

Research Article

Transdermal Patch and Oral Routes of Administration of Diclofenac for the Control of Postoperative Sequelae after Third Molar Surgery: A Single-Blinded, Randomized Clinical Trial

Aimuwamwosa OD, Ekaniyere EB* and Obuekwe ON

Department of Oral and Maxillofacial Surgery, University of Benin Teaching Hospital, Benin-City, Nigeria

*Corresponding author: Edetanlen Benlance Ekaniyere, Department of Oral and Maxillofacial Surgery, University of Benin Teaching Hospital, Nigeria

Received: May 04, 2020; Accepted: June 02, 2020;

Published: June 09, 2020

Abstract

Objectives: The study aimed to compare the effect of transdermal patch and oral routes of administration on the control of pain, oedema, and trismus following the extraction of third molars.

Materials and Methods: Sixty-eight patients with moderate Pederson index mandibular tooth impaction underwent surgical extraction and received diclofenac sodium through oral route (control group) or transdermal route (study group). Pain (visual analogue scale, VAS), facial swelling, maximum mouth opening, number of paracetamol, duration of surgery were determined. Data were descriptively and inferentially analysed with a choice of p-value less than 0.05.

Results: The mean age of subjects recruited was 29.97±8.08 years with age range of 18-55 years. There were 29 males and 39 females. Pain was clinically and statistically better at first and second after surgery in the transdermal diclofenac group compared to the oral diclofenac group (P<0.05). Mouth opening was clinically and significantly better at seventh day post operation in the transdermal group (P<0.05). There was no difference in the control of swelling between both groups (P>0.05).

Conclusion: Transdermal diclofenac is as effective as oral diclofenac in the control of pain, swelling and trismus and can serve as a useful alternative to oral diclofenac in patients undergoing third molar surgery.

Keywords: Diclofenac sodium; Transdermal; Oral; Impacted tooth; Postoperative complications

Introduction

The surgical removal of third molars is the most frequently performed oral surgical procedure worldwide [1]. The most common indications for this procedure include caries, pericoronitis, cyst formation, and periodontal problems as well as removal for orthodontic indications. Due to the presence of loose connective tissue and high vascularity, even a meticulous surgical technique can result in considerable pain, swelling and trismus. Most complications or postoperative discomforts-particularly pain, swelling and trismus-are triggered by inflammatory processes initiated by surgical trauma. These postoperative complications can cause great distress, and anything that compromises quality of life even for a short period of a few days is unacceptable to the highly cognizant and extremely busy generation of today [2]. Thus we as medical professionals, are obliged to render better control of this postoperative discomfort for patients undergoing third molar surgery. Modalities to alleviate these postoperative sequelae have been the focus of several experimental studies. These includes different closure techniques with or without incorporation of drains [3] use of drugs such as analgesics [4], corticosteroids [5] and antibiotics [6].

Diclofenac, as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are amongst the most widely prescribed therapeutic class of analgesic used to ameliorate post extraction pain, swelling and trismus for several decades [7]. Their mechanism of action depends on whether they inhibit cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), or both, which are responsible for the synthesis of different prostaglandins found in pathological situations (COX-2 is more expressed in inflammatory conditions) [8]. Diclofenac can be administered in a variety of routes, including oral, parental, inhalation as well as transdermal. Though oral route is considered the gold-standard, readily available, self-administered and most frequently used routes of administration globally, it carries risk of first pass metabolism and loss of substantial quantities of the drug before it is absorbed systemically. Gastrointestinal side effects are also seen with the oral routes. Parental administration of drugs can be extremely painful and sudden increase in drug concentration in the plasma could lead to certain adverse effects. Transdermal administration has the advantages of being easy, better patient compliant, simple route of administration without the disadvantages of routes mentioned above and also comparatively fewer side effects and complications [9].

