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Effectiveness of Alpha Lipoic Acid on Postoperative Sequelae on Lower third molar surgery -A Randomized control clinical trial

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ABSTRACT

Introduction: Alpha-lipoic acid (ALA) is a compound found in every cell of the human body produced in mitochondria of cells. ALA is powerful antioxidant, and has anti inflammatory and has excellent wound healing property.Many clinical trials has been done to prove the effect of ALA in particular diseases , including diabetic neuropathy, obesity, schizophrenia, alzheimer's disease, Multiple sclerosis, abnormalities in pregnancy and organ transplantation. Here in this randomized control trial, we are going to check the effectiveness of alpha lipoic acid and compare it with corticosteroids in post operative swelling and healing in third molar surgery.

Aim: To check the effectiveness of alpha lipoic acid in comparison with corticosteroids in swelling and postoperative healing on patients undergoing third molar surgery.

Materials And Methods: The total number of participants in this study is 200 undergoing third molar impaction surgery (Class 1,Class 2 position B- Mesio angular impaction of third molar). Before study,participants were informed about the study by the principal investigator and gave informed written consent.

Case group is 100 patients subjected with 300 Mg of Alpha lipoic acid for 7 days

Control Group is 100 patients given prednisolone 5 mg (wysolone 5) for 3 days

Results: Out of 200 patients, the group which uses alpha lipoic acid has good wound healing when compared to the patient who uses corticosteroids. The inflammation is found to be less in patients who use alpha lipoic acid than corticosteroids.

Conclusion: It can be concluded that steroids can be extremely beneficial, and have serious side effects. ALA has excellent wound healing properties and acts on inflammation similar to corticosteroids but with little or no adverse effects. It's a good idea to understand the benefits and risks of corticosteroids and replace them with alpha lipoic acid which prevents inflammation and promotes wound healing.

Keywords: *Alpha lipoic acid, impaction surgery, healing, dental , age*

INTRODUCTION

The Surgical removal of wisdom teeth is a common surgical procedure in oral and maxillofacial surgery [1] and is associated with various adverse effects like pain , inflammation and trismus, [2]these patients experience significant postoperative distress [3], anxiety and thereby overall decline in their quality of life (QoL) [4]. There are various methods adopted for controlling the healing [5] and inflammatory response associated with the third molar surgery such as using different surgical techniques [6] , closure modifications [7] , with or without incorporation of drains, [8]mouth washes ,application of gels , gauze pack, various pharmacological against like steroids [9] , serratiopeptidase [10] , ice packs, packing of socket with different therapeutic agents [11] , physical therapeutic methods such as cryotherapy , TENS therapy and LASER application . Corticosteroids like dexamethasone and prednisolone reduces the manifestations of inflammation such as swelling, irritation redness, warmth, and tenderness.where the use of it has many potential complications include myopathy, ,elevated sugar level, peptic ulcer, cataract, glaucoma ,central nervous system effects, osteoporosis, altered distribution of body fat, lower resistance to infection, suppression of pituitary and adrenal function, hypertrichosis and poor wound healing [12].

Alpha lipoic acid (ALA), or thioctic acid or 1,2-dithiolane-3-pentanoic acid [13], is a compound commonly found in mitochondria, necessary for different enzymatic functions. ALA was first isolated by Reed and coworkers in 1951 as an acetate replacing factor [14]. ALA is an organosulfur compound [15] obtained from plants like , animals, and humans. ALA plays an important role in various chemical reactions in Krebs cycle, by acting as a cofactor for some enzymatic complexes which are involved in energy transfer [16]. Alpha Lipoic acid is present in different foods like broccoli, spinach and meat [16]. ALA acts as an antioxidant as it improves and restores the intrinsic antioxidant systems and their production in the human body. It also efficiently removes heavy metals and toxins that are responsible for oxidative stress from blood stream [17–20].It acts as an enzymatic cofactor [21] and is also involved in glucose and lipid [22] metabolism and manages gene transcription[23]. The bioavailability of ALA is 30%. The absorption takes place via the small intestine and is distributed to the liver through the portal vein and through the systemic circulation , it reaches the other organs in the body [24] . Alpha Lipoic acid and its reduced form, Dihydrolipoic acid (DHLA), is referred to as "a universal antioxidant" and they functions in both membrane and aqueous phases.[25]

Surprisingly, ALA has numerous clinically valuable properties [26]. A lot of clinical trials have proven that its efficiency in particular diseases like diabetic neuropathy,Rheumatoid arthritis, obesity, schizophrenia, Alzheimer's disease, Multiple Sclerosis, abnormalities in pregnancy,Alcoholic liver problem and organ transplantation, with little or no adverse effects.[27] Researchers have proven that ALA seems to be a promising agent to improve quality of life, and neuropathic symptoms by reducing the use of rescue drugs, which are comused by patients with chronic illness[28].The aim of the study is to compare the effects of alpha lipoic

acid and corticosteroids in post operative healing and swelling in third molar surgery.

