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RESEARCH ARTICLE

EVALUATION OF COMBINATION OF ANTIBIOTIC AND ANTI-INFLAMMATORY INTRA-SOCKET MEDICATION ON POST-OPERATIVE COMPLICATIONS FOLLOWING MANDIBULAR THIRD MOLAR SURGERIES

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ABSTRACT

Aim: To evaluate the efficacy of combined antibiotic and anti-inflammatory intra-socket medication (ophthalmological combination medications containing dexamethasone-neomycin and chloramphenicol) on post-operative pain, swelling and dry socket following mandibular third molar surgeries.

Material and methods: The study was conducted among 60 subjects randomly divided into two groups of 30 each. Control group received only gelfoam and study group received eye /ear drops containing chloramphenicol (Chlorocol) & dexamethasone with neomycin (Dexacort N) along with gelfoam as an intra-socket medication after mandibular third molar removal procedure, both followed by suturing of extraction site. The surgeries and follow up examinations were performed by the same surgeon. The follow upvisits were performed at 24 hours and on day six, post-surgery where presence or absence of dry socket was evaluated and pain intensity by Visual Analogue Scale (VAS) 0 - 10 was observed. Obtained data was analyzed using SPSS 16 for comparison of pain experience, swelling and dry socket incidence among both the groups.

Results: In the present study, subjects in study and control groups suffered from moderate to severe pain 24 hrs after third molar extraction procedure ($p<0.05$), whereas after 6 days, subjects in both the groups suffered from mild to moderate pain ($p<0.05$). After 6 days of surgery, no swelling was seen in study group whereas 9 patients in the control groups had swelling. 4 subjects (13.3%) in the study groups suffered from dry socket as compared to 10 subjects (33.3%) in control group ($p<0.05$).

Conclusion: The application of combined antibiotic and anti-inflammatory intra-socket medications significantly reduced the incidence of post-operative complications following third molar extraction.

INTRODUCTION

One of the most common post-operative complications following tooth extraction is dry socket (DS) or alveolar osteitis (AO) [1]. Previous studies have reported the incidence of dry socket between 1-4% after routine extraction and between 5-30% after surgical extraction of mandibular third molars [2,3]. Risk of occurrence of dry socket after extraction of mandibular third molars is ten times more than maxillary third molars [4]. Apart from dry socket, removal of third molars is also frequently associated with considerable postoperative discomfort such as pain, trismus and edema [5,6].

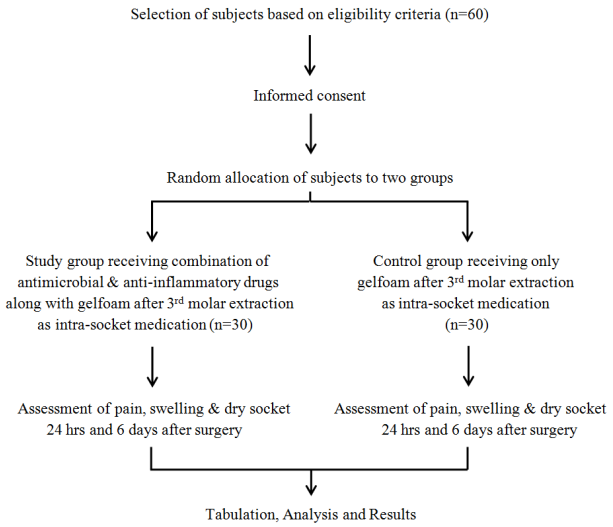
Pain generated following extraction is of short duration and moderate intensity and frequently gets relieved by analgesic medication. Swelling is correlated to extensive soft tissue manipulation, reflection of mucoperiosteum and duration of surgery. Dry socket most commonly occurs the removal of impacted lower third molar and is characterized by: constant radiating pain beginning 2 to 4 days post-operatively which is not relieved by analgesics; partial or total absence of blood clot; tenderness to palpation; pain relieved by placement of eugenol iodoform dressing and malodour [7]. The etiology of dry socket is not completely known but fibrolysis albeit bacterial or as a result of release of local acute inflammatory mediators is thought to play major role in dry socket formation [7].

Risk factors that have been associated with the formation of dry socket include gender (Female>Male), oral contraceptive use, smoking, surgical trauma and the difficulty of extraction, age(most common in third and fourth decades), systemic diseases, bacterial infection, experience of surgeon, etc [8].The morbidity related with dry socket formation has led to a rigorous effort in the literature to demarcate treatment modalities that help in prevention of this complication which include intra-operative irrigation, placement of clot stabilizing factors, anti-fibrinolytics, topical medications in socket, anti-microbial rinse and systemic antibiotics [9-13].

