ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 04, pp.3336-3340, April, 2019

DOI: https://doi.org/10.24941/ijcr.34921.04.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

COMPARING THE ROLE OF OZONE GEL AND PLATELET-RICH FIBRIN (PRF) WITH CONVENTIONAL METHOD IN HEALING OF SURGICALLY EXTRACTED LOWER THIRD MOLAR SOCKET

[1,*]Dr. Vidhya Bharathy, S., [2]Dr. Srinivasan, H., [3]Dr. Loganathan, S. [4]Dr. Jawahar Babu, S. and [5]Dr. Tamil Selvi, S.

[1]Priyadarshini Dental College and Hospital, India
[2] Head of the Department, Oral and Maxillofacial Surgery, Priyadarshini Dental College and Hospital, India
[3]Professor, Oral and Maxillofacial Surgery, Priyadarshini Dental College and Hospital, India
[4]Senior Lecturer, Oral and Maxillofacial Surgery, Priyadarshini Dental College and Hospital, India

ARTICLE INFO

Article History:
Received 20th January, 2019
Received in revised form
16th February, 2019
Accepted 24th March, 2019
Published online 30th April, 2019

Key Words:

Impacted Third Molars,
Ozone, PRF, Metronidazole,
Swelling, Antibiotics.

**Corresponding author:*
Dr. Vidhya Bharathy, S.,

ABSTRACT

Background: Healing followed by the surgical removal of third molar is known to cause increased discomfort to the patients. Many theories and ideas have been idealized to reduce this discomfort. Traditionally, systemic antibiotics were used. But due to the phenomena of antibiotic resistance to multiple microorganisms we are constantly on the process of discovering new methods and modifying age-old methods for the better usage of antibiotics in future by either finding a supplement or an alternative. Ozone is one of such old methods which is found to be effective. It meets all the expectations as an alternative for antibiotics and also ful fills the application of it in the needed area alone thereby, restricting the systemic use of antibiotics. Platelet rich fibrin (PRF) is well known as the gold standard material for promoting healing.In this study, topical ozone gel and platelet-rich fibrin(PRF) are compared with the conventional method to evaluate their effectiveness in the healing of surgical extraction of impacted mandibular third molars. **Materials and Methods:** A double-blinded randomized controlled clinical trial was designed involving the patients who required removal of impacted mandibular third molars. The sample size was estimated as 60 individuals with 20 in each group. Of the study groups, one received topical ozone without post-operative systemic antibiotics, another received metronidazole with PRF while the control group received systemic antibiotics. All the groups were prescribed standard analgesics for 3 days. Postoperatively, the patients were reviewed at 24 hours, 3rd day and 7th day. **Results:** Data were collected and analysis involved independent sample 't' test. The study groups, ozone gel application and metronidazole with PRF demonstrated statistically significant ($p<0.05$) reduction in post-operative pain, swelling, and incidence of alveolar osteitis with increased mouth opening. No adverse effects of ozone gel were observed in any of the patients. **Conclusion:** In this study, it is concluded, that ozone can be considered as a potent topical antibiotic with healing property and also as an adjunct analgesic.

***Citation: Dr. Vidhya Bharathy, S., Dr. Srinivasan, H., Dr. S. Loganathan and Dr. Jawahar Babu, S. and Dr. Tamil Selvi S.,* 2019.** "Comparing the role of ozone gel and platelet-rich fibrin (prf) with conventional method in healing of surgically extracted lower third molar socket.", *International Journal of Current Research*, 11, (04), 3336-3340.

INTRODUCTION

Impacted third molar is one of the major and common oral problems reported by patients due to pain. The surgical extraction of impacted tooth has been widely practiced in everyday's dental practice by oral surgeons. Postoperatively, swelling and trismus causes increased discomfort to the patient. There are many factors that can contribute to postoperative discomfort, but they all were initiated with inflammatory process as the result of trauma caused during surgery. Several ideologies have been put forward to reduce the postoperative complications such administration of corticosteroids locally or systemically, use of nonsteroidal anti-inflammatory drugs, inserting a tube drain to minimise the inflammation, using different types of incisions that can minimise the trauma to patient (Gungormus, 2002; Mehrabi, 2007; Buyukkurt, 2006; Buyukkurt *et al.,* 2005; Mocan, 1996; Walsh, 1997). With all these methods used, recently ozone has been used to find its effectiveness in controlling the inflammation, pain and promoting healing. Ozone is a natural compound consisting of three oxygen atoms and is found in nature as a form of gas in the stratosphere of the earth, with the concentration of 1–10 ppm, being continually created from and broken down into molecular O2 (Baysan, 2005; Lynch, 2008). The possible benefits of ozone aredue to its disinfectant, antimicrobial, and healing properties. Its unique properties include analgesic, antihypnotic, immunostimulant, detoxicating, and biosynthetic actions. Its painless, non-invasive nature, and relative absence of discomfort and side effects makes it an ideal treatment choice. In addition, Bocci et al. have stated that a small dose of ozone can initiate several biochemical mechanisms and reactivate the antioxidant system (Bocci, 2009; Daniluk *et al.,* 2000; Bocci *et al.,* 2012).