MATERIALS AND METHODS

Study design

The current study was a single centered, double-blinded,randomized clinical trial, performed between August 2021 and January 2022 at Saveetha Dental college and hospitals,Chennai, Tamil Nadu.

Participants

The sample size is 200 (case group-100;control group_100) who were consecutively and randomly recruited from normal healthy subjects (ASA I, according to the American Society of Anaesthesiology classification), who required the surgical removal of an impacted third molar in the mandible.All the impacted mandibular third molars were classified according to Winter's classification and Pell and Gregory classifications using Panoramic radiographs.(fig 1) The reasons for extraction and location of impacted teeth were also recorded.

The inclusion criteria were: (1) age between 18 and 25 years with good general health; (2) the presence of impacted third molar in the mandible with mesioangular impaction, class I and II with position, A and B impaction; (3) absence of pericoronitis or signs of inflammation during the last 30 days. The exclusion criteria were: (1) the presence of any systemic disease; (2) consumption of Corticosteroids or other medications for any other illness; (3) consumption of any immunosuppressive or anti-inflammatory drugs in 3 months prior to the study; (4) status of pregnancy or lactation or usage of oral contraceptives; (5) previous history of excessive drinking;or smoking habit (6) allergy to local anesthetic.

The study was performed according to the CONSORT guidelines (Consolidated Standards Of ReportingTrials) Patients were excluded if they did not complete the study or if they did not follow the study protocol or in case of surgical time exceeding 30 minutes. All subjects were informed about the objectives and procedure of this study, and a written consent was also obtained from each participant. Preoperative data were obtained from the subjects: Demographics (age, sex), indications for surgical removal , location of the third molar (left or right), type of impaction, and the degree of impaction.

The participants were divided into 2 groups - case group and control group

Case Group is 100 patients subjected with 300 Mg of Alpha lipoic acid tablets(Health vit) orally for 7 days.

Control Group is 100 patients given prednisolone 5 mg tablets orally (wysolone 5) for 3 days.

Operative Procedure: All surgeries were performed by the same surgeon to avoid any possible bias such as surgeon variability. Surgery was carried out under local anesthesia with 2% lignocaine hydrochloride with 1:2,00,000 adrenaline. The inferior alveolar nerve and lingual nerve anesthesia were achieved using the conventional technique, whereas the standard buccal nerve block technique was used to achieve long buccal nerve anesthesia. An envelope mucoperiosteal flap was raised for access (fig 2). The buccal guttering technique was used to expose and the bone was removed with a round bur in a straight hand-piece under copious irrigation with normal saline. In all subjects ,tooth sectioning and removal of the third molar was performed, granulation tissue was removed and following tooth delivery, copious irrigation of the surgical site with normal saline was done. The flap was repositioned and secured with 3-0 black silk interrupted sutures.(fig 2)

FIG 1: represents the orthopantomogram showing the mesioangular impaction of 48 with position A and class 1.