The use of antibiotics as intra-socket medications for prevention of post-extraction complications has been well reported in the literature [14-16]. However, combination of antimicrobial and anti-inflammatory intra-socket medication has not been explored previously. Hence the presence study was designed with an aim to evaluate the efficacy of combined antibiotic and anti-inflammatory intra-socket medication (ophthalmological combination medications containing dexamethasone -neomycin and chloramphenicol) on post-operative pain, swelling and dry socket following mandibular third molar surgeries.

MATERIAL AND METHODS

The randomized double blind study (Table/Fig-1) was conducted in the Department of Oral and Maxillofacial Surgery, Vyas Dental College and Hospital, Jodhpur, Rajasthan in the period of January 2016 through June 2016. Before scheduling the present study, the required ethical clearance was obtained from institutional ethical committee of Vyas Dental College and Hospital and permission to conduct the study was obtained from the head of the department.



Tables/Fig 1 Flow chart of the study

Study Sample

The study was conducted on total of 60 subjects who met inclusion criteria. The sample size for the study was derived using GPower 3.1 software based on the data obtained from the previous study [17]. Sample size of 60 was calculated based on data obtained from previous studies considering effect size f = 0.8, α = 0.05 and 90% power of the study.

Inclusion criteria

Subjectsin the age range of 16-32 years with no pericoronal infection preceding the surgery, no antibiotics in the period leading up to the surgery, no anti-inflammatory medication leading up to the surgery, unilateral impactions which were determined from clinical and radiological examination, subjects with no associated co-morbidity were included.

Exclusion criteria:

Subjects with history of hypersensitivity to any of the components of the medicine, medically compromised subjects, with acute purulent infections (may be masked or enhanced by the presence of steroid), mentally retarded subjects who were unable to communicate, subjects with smoking history, who were taking any medication or oral contraceptives, those using antibiotics or requiring antibiotics 10 days prior to surgery were excluded from the study.

Surgical procedure

All the subjects were asked to read and sign an informed consent to be included in the study. 60 subjects were divided randomly using lottery technique into two groups of 30 each which were: 30 subjects in the control group who were treated with gel foam and 30 subjects in the study group who were treated with eye/ear drops containing chloramphenicol (Chlorocol) & dexamethasone with neomycin (Dexacort N) along with gelfoam. The subjectss were blinded to the type of medication. Surgery was performed in the operating theater following the standard infection control guidelines for surgery using 1% and 10% betadine for intra- and extraoral surgical field disinfection, respectively, and covered with sterile surgical drapes. All the surgeries and follow up visits were performed by the same operating oral surgeon.

Appropriate local analgesia was secured for all surgeries using 4 ml of 2% Lidocaine with 1:800,000 Adrenaline to give Inferior Alveolar Nerve Block (IANB) injections. Where indicated a standard mucoperiosteal flap was raised and the necessary bone removal and/or tooth sectioning was carried out. Once the tooth was removed, the surgical field was well irrigated with normal saline solution and surgical debris was removed. In the control group, the socket was then closed with standard manner using free silk suture following application of plane gelfoam in the surgical side and in the study group, eye /ear drops containing chloramphenicol (Chlorocol) & dexamethasone with neomycin (Dexacort N) along with gelfoam was introduced into the surgical side followed by closure. The inert gelfoam carriers are resorbable and were left in situ. Dexacort N ointment®, which is a commercially prepared ophthalmological combination medication, was chosen for the this study. It contains Dexamethasone Sodium Phosphate (0.1 %W/w), Neomycin Sulphate (0.5 %W/w) of preparation.

Scoring pattern

The post-operative pain was scored using a visual analogue scale for each side with 0 indicating no pain and 10 the worst pain imaginable (0 = no pain; 1-3 = mild pain; 4-6 = moderate pain; 7-10 = sever pain). The pain scores were recorded 24 hours after the surgery and on the 6th day after surgery. In the post-operative phase, the subjects were asked to note the occurrence of the swelling, the time of onset and disappearance of post-operative swelling and the time when the swelling reached the maximum. The subjects were examined clinically on 6th day by an independent surgeon blinded to the side of intra-socket medication. The subjects were assessed for postoperative complications including dry

socket and post-operative infection. Dry socket was diagnosed if the following criteria were met: i) constant radiating pain beginning 2 - 4 days postoperatively which was not relieved by analgesics, ii) partial or total absence of a blood clot, iii) tenderness on palpation and iv) pain relieved by the placement of eugenol iodoform dressing. Post-operative infection was assessed using the following criteria: i) presence of cellulitis ii) presence of fluctuance iii) presence of purulent or non-purulent drainage from the socket iv) pain and swelling that failed to improve 48 hours after surgery v) hyperpyrexia > 37.8°C, 48 or more hours after surgery without local signs or symptoms if no other source of infection can be found.