Much have been studied on the effectiveness of oral versus transdermal route of administration of diclofenac sodium in the fields of dentistry [10-18] and other fields of medicine ranging from anesthesiology to traumatology [11-28] globally. However, inconsistencies in the optimal and appropriate route of administration of diclofenac prevail and all these studies [10-28] except one study [10] focus only on analgesic efficacy despite well reported role of diclofenac sodium in controlling postoperative complications such as pain, swelling and trismus. This study attempts to compare different delivery systems in the management of postoperative pain, swelling, and trismus following surgical removal of impacted mandibular third molars using diclofenac sodium as a standard drug which was administered in two different routes, oral and transdermal. The null hypothesis of the present study was that the efficacy of control of pain, swelling and trismus after third molar surgery of transdermal diclofenac would be as effective as oral diclofenac.

Materials and Methods

Study design

To address the purpose of the study, a double-blinded randomized clinical trial was conducted. This study was approved by the Research Ethics Committee (REC) and was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The trial was also registered with Pan African Clinical Trial Registry (PACTR201809637478809). All patients involved signed an informed consent agreement describing the procedures and the objectives of the study prior to their inclusion in the research

Sample selection and eligibility criteria

This study was carried out at the Department of Oral and Maxillofacial Surgery Clinic, University of Benin Teaching Hospital (UBTH), Benin City, Edo State, Nigeria, from November 2018 to June 2019. The sample size was obtained using the formula for comparing means between two groups [29].

$$n = n1 = n2 = \frac{2(\frac{Z\alpha}{2} + z_{1-\beta})^2 \delta^2}{(\mu_1 - \mu_2)^2}$$

where n is the minimum sample size required to detect meaningful statistical differences between the two group; $Z^{1-\alpha/2}$ taken as 1.96 at confidence interval (α) of 0.05; $Z^{1-\beta}$ taken as 0.84 at a statistical power of 80%; the population standard deviation (δ) of characteristics of interest, from previous study design [2] was 2.7; the population mean (μ_1) pain score for population 1 at 12-hour post operatively from a previous study [11] was 2.8, and the population mean (μ_2) pain score for population 2 at 12-hour post operatively was 0.8. A minimum sample size 29 was gotten and with 10% estimated non-response or drop out due to attrition, the sample size was 34 for each group given a total minimum sample size of 68. Subjects aged between 18 and 55 years, who were healthy according to their medical history and physical examination were recruited. The inclusion criteria was an indication for extraction of single mandibular third molar with moderate difficulty, using the Pederson's difficulty index [4]. Other inclusion criteria were the absence of pain, facial swelling or limitation of mouth opening from any cause within 10 days preceding surgery. The following was considered exclusion criteria: patients who declined to participate in the study; history of allergy to diclofenac; pregnancy or lactation; patients who are medically compromised;

patients on anticoagulant therapy; patients on analgesics at the time of presentation; patients on oral contraceptives; patients on corticosteroids; surgical procedure that extended beyond 45 minutes.

Randomization

All consecutive participants who met the inclusion criteria were randomly allocated to the type oral diclofenac (control) or transdermal diclofenac (study) group. Computer was used to generate table of random numbers, a total of 68 identical opaque envelopes were serially numbered by an individual external to the research team, who also inserted markers "oral" or "transdermal", based on the group allocated to and the envelope properly sealed. These envelopes were then kept in the custody of a nurse (also external to the research team). The study subjects were each required to pick an envelope from a closed box, as they presented in the clinic after recruitment. The corresponding envelope was retrieved from the subject, the opaque envelope was unsealed and the group identified.