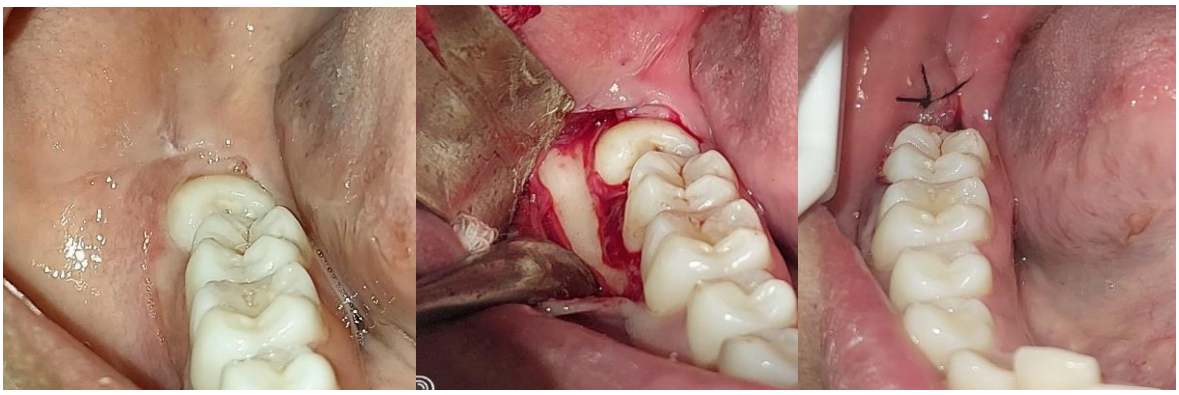

FIG 2: represents the preoperative (left) and intra operative image for removal of 48 (center) and closure of 48 with 3-0 Braided silk sutures (right)

Both the groups were subjected to postoperative medications antibiotics Amoxicillin 500 mg (CIPMOX 500) thrice a day after food for 3 days; analgesic Aceclofenac 100 mg and paracetamol 325 mg (Zerodol p) twice a day after food for 3 days and pantoprazole 40 mg tablets (PAN 40) for twice a day before food for 3 days. Immediately after surgery, postoperative instructions were given to the patients. They were instructed to follow a soft diet for 3 days and advised not to do forceful activities like spitting,using chewing gums, poking the surgical site with tongue. Patients were also encouraged to maintain good oral hygiene and were informed about possible surgical complications such as pain, swelling, discomfort , trismus and fever and the risks due to drug intolerance like gastrointestinal disturbances . Throughout the study, all patients were assisted by the surgical team for any postoperative complications, like infection, pain, fever, or other complications due to the drug intolerance.

Randomization and masking

At time of randomization, the 200 patients were randomly allocated to receive either alpha lipoic acid 300 mg Alpha lipoic acid tablets(Health vit) for 1 week after impaction surgery at the dose of 300 mg twice/day orally (case group), while the control group received prednisolone 5 mg (wysolone 5) tablet twice/day for 3 days .Allocation to either one of the two groups was in a 1:1 ratio. The principal investigator and participants were both blinded in this trial. The participants were monitored for possible side effects or drug discontinuation during the follow-up.

Ethical consideration

The study purpose and procedures were explained to all enrolled participants and a written informed consent was obtained from each participant. The study was approved by the Ethical and Research Committee of the Saveetha

Dental College. (IHEC/SDC/2002/21/OSURG/590)

Outcome measures

After surgery,precise details of each operation were documented, with the duration of surgery amount of local anesthesia given. The outcome variable measured was post operative swelling and post operative healing

Swelling Index

Facial width was determined preoperatively using the tape measuring method described by Gabka and Matsumura(fig 3)

Three measurements were made as follows:

Lateral canthus of the eye to the angle of the mandible ipsilaterally (line A)

The tip of the tragus to the ipsilateral oral commissure (line B),

The tip of the tragus to the soft tissue pogonion ipsilaterally (line C),

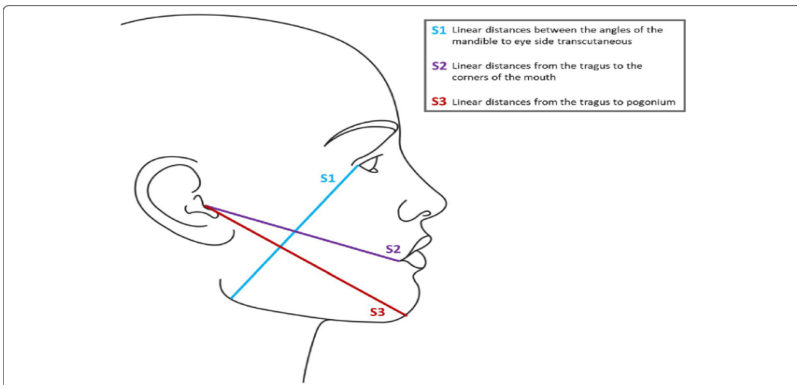

FIG 3: represents the measurements of Facial width using the tape measuring method described by Gabka and Matsumura.