Statistical analysis

The data obtained was compiled and subjected to statistical analysis using SPSS 16 software. Subject characteristics such as age-wise distribution, gender distribution, pain score, swelling and dry socket scores were presented as frequencies and percentages. To analyze and determine, the differences between the two groups (control and study), Chi square test (X^2) was used for comparison of qualitative variables. Significance was assessed at 5% level of significance ($p<0.05$).

RESULTS

Table/Fig - 2 shows age-wise distribution of subjects among control and study groups who had undergone mandibular third molar surgeries.

Table/Fig -2 Distribution of study subjects age-wise and gender-wise

Variables	Control Group n(%)	Study Group n(%)
Age		
16-20 years	15(50%)	13(43.3%)
21-25 years	9(30%)	15(50%)
26-32 years	6(20%)	2(6.7%)
Gender		
Male	13(43.3%)	16(53.3%)
Female	17(56.7%)	14(46.7%)

Table/Fig - 3shows frequency of study subjects having pain among control and study group after 24 hrs and after 6 days of third molar surgery. Among control group subjects6 hrs after surgery, 18 (60%) subjects had moderate pain, 12 (40%) subjects reported severe pain score and after 6 days of surgery, 19 (63.3%) subjects had mild pain whereas 11(36.7%) subjects reported moderate pain. Among study group subjects6 hrs after surgery, 19 (63.3%) subjects had moderate pain score, 11 (36.7%) subjects had severe pain score and after 6 days of surgery, 19 (63.3%) subjects had mild pain score, 11 (36.7%) subjects had moderate pain score. Differences seen in the pain score among study and control groups 24 hrs after surgery and after 6 days were statistically significant ($p<0.05$)

Table/Fig 3 Frequency of study subjects having pain among control and study group after third molar surgery

Variables	After 24hrs n(%)	After 6 days n(%)
Control Group		
Mild	0(0%)	19(63.3%)
Moderate	18(60%)	11(36.7%)
Severe	12(40%)	0(0%)
Study Group		
Mild	0(0%)	19(63.3%)
Moderate	19(63.3%)	11(36.7%)
Severe	11(36.7%)	0(0%)

(Table/Fig -4).

Table/Fig 4 Comparison of pain among study and control groups

Pain	Control Group	Study Group	Chi square value	p-value
		After 24 hrs		
Moderate	18	19	26.053	0.001*
Severe	12	11		
		After 6 days		
Mild	19	19	26.053	0.001*
Moderate	11	11		

Chi-square test; * significant at $p<0.05$

Table/Fig – 5 shows frequency of incidence of swelling among study and control groups. Statistically significant difference was seen for the presence of swelling after 24 hrs and after 3 days in study subjects as compared to control subjects ($p<0.05$). It was observed that there were no swelling in study group on 6th day whereas 9 subjects from control group were still having swelling.

Table/Fig 5 Comparison of incidence of swelling among study and control groups

Day	Control Group	Study Group	Chi-square value	p-value
1st Day	8(26.7%)	16(53.3%)	9.545	0.003*
3rd Day	13(43.3%)	14(46.7%)	26.218	0.001*
6th Day	9(30%)	0(0%)		--

Fisher exact test; * significant at $p<0.05$

Table/Fig - 6shows frequency of incidence of dry socket among study and control groups. 4(13.3%) subjects in the study group suffered from dry socket as compared to 10(33.3%) subjects in the control group. This difference was statistically significant ($p=0.008$).

Table/Fig 6 Comparison of incidence of dry socket among study and control groups

Day	Control Group	Study Group	Chi-square value	p-value
Absent	20(66.7%)	26(86.7%)		
Present	10(33.3%)	4(13.3%)	9.231	0.008*

Chi-square test; * significant at $p<0.05$

DISCUSSION

Extraction of impacted lower molars perpetually causes some degree of pain, swelling and trismus. The mechanism of pain has been characterized as consisting of four distinct physiologic processes: transduction, transmission, modulation, and perception. For the purposes of this discussion, it is appropriate to consider the therapeutic modalities that affect transduction as it is at this station along the pain pathway that the topical application of dexamethasone is probably effective. Agents that serve to alter peripheral transduction include the glucocorticosteroids and the non-steroidal anti-inflammatory agents. The glucocorticosteroids have the capacity to dramatically reduce the manifestations of inflammation and exert their effects in the periphery by a number of mechanisms [18, 19]. Previous studies have proven the efficacy of pre-operative or post-operative administration of corticosteroids such as dexamethasone, prednisolone, etc. by different routes in third molar extraction surgeries in reducing incidence of pain, swelling, trismus, etc. [20-22]. Hence, the use of local glucocorticosteroid therapy may provide means of delivering large amounts of steroid to the diseased tissue with reduced systemic effects. However, data on efficacy of topical application of corticosteroids to the surgical site in reducing

post-operative complications is lacking. Hence the present study evaluated the combined efficacy of a corticosteroid along with an antibiotic on post-operative pain, swelling and dry socket following mandibular third molar surgeries.