Surgical protocol

The surgical procedure was performed by same experienced surgeon and assistant under same environment to eliminate operator-induced bias. All patients were made to perform oral rinse with an aqueous solution of 0.2% chlorhexidine digluconate for 1 minutes prior to surgery. Local anaesthesia was provided by technique of regional blockade of the inferior and lingual alveolar nerves, with supplementary buccal nerve infiltration. A careful and slow injection of the solution was conducted after negative aspiration, with a maximum volume of 3.6 ml of local anaesthetic with 2% lidocaine and 1:100,000 epinephrine. An anterior relieving incision was made from the vestibule upwards towards the midway of the marginal gingiva of the second mandibular molar at an angle. The incision was extended along the buccal gingival sulcus to the external oblique ridge where the posterior relieving incision was placed. Howarth's periosteal elevator was used to reflect a full thickness mucoperiosteal flap and retracted with a Bowdler-Henry's rake retractor. Buccal and distal bone removal was done with a round bur on a straight hand piece under constant irrigation with 0.9% sterile normal saline solution and guttering done a little beyond furcation. The teeth were delivered with sectioning of the crown. The socket was inspected, irrigated and flap sutured with a 3-0 polyglactin 910 suture (vicryl). One suture was placed just distal to the lower second molar and another on the distal aspect of the extraction socket. Duration of surgical procedure was recorded.

Postoperative care

Following removal of the impacted mandibular third molar, the oral diclofenac group was given 50mg diclofenac tablet (Voveran SR) thrice daily immediately while the transdermal diclofenac group was given diclofenac patch (Nu patch) 100mg 30 minutes after surgery daily for three consecutive days. Diclofenac transdermal patch was placed on its longitudinal axis on the skin above the third molar-ascending ramus region with its highest point on the tragal-alar line and lowest point 3mm below the lowest margin of the posterior mandibular region in all the patients. Information on regimen and application of oral and transdermal diclofenac was obtained from previous study. [11] Patients were instructed to apply 0.12% chlorhexidine digluconate aqueous solution to control dental plaque from the second day, every 12 hours for 7 days. All patients were given

Table 1: Baseline characteristics of the subjects in the two route of administration groups.

Variable	Oral group (n=34)	Patch group (n=34)	p-Value
Mean age Gender	31.38±9.28	28.94±6.87	0.222
Male	16(23.53)	13(19.12)	0.803
Female	18(26.47)	21(30.88)	
Indication			
Pericoronitis	19(27.94)	20(29.41)	0.78
Dental caries	14(20.59)	11(16.18)	
Orthodontic treatment	1(1.47)	3(4.41)	
Pederson's difficulty index	5.9(1.52)	5.7(1.86)	1



Figure 2: Evaluation of facial swelling (oedema).

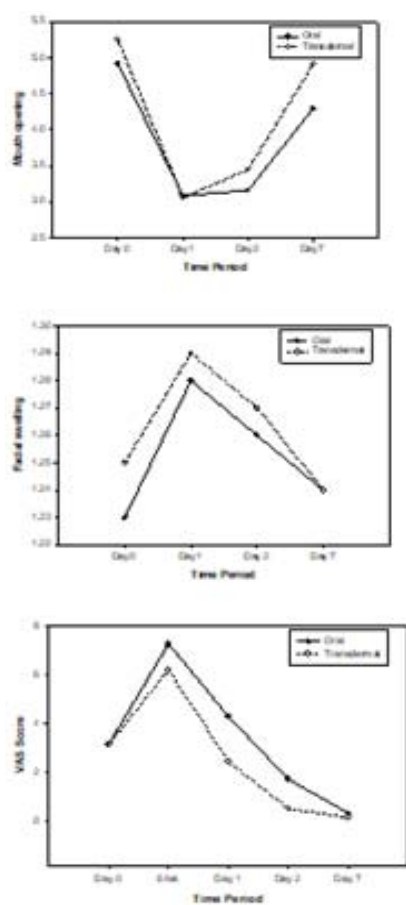


Figure 1: Evaluation by three points.

amoxicillin trihydrate. (Vamoxil®, Vadis, Nigeria) 500mg 8 hourly or erythromycin(Eromycin® Fidson, Nigeria) 250mg 6 hourly for those who were allergic to penicillin, metronidazole (Loxagyl®, May & Baker Plc, Nigeria) 400mg 8 hourly, both for five days. These drugs were commenced immediately after surgery. Paracetamol tablets 1000mg every 8 hours was prescribed as rescue analgesic and patients were instructed to take it only if needed. All subjects received verbal and written post-operative instructions Subjects were instructed to present to the dental clinic or emergency room in the event of delayed post extraction complications like uncontrolled bleeding and unbearable pain. The Sutures was removed after 7 days after surgery.