Initially Preoperative measurement was taken and after postoperative measurements were taken after 2 nd and 7 th postoperative day. (fig 4)The three measurements were taken , and the average was recorded in centimeters. All measurements were done by a single operator for all subjects and recorded.

FIG 4: represents the swelling recorded on case group on postoperative third day and seventh day respectively

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Healing Index

The secondary outcome is Healing index was recorded at 2nd and 7 the postoperative day during follow up sessions. (fig 5)

FIG 5: represents the post operative healing of the case group on third day (left) and seventh day (right) respectively

Scores for Healing Index

Healing index 1: Very Poor. Has 2 or more of the following: Tissue color: >= 50% of gingiva red Response to palpation: bleeding granulation tissue: present incision margin: not epithelialized, with loss of epithelium beyond incision margin suppuration present

Healing Index 2: Poor tissue color: >= 50% of gingiva red response to palpation: bleeding granulation tissue: present incision margin: not epithelialized, with connective tissue exposed

Healing Index 3: Good tissue color: >= 25% and < 50% of gingiva red response to palpation: no bleeding granulation tissue: none incision margin: no connective tissue exposed

Healing Index 4: Very Good tissue color: < 25% of gingiva red response to palpation: no bleeding granulation tissue: none incision margin: no connective tissue exposed

Healing Index 5: Excellent tissue color: all tissues pink response to palpation: no bleeding granulation tissue: none incision margin: no connective tissue exposed

TABLE 1: represents the scoring of healing index used in this study Healing was assessed using the standardized index by Landry, Turnbull, and Howley

Healing Index	Tissue colour	Response to palpation	Granulation tissue	Incision margin
Very poor 1	: >= 50% of gingiva red	Bleeding	Present	Not epithelialized, with loss of epithelium beyond incision margin
Poor 2	>= 50% of gingiva red	Bleeding	Present	Not epithelialized, with connective tissue exposed
Good 3	>= 25% and < 50% of gingiva red	No bleeding	None	No connective tissue exposed
Very good 4	<25% of gingival red	No bleeding	None	No connective tissue exposed
Excellent 5	All tissue pink	No bleeding	None	No connective tissue exposed

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RESULTS

Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows (version 2). The independent t test and Mann-Whitney test were used to measure difference in swelling and healing respectively. The critical level of significance was set at $P < 0.05$.(table 2 and 3).

Table 2 shows that the mean differences in swelling measurement between pre operative and 2nd day for Group A was 4.04±2.332 while for Group B, 3.16±1.635, which was statistically significant with the p value of 0.004 (<0.005). The mean differences in swelling measurement between 2nd day and 7th day for Group A was 1.16±1.172 while for Group B, 1.12±1.227, which was statistically significant with the p value of 0.005 (p =0.005). This shows that Group A had a significant reduction in swelling at both 2nd and 7th day of intervention.(fig 6).

TABLE 2: Differences in swelling between Group A and Group B

Groups	Swelling difference b/t pre op and 2nd day			Swelling difference b/t 2nd and 3rd day		
	Mean	SD	P value 0.004*	Mean	SD	P value 0.005*
GroupA (n=100)	4.04	±2.332		1.16	±1.172	
GroupB (n=100)	3.16	±1.635		1.12	±1.227	

*Significant difference exists between groups

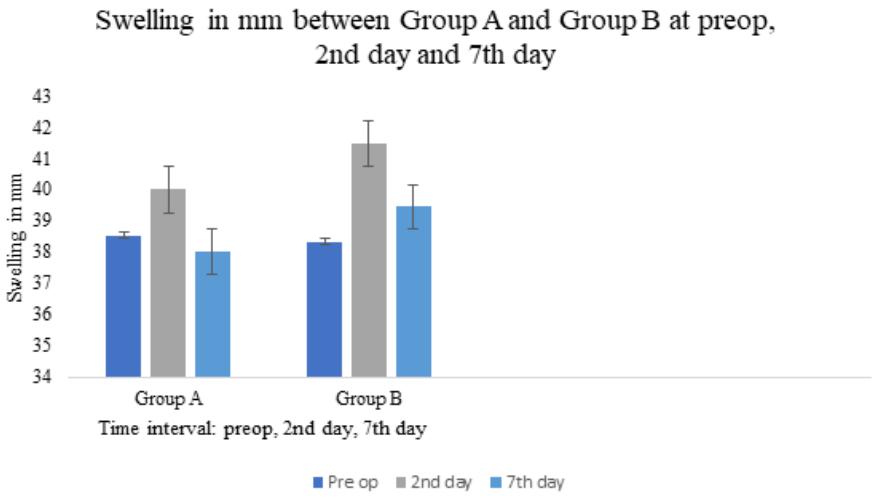

FIGURE 6: shows the graphical representation of differences in the swelling measurement at time intervals, preoperatively, 2nd day and 7th day.