Dry socket is another frequently reported complication of third molar removal and usually follows the extraction of impacted lower third molars. Although exact mechanism behind occurrence of dry socket is not completely understood, researchers attempt to explain number of risk factors associated with dry socket such as age, gender, use of oral contraceptives, smoking, traumatic extraction and infections [8]. Investigators who favour the use of antibiotics for management of dry socket include those stressing on direct application within sockets as well as those favouring systemic antibiotics. Antibiotics placed directly into the socket including tetracycline, metronidazole and both lincomycin and oxytetracycline have been shown to be very effective in reducing significantly the incidence of alveolar osteitis (dry socket)[23-26]. Since it has been shown that glucocorticosteroids stabilize cellular lysosomal membranes with subsequent inhibition of the release of vasoactive kinins and destructive enzymes it was inevitable that the efficacy of steroids in the prevention of dry socket would be tested. Julius and his co-workers were unable to demonstrate any benefit by the addition of a topical glucocorticosteroids to an antibiotic dressing in the incidence of dry socket formation [27]. Furthermore Chapnick *et al*. in their review of dry socket report that although glucocorticosteroids decrease immediate post-operative complications they fail to reduce the occurrence of dry socket after extractions [23].

Chloramphenicol is a broad spectrum antibiotic with gram positive, gram negative and anaerobic activity. The systemic use of chloramphenicol is indicated only in certain life threatening infections, because of its potential toxicity and the availability of other effective drugs. It is however used topically in the treatment of eye infections because of its wide antimicrobial activity and its penetration of ocular tissues and aqueous humor [28]. Neomycin is an aminoglycoside antibiotic active against gram negative organisms including Escherichia coli, Proteus, Klebsiella and Enterobacter. Its topical use rarely results in detectable serum concentrations. A study reported the use of Neomycin-bacitracin cones in impacted third molar sockets and found the topical application of neomycin to effectively reduce the incidence of post-operative infection and associated pain [29]. The addition of this agent thus improves the gram-negative spectrum of any preparation without significantly compromising the safety of the preparation.

In the present study, it was found that on the day of extraction, pain experience for both the groups was almost similar i.e. in the range of moderate to severe; but on the 6th day, the pain became mild in nature in both the groups. The similar findings were also found by various authors Neupert *et al*. [30] and Schultze *et al*. [31]. The co-administration of topical combination of dexamethasone with neomycin and chloramphenicol postoperatively, produced a clear reduction in postoperative pain and cheek swelling. Subjects in the study group showed reduction in swelling from 1st day to 6th day after surgery as compared to control group. Similar results were obtained from the studies conducted by Neupert *et al* [30], Huffman GG [32]. Sortino *et al* also recommended use of corticosteroids to inhibit postoperative swelling following removal of impacted lower third molar [33].

The results from this study indicate an overall dry socket incidence of 13.3% among study group, whereas it was 33.3 % among the control group. The reported incidence of dry socket formation varies greatly from one study to another which is probably due to the criteria used for making the diagnosis, the teeth involved, and the incidental treatment of the socket at the time of surgery. It is difficult to determine which of the ingredients in the combined intra-socket medication is responsible for the improvement in the dry socket incidence but if the literature is accurate it would seem as though the primary effect resides with the antimicrobial agents [34]. It would thus seem that the wide spectrum of chloramphenicol with the reinforced gram negative cover of neomycin effectively reduces or alters the microbial environment within the extraction socket in such a way as to reduce the incidence of dry socket formation. Moreover different methodological approaches have been described employing different antimicrobials such as topical Chlorhexidine gel along with gelfoam and they have been shown to be effective in reducing post-extraction complications such as pain, swelling, dry socket, etc. [17, 35]

CONCLUSION

It can be seen from the results that the common post-operative complications of lower third molar removal such as pain, swelling and dry socket may be effectively minimized by topical application of combination of dexamethasone, neomycin and chloramphenicol in the socket. Moreover, when surgical removal of the third molar is performed under local anesthesia, it is convenient for both the surgeon and the patient to use the submucosal route, as effectiveness of the oral administration route depends on patient compliance, and repeated dose is required to maintain adequate blood levels during the postoperative period. However, further research employing large samples are required to establish the best treatment practices to prevent these highly uncomfortable post extraction complications.

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