The topical application of ozone gel or ozonated oils are now more actively used in dentistry. In oral surgery, it has been theorized that the use of ozone can be preferred during the surgical intervention and also during post-surgery as a topical disinfectant and healing agent. Despite the increasing number of studies focusing on the effects of ozone in dentistry, the number of scientific papers revealing their usage in oral surgery and their effects on the healing of extraction sockets have not yet been evaluated scientifically. Platelet-rich fibrin (PRF) is a second generation platelet concentration is considered to be an excellent promoter of healing. PRF consists of fibrin matrix polymerized in a tetra-molecular structure along with the embodiment of platelets, leukocytes, cytokines, and the presence of circulating stem cells (Dohan, 2006; Gaultier, 2004; Simonpieri, 2004). There are limited studies on the effects of PRF on postoperative pain and swelling but are proved to have an effect on the post-operative swelling and pain (Singh, 2012; Kumar, 2014). Metronidazole is an anti-microbial agent and an effective agent in reducing the incidence of 'alveolar osteitis'. It has an effective antibacterial action against anaerobes. In this study, PRF is used along with metronidazole for its antimicrobial activity. Thus, the aim of this study is to assess, evaluate and compare the effectiveness of topical ozone gel application with metronidazole along with PRF and the conventional method of surgical extraction of third molars.

MATERIALS AND METHODS

The study was conducted as a double-blinded trial in the Department of Oral and Maxillofacial Surgery, Priyadarshini Dental College and Hospital, India.The study was presented to and was approved by the Institutional Ethical Committee Board of Priyadarshini Dental College and Hospital.

Sample selection: The procedure in toto, the materials used and their actions were well explained to the patients and a written consent was obtained. The trial was conducted in three groups with sample size estimated as n=20 in each group and the patients were randomly placed in the groups. Group A consisted of patients receiving topical ozone gel, group B consisted of patients receiving metronidazole application with PRF placed in the socket and group C being the conventional group. The inclusion criteria for the trial was patients with impacted third molar of same difficulty index and are willing to undergo the trial. The difficulty index was assessed by Pell and Gregory classification for impacted third molars. The exclusion criteria was patients who were not willing to participate in the trial. Patients with any systemic diseases or conditions, with bleeding and clotting disorders. The patients were randomly placed in the groups and were kept blinded regarding the material placed in the tooth socket to avoid bias.

The expected outcomes were measured with post-operative pain, swelling, incidence of alveolar osteitis and mouth opening.

The data collection methods were as follows:

The post-operative pain was assessed using a numeric pain rating scale

VAS (Visual Analog Scale) The severity of pain was rated by the patients. The scorings were as follows:

- Score 0 to 1 : No pain
- Score 1 to 3 : Mild pain
- Score 3 to 6 : Moderate pain
- Score 6 to 8: Severe pain
- Score 8 to 10: Very severe pain

- Interincisal mouth opening was measured in millimetres using callipers.
- Facial swelling was measured in millimetres with a non-flexible black silk threadusing the following 2 reference planes:

Swelling A to B: Canthus of the eye to angle of the mandible

Swelling C to D: Tragus of the ear to angle of the lip

- Alveolar osteitis was observed by clinical examination.

Surgical procedure

- Pre operatively, blood sample was collected from all the patients and Hb% was analysed for all the patients undergoing the procedure. Their demographic details and medical history were collected.
- The patients under the study groups as well as the control group underwent surgical removal of the impacted teeth under local anaesthesia, by asingle operating surgeon. The preoperative mouth opening and facial measurements were noted in millimetres.
- A standardized surgical procedure was adopted; Surgical site preparation with 5% povidone-iodine solution, anesthetising the inferior alveolar, lingual and buccal nerves, using 2% lignocainehydrochloride with 1:2,00,000 adrenaline bitartarate, reflection of a mucoperiosteal flap was done with a conventional Ward's incision, surgical exposure & extraction of the tooth by bone removal using a surgical drill under saline irrigation. Wound closure was performed with simple interrupted sutures using 3-0 braided non resorbable black silk.
- Post-extraction wound management varied between the study and the control groups.
  - Study group received topical ozone gel application, filling the entire socket and as a smear over the incision for 2minutes, 2 times a day, for 3 days.