Table 2 shows the mean rank of the healing index between Group A and Group B were 132.82 and 70.18 respectively with the p value of 0.000 (<0.005) at 2nd day. For 7th day, the mean rank of the healing index between Group A and Group B were 131.91 and 71.09 respectively with the p value of 0.000 (<0.005). The higher mean rank in Group A with statistically significant value shows that it has better healing than Group B both at 2nd and 7th day. (fig 7).

TABLE 3: Differences in healing between Group A and Group B

Groups	Healing in 2nd day		Healing in 7th day	
	Mean Rank	P value	Mean Rank	P value
GroupA(n=100)	132.82	0.000*	131.91	0.000*
GroupB(n=100)	70.18		71.09	

*Significant difference exists between groups

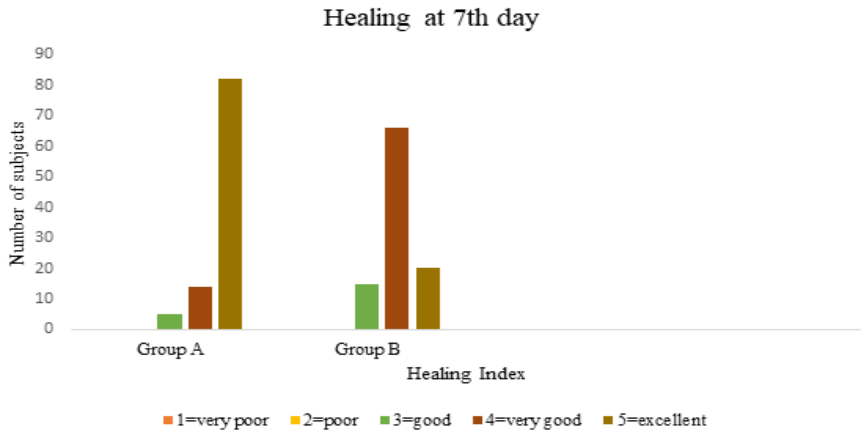

FIGURE 7: shows the distribution of subjects with different healing index scores at post operative 7th day

DISCUSSION

During recent years, corticosteroids have been demonstrated to be effective drugs for the postoperative management of swelling following the surgical removal of impacted third molars. However, several studies have demonstrated adverse drug effects in patients on corticosteroids like peptic ulcer, immune suppression, water and electrolyte balance, muscular atrophy, osteoporosis, obesity, Cushing syndrome[29], avascular osteonecrosis, lessened resistance to infection, hirsutism, amenorrhea, acne, hyperglycemia or hypertension [30,31]Corticosteroids exert potent anti-inflammatory effects and have been used in different dosage regimens and routes of administration to reduce the inflammatory effects of surgical removal of third molars.[32]Over the past 60 years, the use of corticosteroids for impaction surgery has been extensively studied in different formulations, doses, routes, and sites of administration [25]. These corticosteroids include dexamethasone (oral/p.o.), dexamethasone acetate (intramuscular), dexamethasone sodium phosphate (iv and im), methylprednisolone (p.o.), methylprednisolone acetate, and methylprednisolone sodium succinate (both iv and im). A recent review concluded that there are benefits that can be obtained from the short-term use of corticosteroids in reducing these inflammatory sequelae with no adverse effects observed [25] Ngeow and Lim [25] reviewed 34 studies for different routes of administering corticosteroids which includes intravenous, intramuscular, oral and submucosal administration. They found that benefits can be obtained from the short-term use of corticosteroids in terms of pain, swelling, and trismus control following third molar surgery, with no adverse effects observed. However, another study by Chopra et al found that 19% of all patients experienced adverse reactions after post-operative oral administration of 0.5 mg of betamethasone[33] . In a retrospective study,Thoren et al reported that the rate of deterioration in surgical wound healing in patients who received perioperative steroids doubled (6.0%) that in patients who did not

receive steroids (2.8%), but this difference was not statistically significant. [34]