Evaluation procedure

The patients were evaluated in a blinded manner by the same independent observer who was calibrated for the evaluation. Pain was evaluated using a 10 cm Visual Analogue Scale (VAS) (Figure 1). The assessment of pain was done at five time points: preoperative, 6 hours, 1, 2 and 7 days postoperative. The facial swelling (oedema) was determined with a tape measure according to the method described by Gabka and Matsumura (1971) [30] (Figure 2). Three measurements were performed between the five reference points: tragus, pogonion (soft tissue), lateral corner of the eye, angle of the mandible, and external corner of the mouth. The measurements, in cm, were obtained preoperatively (baseline) and at day 1, 2 and 7 postoperatively. Maximum mouth opening was used to assess the level of trismus. It was evaluated by measuring the distance between the mesial-incisal corners of the upper and lower central incisors at maximum opening in cm, preoperatively, and at first, second and seventh postoperative days, using Vernier caliper.

The duration of surgery was recorded with stopwatch in seconds, from the time of the initial incision to the time of last suture. The number of paracetamol tablets taken after surgery was recorded by the patients by the seventh day postoperative day.

Data Management

In the descriptive statistic, continuous variables were summarised in ranges and means with standard deviation while the categorical data were presented in frequency and percentages. Prior to inferential statistics, normality of continuous variables were performed with Shapiro-Wilk test. The chi square χ^2 test was used to compare the percentage of categorical variable between the two groups, while the independent t test was used to compare the means of continuous variables between the two groups at a 95% confidence interval. The data were analysed using Statistical Package for the Social Science (SPSS) software version 22 (SPSS Inc., Chicago, USA). Using two-tailed test, a p-value of less than 0.05 was taken as significant.

Results

All the 68 recruited subjects fully participated in the study. The mean age of subjects recruited was 29.97±8.08 years with age range of 18-55 years. There were 29 males and 39 females. The mean (SD) of surgery time in the transdermal and oral diclofenac group were 35(3.62) minutes and 34(5.50) minutes respectively but the

Table 2: Comparison of VAS scores (Mean (SD) in centimeter (cm); n = 86).

Groups	Preoperative	6 Hours	1 Day	2 Day	7 Day	Repeated Measures
Oral	3.13(2.48)	7.25(1.54)	4.28(1.80)	1.72(1.71)	0.34(0.87)	F=88.711; P=0.000
Transdermal	3.12(0.64)	6.71(1.17)	2.44(1.28)	0.53(0.83)	0.15(0.44)	F=136.469; P=0.00
P-Value	0.99	0.107	0.001	0.0001	0.254	

SD: Standard Deviation; VAS: Visual Analogue Scale

Table 3: Measurement of facial swelling (Mean (SD) in centimeter (cm); n=86).

Groups	Preoperative	Day 1	Day 2	Day 7	Repeated Measures
Oral	1.23(0.56)	1.26(0.68)	1.28(0.65)	1.24(1.31)	F=3.262; P=0.000
Transdermal	1.25(0.66)	1.27(0.60)	1.29(0.56)	1.24(0.54)	F=17.038; P=0.000
P-Value	0.07	0.403	0.435	0.778	

SD: Standard Deviation

Table 4: Measurement of trismus (Mean (SD) in centimeter (cm); n = 86).