Ozone gel (AQUA OZONE, Akaroa, New Zealand), a natural product composed of a suspension of un-oxidisedolive oil and medical grade ozone (a mixture of ozone and oxygen in the ratio of 0.25 parts ozone to 99.75 parts oxygen) was used for the study.

- Another study group received PRF with topical Metronidazole application filling theentire socket. Cap. Amoxicillin 500mg was prescribed twice a day for three days.

Around 5ml of whole venous blood was collected from the patients in each of the two sterile vacutainer tubes of 6ml capacity without anticoagulant. The vacutainer tubes are then placed in a centrifugal machine at 3000 revolutions per minute for 10 minutes. The middle fraction containing fibrin clot is then collected 2mm below lower dividing line to obtain the PRF.

Table 1. Pain Score As Analysed By Visual Analog Scale

		Mean	Significance
Pain score - 24 hours post op	Ozone	4.35±1.565	
	PRF	6.05±0.759	.000
	Conventional	6.60±1.046	
Pain score - 3 rd day post op	Ozone	1.55±1.538	
	PRF	4.00±0.973	.000
	Conventional	4.45±1.050	
Pain score - 1 st week post op	Ozone	.25±0.639	
	PRF	1.70±0.865	.000
	Conventional	2.80±0.696	

			Mean	Sig
24 Hours post op	A to B (mm)	Ozone	103.70±7.841	
		PRF	119.90±7.312	.000
		Conventional	120.00±9.148	
	C to D(mm)	Ozone	114.65±7.400	
		PRF	133.40±6.747	
		Conventional	135.25±9.716	.000
3rd day post op	A to B (mm)	Ozone	100.05±7.749	
		PRF	112.30±6.165	.000
		Conventional	115.60±9.338	
	C to D (mm)	Ozone	110.75±6.843	
		PRF	127.70±6.140	
		Conventional	129.55±9.389	.000
1st week post op	A to B (mm)	Ozone	96.55±8.016	
		PRF	106.50±9.622	.000
		Conventional	109.90±6.215	
	C to D (mm)	Ozone	107.00±5.694	
		PRF	120.75±5.505	
		Conventional	122.30±10.408	.000

Table 3. Mouth opening as measured as the interincisal distance in mm

		Mean	Sig
Mouth opening - 24 hours post op	Ozone	35.25±5.684	
	PRF	33.65±5.833	.016
	Conventional	30.15±5.040	
Mouth opening - 3 rd day post op	Ozone	44.00±5.037	
	PRF	42.25±5.466	.001
	Conventional	37.85±4.158	
Mouth opening - 1 st week post op	Ozone	49.25±3.127	
	PRF	49.65±5.133	.007
	Conventional	46.00±2.847	

The mechanism followed here is that fibrinogen which is initially concentrated in the high part of the tube, combines with the circulating thrombin due to centrifugation, to form fibrin. A fibrin clot is then obtained in the middle of the tube just between the red corpuscles at the bottom and a cellular plasma at the top. Platelets are trapped passively in the fibrin mesh.

The control group received systemic antibiotics

The antibiotics prescribed were

- Cap. Amoxicillin 500mg
- Tab. Metronidazole 400 mg.

Antibiotics were initiated postoperatively, 2 times a day for3 days.

Both the control and study groups received post-operative analgesics for 3 days: Tab. Aceclofenac 100mg two times a day, for 3 days. An investigator who was blinded to the study and control groups assessed the outcome parameters on 1st, 3rd and 7th days postoperatively.

Statistical analysis: The data were collected and are statistically analysed by SPSS software for Windows (version 17) with significant value of $p<0.05$

RESULTS

On statistical evaluation, Table 1 shows the pain score as analysed by Visual Analog Scale (VAS). The pain was observed significantly less in study group which received Ozone gel application followed by the group that received PRF. Table 2 shows the amount of swelling as measured from the can thus of eye to the angle of mandible and from the tragus of ear to the angle of the lip by a non-elastic black silk thread respectively. On comparison between the study and control groups, individuals who received ozone gel application showed statistically less swelling than the other two groups postoperatively. On comparing the group that received PRF with the control group, clinical significance was observed in postoperative swelling. Both the study groups which received ozone gel and PRF respectively showed statistical significance in postoperative mouth opening (Table 3).