The use of corticosteroids may cause a negative feedback effect on the suppression of normal secretion of endogenous cortisol[31] .These side effects are frequently cited as a reason against the use of corticosteroids in routine clinical dentistry practice. It is time for dentists to reconsider their reluctance to use short-term corticosteroids in all minor oral surgeries [32].Because of such side effects of corticosteroids,various researches are ongoing to replace corticosteroids with appropriate drugs. This study investigates the role of alpha lipoic acid in improving healing and swelling after surgical removal of the lower third molars proved that alpha lipoic acid proved that ALA significantly promotes wound healing and controls inflammation. In this study, 300 mg Alpha lipoic acid tablets(Health vit) for 1 week after impaction surgery was found to be more effective in healing , when compared wysolone 4 mg tablets twice/day for 3 days. Surprisingly, efficiency in reduction of swelling was found to be equal in both the groups.Data from clinical trials reveals that ALA has efficient role in particular diseases like diabetic neuropathy, obesity, schizophrenia, Multiple Sclerosis, alzheimers disease, organ transplantation, and has excellent wound healing properties [35].

In the randomized, double-blind study of Ziegler et al., ALA has been shown to be effective against diabetic sensorimotor polyneuropathy (DSPN). Oral treatment of diabetic patients with mild-to-moderate DSPN with 600 mg of ALA daily increased the neuropathy deterioration score of the lower extremities after four years [33]Another study by Khalili et al., the anti-inflammatory effects of alpha lipoic acid [34] were found to be a remarkable reduction in the levels of INF-γ, ICAM-1,IL-4 and TGF-β

Sammour et al.,[36] studied the effect of alpha lipoic acid in healing after casesserian surgery, by oral administration of ALA for 6 weeks postpartum in women after primary Cesarean with hysterotomy closure with sutures, which shows reduction in the incidence and size of scar defects and promoted the healing process .

In addition, alpha lipoic acid has the potential to alleviate the symptoms of CNS-related diseases (schizophrenia and MS), [36]as well as improve lipid metabolism and promote weight loss in obese patients., ALA has some positive results in Multiple Sclerosis patients, while reducing the levels of certain proinflammatory factors associated with MS progression. ALA is also effective in reducing the levels of inflammatory factors and showing protective effects against hypoxia and oxidative stress in organ transplantation[37] patients.A randomized, double-blind, placebo-controlled trial done by Freimer shows the effect of [38] oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy.

Another study by Renata Alleva evaluated the adjuvant effects of alpha-lipoic acid in patients affected by chronic wounds undergoing Hyperbaric oxygen therapy treatment found that alpha lipoic acid accelerates wound healing by interacting with free radicals[39]. Taken all into consideration, ALA may be regarded as one of the ideal drug for replacing corticosteroids in impaction surgery.During the last few decades,researches are conducted with the advent of newer drugs in reducing postoperative discomfort by helping to reduce pain ,swelling, trismus following surgery without causing adverse effects. Identifying even more effective drugs or combinations of drugs for the management of pain, swelling and healing following third molar surgery, with the purpose of discovering treatment strategies other than NSAIDs or corticosteroids, should be encouraged. This study suggests that alpha lipoic acid used as postoperative therapy after third molar surgery shows favorable outcome in the management of postoperative complications in third molar surgery.Alpha lipoic acid was found to be safe and simple to use in the postsurgical management of discomfort following third molar surgery. The results of this preliminary study are encouraging; however, more controlled and robust clinical trials with larger sample size and different impaction levels must be designed for investigating ALA therapeutic effects. required to provide a better understanding of the potential

benefits of ALA in postoperative therapy following impacted third molar surgery.

CONCLUSION

Out of 200 patients, the group which uses alpha lipoic acid has good wound healing when compared to the patient who uses corticosteroids.Out of 200 patients, the group which uses alpha lipoic acid has good wound healing when compared to the patient who uses corticosteroids. The inflammation is found to be less in patients who use alpha lipoic acid than corticosteroids..It can be concluded that steroids can be extremely beneficial, and have serious side effects. It's a good idea to understand the benefits and risks of corticosteroids and replace them with alpha lipoic acid which is cost effective and has no adverse effects. The usage of alpha lipoic acid in third molar surgery for preventing inflammation and for better wound healing should be encouraged for future research.

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