Groups	Preoperative	Day 1	Day 2	Day7	Repeated Measures
Oral	4.92(0.66)	3.09(1.07)	3.16(0.98)	4.30(0.83)	F=58.020; P=0.02
Transdermal	5.25(0.50)	3.06(0.78)	3.45(0.61)	4.91(0.91)	F=99.223; P=0.00
P-Value	0.61	0.911	0.15	0.006	

SD: Standard Deviation

mean difference was not statistically significant (P = 0.57). None of the groups took the rescue drug in the course of the study. The baseline characteristics of the subjects in the two routes of diclofenac administration is given in (Table 1). There was no statistical difference between two groups with regard to age (P = 0.222), gender (P = 0.803), indication for surgery (0.780) or surgical difficulty of the procedure (1.000).

Table 2 presents the comparison of VAS between the oral diclofenac (control) and transdermal diclofenac (study) group. On the sixth hours after surgery, pain was significantly increased to reach its peak and gradually decreased in the second and seventh day postoperatively in both groups when compared to preoperative measurements. The intensity of pain was significantly lower (p< 0.05) at first and second day after surgery in the study (transdermal diclofenac) group compared to the control (oral diclofenac) group (table 2 and figure 3). The facial swelling significantly increased and reached its peak at day 2 after operation and gradually reduced at day 7 postoperatively in both groups compared to the preoperative measurement. There was no statistical difference between the two groups at every time point of measurement of swelling (Table 3). With regard to trismus, both groups experienced significant highest level of trismus at day 1 after surgery compared to the preoperative measurement (Table 4). The intensity of trismus was lower in the study (transdermal diclofenac) group compared to the control (oral diclofenac) group at day 7 postoperatively (Table 4). None of the patients displayed alveolar osteitis, postoperative infection, an allergic reaction to any of the drugs, or neurological disturbances.

Discussion

This study was aimed to compare different delivery systems in the management of postoperative pain, swelling, and trismus following surgical removal of impacted mandibular third molars using diclofenac sodium as a standard drug which was administered in two different routes, oral and transdermal.

NSAIDs have the ability to reduce both pain and inflammation as

a result they are the ideal analgesic agents for the control of pain in the events of surgical removal of mandibular third molar impactions [8]. The use of topical NSAIDs for acute pain relief is one of the most controversial issues in analgesic practice. While they are commonly prescribed in some parts of the world (such as Western Europe), in other areas they are almost regarded as a placebo [8]. A systematic review has confirmed the efficacy of topical NSAIDs compared to that of placebo in both acute and chronic pain management [7]. Analgesic patches are one of the well-established approaches to topical NSAIDs administration. Diclofenac sodium is a commonly prescribed NSAID, which exhibits anti-inflammatory, analgesic and antipyretic activity. If given orally, only 50% of the absorbed dose of diclofenac becomes systemically available, due to the first pass metabolism [8]. Also, due to the high plasma concentration, oral diclofenac carries the potential for significant adverse reactions, particularly those involving the gastrointestinal tract. Transdermal patches have in the recent past been developed as innovative topical delivery systems for diclofenac and other NSAIDs, offering the advantage of sustained drug delivery with reduced incidence of systemic adverse effects due to lower plasma concentrations. The transdermal patch is used to relieve mild to moderate pain, it is applied once daily for duration of 24 hours and produces rapid pain relief with minimal or no side effect. It comes in 2 strengths of 100mg and 200mg. The 100mg patch is 50mc sq and 200mg in 75cm sq. The patch achieves plasma level ranging from 20-50 ng/ml, which is lesser when compared to oral route but these levels are sustained for longer period. The bioavailability of transdermal diclofenac sodium is 1% that of oral diclofenac. Transdermal has long analgesic effect compared to oral that have short-term analgesic effect. The patch delivers slow release of drug into the body over time, resulting in long-term effectiveness and an added convenience (transdermal is applied once daily while oral is taken thrice daily). In the last few decades, transdermal patches have gained popularity as an effective analgesics modality, owing the advantages such as ease of application, reduced risk of dose dumping compared with cream, constant and prolonged duration of action, self-administration capability and ease of termination. These advantages also lead to

better patient compliance. The application of transdermal drugs in the field of oral and maxillofacial is gaining significant credibility [9].