Of all the patients who participated in the trial, none of them reported with the incidence of alveolar osteitis.

DISCUSSION

Removal of the impacted third molar leads to postoperative complications like swelling, pain, trismus and alveolar osteitis. Ozone is a natural compound containing three oxygen atoms. Rich supply of oxygen is hypothesised to promote wound healing. Kazancioglu et al reported that use of ozone gas extraorally facilitated wound healing after removal of third molar (Kazancioglu *et al.,* 2014). The possible mechanism as suggested by Craig L Broussard was that disruption of microcirculation is the first event causing wound hypoxia. Cellular energy metabolism is dependent on oxygen supply, particularly the production of adenosine triphosphate (ATP). Though cellular energy metabolism can also exist in an anaerobic state it leads to acidosis. Oxygen consumption is increased as leukocytes migrate to the wounded area. The ability of macrophages to phagocytize bacteria is greatly reduced in hypoxic tissue as it decreases the oxidative killing of bacteria. Epithelial growth factor is present with decreased epithelialization in a hypoxic environment (Craig, 2004). Ozone has rich supply of oxygen and application of ozone gel in the extracted socket improves various properties of erythrocytes, resulting to oxygen release in the tissues causing vasodilatation, improving the blood supply to the ischemic zones and promoting wound healing and reducing postoperative swelling.

Kumar et al conducted a study with PRF to find its effect on postoperative pain, swelling and trismus and observed increased periodontal healing[16]. Similarly, Zhang et al used PRF to study and evaluate the bone regeneration in sinus augmentation and found no significant difference (Zhang *et al.,* 2012). PRF has a natural fibrin and the ability to prevent the growth factors from proteolysis. PRF releases three main growth factors transforming growth factor β-1 (TGF beta-1), platelet-derived growth factor AB (PDGF-AB), vascular endothelial growth factor (VEGF), and an important coagulation matrix cellular glycoprotein (thrombospondin-1, TSP-1). Apart from these PRF also secrete epidermal growth factor (EGF), fibroblast growth factor (FGF), and three important proinflammatory cytokines such as Interleukin -1b (IL-1b), Interleukin-6 (IL-6), and Tumor Necrosis Factor-α (TNF-α) to stimulate several biological functions like chemotaxis, angiogenesis, proliferation, differentiation, modulation for a more rapid and effective regeneration of hard and soft tissues (Singh, 2012; Kumar *et al.,* 2014; Choukroun, 2001).

In this study, it was observed there was decreased pain and swelling (Table 1 & 2) in those who received ozone followed by the group that received PRF compared to conventional method. Presence of pain after any surgical procedure is a common clinical presentation. The surgical trauma leads to up regulation of the biochemical mediators of pain and inflammation, such as prostaglandins, histamine, bradykinin, and serotonin. The decrease in pain intensity in topical ozone gel application is due to its vasodilation and anti-inflammatory property. These reasons probably owes to the analgesic property of ozone. Ozone is well known for its antimicrobial activity. The main reason for cell death is due to ozonolysis of dual bonds, ozone-induced modification of intracellular contents due to secondary oxidants effects. This action is non-specific and selective to microbial cells and does not damage human cells because of their major anti-oxidative ability. Ozone is also very efficient in antibiotics resistant strains. Therefore, application of ozone in the extraction socket has anti-microbial effect. In this study, metronidazole is given along with PRF for its anti-bacterial action. It inhibits the nucleic acid synthesis by disrupting the DNA of microbes. Since its action is towards anaerobes it has very little action against human cells. The effect of ozone on mouth opening could be due to the process of better wound healing by the biosynthetic and analgesic properties of ozone (Table 3). Ozone exhibits potent anti-hypoxic action by increasing the partial pressure of oxygen in tissues and, hence, activation of intracellular aerobic processes (Shilpa, 2013). To the best of our knowledge, this study was conducted to find a possible measure to reduce the postoperative complications after removal of third molar. The limitations were the sample size, the microbial activity of ozone gel application was not analysed and the histopathology of healing could have been observed and analysed.

Conclusion

The application of ozone gel reduces the postoperative complications by stimulation of blood flow, activation of osteoblasts and osteosynthesis, decrease in osteoclastic activity and anti-inflammatory activity allowing to good healing. PRF with the presence of growth factors plays an important role in healing. But for PRF venous blood has to be drawn from the patients whereas for ozone gel application no invasive procedures were involved. Along with this, our data also suggests that ozone applications has better effect on post operative complications over the other two methods. But still, further research and clinical trials are required with increased sample size to understand their effectiveness.

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