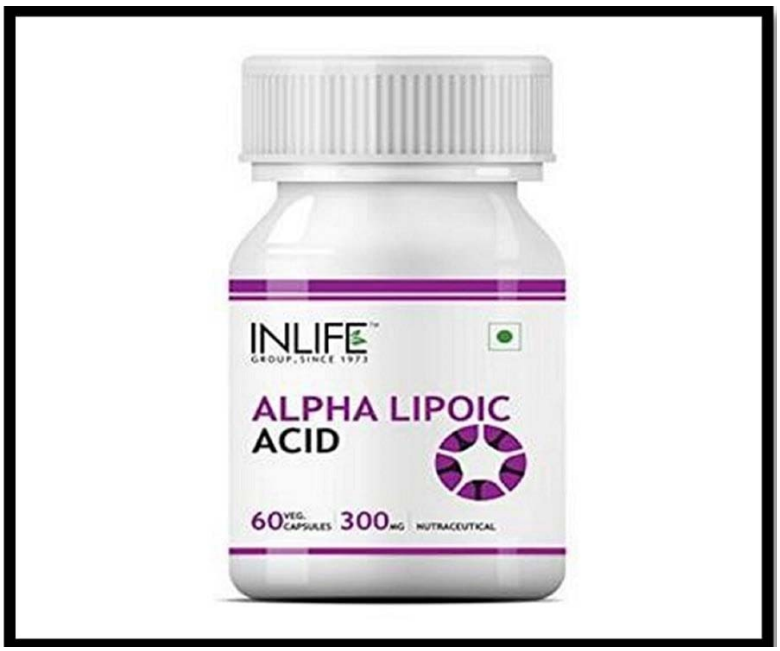

Fig 3: Open flap debridement