In this study, we standardized the level of difficulty of the procedure, operator variability, and patient inclusion and exclusion. In this study, confounding factors such as duration of surgery and surgical difficulty were minimized by using same surgeon for all surgeries. Also recruiting of only patients with Pederson's moderate difficulty index minimizes patient selection bias. Both groups had a comparable mean age and keeping the operation time with certain duration minimizes the confounding effect of gender. In this study, 50 mg of oral diclofenac sodium was given thrice daily because its elimination half-life is 1.2-2.0 hours while that of transdermal patch is 12 hours and hence was given in the present study 100 mg daily [8]. The oral diclofenac was given immediately after the procedure while transdermal diclofenac was given 30 minutes after surgical procedure since they reach their maximum efficiency at 5-7 hours and 4-6 hours of administration respectively [11].

Post-operative pain is a unique and common form of acute pain. Patients typically associate dental care with pain and an experience of poorly managed pain related to dental treatment can lead patients to avoid or postponed treatment, as well as make them more difficult to treat. Pain which is one of the classical sign of inflammation, involves several inflammatory mediators such as: prostaglandin, histamine, bradykinin and serotonin. These mediators are produced by cells of the reticuloendothelial system, injured surrounding tissues, plasma and nociceptive terminal nerve endings. These chemical mediators and series of chemotactic agents are released in response to trauma. The most commonly used analgesics after third molar surgery are paracetamol and the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) either alone or in combination with opioids [8].

In this study, the pain scores were significantly lower in the transdermal diclofenac group at first and second day postoperative. However, there was no difference in pain intensity at the seventh day after surgery between both groups. This findings have demonstrated that the transdermal diclofenac is as potent as oral diclofenac as analgesia drugs. This findings are consistent with the results previous studies. However, this findings is not comparable with other previous studies. Bhasker et al. [12] compared analgesic effects of 100mg oral diclofenac sodium with 100 mg transdermal diclofenac among 20 patients receiving orthodontic treatment and they found similar analgesic effect for both application but they have advised transdermal application for its comfort and much more less complication. [9] Ural et al. [19] compared the analgesic effect of oral, Intra Muscular (IM) and transdermal diclofenac in 90 patients that undergone laparoscopic cholecystectomy operation and reported that oral diclofenac sodium provide less analgesic effect and causes increase in postoperative tramadol consumption compared with transdermal and IM diclofenac. They also concluded that oral diclofenac will increase gastrointestinal complaints in patients already stressful in preoperative period. Rajeswari et al. [14], in their study to compare the analgesic efficacy and safety between oral and transdermal diclofenac in 20 patients that undergone dental implant surgery reported that transdermal diclofenac is a viable option for postoperative pain management. Murthykumaret al [16] who reported that pain intensity was significantly lower on the oral diclofenac group compared to the transdermal diclofenac group in

15 patient that underwent periodontal surgery. Baccalli et al. [11], compared analgesic effect of 100mg oral diclofenac once daily with 100mg transdermal diclofenac once daily among 20 patient that has surgical extraction for impacted third molar and reported that oral diclofenac has better analgesic efficacy. It is generally accepted that pain following third molar surgery reaches moderate to severe intensity within the first 5 to 8 hours [8] and in most cases patient require analgesic treatment. In our study, pain was at its peak at 6 hours after the third molar surgery in both groups.

Postoperative swelling or oedema is a direct and immediate postoperative tissue reactions as a consequences of the surgical procedure or can be a normal part of the healing process. The surgical injury results in production of mediators which are derived from plasma and immune cells, these mediators act on vessels leading to increased vascular permeability. Vascular leakage can also occur through a direct vascular injury. The increased permeability is the cause of oedema which is obviously evident clinically as swelling [2]. The onset of swelling is gradual and usually reaches maximum at 1-2 days after surgery; it begins to subside on the third or fourth day and has usually resolved by the end of the first week. [5] In the present study, there was no significant difference in the facial swelling between oral and transdermal route of diclofenac administration at every time point of measurement. This is an indication of effectiveness of both routes in controlling facial swelling. This findings is at par with the findings of Dastagir and Balamurugan, who reported that transdermal diclofenac significantly reduced facial swelling at day 2 and 7 compared to oral diclofenac following removal of lower impacted third molars [10].

Maximum mouth opening or trismus is usually caused by inflammation within the muscles of mastication leading to spasm secondary to the raising of a mucoperiosteal flap. Following trauma, chemical mediator results in increase vascular permeability leading to leakage. This fluid accumulates within the masticatory muscles, presenting clinically as limitation of mouth opening [2]. Trismus reaches its maximum peak on second postoperative day and regresses up to seventh day [5]. In our study, transdermal diclofenac had a significant control of trismus than oral diclofenac at the seventh day after surgery. This difference could be explained in part by the fact that transdermal diclofenac has longer effect than oral diclofenac. Dastagir and Balamurugan reported a significant better mouth opening in patients on transdermal diclofenac compared to those on oral diclofenac at day 2 and 7 postoperatively [10].

The main limitation of this study was lack of previous studies as regard effect of oral diclofenac versus transdermal diclofenac on third molar surgery complication, making comparison of our findings with previous findings lacking. Other limitation is the parallel nature of the clinical trial, however the observed differences between the two groups were not significant making the findings statistically acceptable. Conclusively, within the limitation of this study, the transdermal diclofenac is as effective as oral diclofenac in the control of pain, swelling and trismus and can serve as a useful alternative to oral diclofenac in patients undergoing third molar surgery in patient who cannot take oral diclofenac.

References

1. Enabulele JE, Obuekwe ON. Prevalence of caries and cervical resorption on

- adjacent second molar associated with impacted third molar. *J Oral Maxillofac Surg. Medpathol.* 2017; 29: 301-305.
2. Sisk AL, Hamner WB, Shelton DW, Joy ED. Complications following removal of impacted third molars; the role of the experience of surgeon. *J Oral Maxillofac Surg.* 1986; 44: 855-859.
 3. Saglam AA. Effects of tube drain with primary closure technique on postoperative trismus and swelling after removal of fully impacted mandibular third molar. *Quintessence Int.* 2003; 34: 143-147.
 4. De Menezes SA, Cury PR. Efficacy of nimesulide versus meloxicam in the control of pain, swelling and trismus following extraction of impacted lower third molar. In *J Oral Maxillofac Surg.* 2010; 39: 580-584.
 5. Chugh A, Singh S, Mittal Y, Chugh V. Submucosal injection of dexamethason and methylprednisolone for the control of postoperative sequelae after third molar surgery randomised controlled trial. *Int J Oral Maxillofac Surg.* 2018; 47: 228-233.
 6. Sekhar CH, Naranayan V, Baig MF. Role of antimicrobials in the third molar surgery: prospective, double-blind, randomised, placebo controlled clinical study. *Br J Oral Maxillofac Surg.* 2001; 39: 134-137.
 7. Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ.* 1998; 316: 333-338.
 8. Joshi A, Parara E, Macfarlane TV. A double-blind randomized controlled clinical trial of the effect of preoperative ibuprofen, diclofenac, paracetamol with codeine and placebo tablets for relief of postoperative pain after removal of impacted third molars. *Br J Oral Maxillofac Surg.* 2004; 42: 299-306.
 9. Selvi UPG, Kamatchi D, Babu C, Keerthana S, Jeeva S VI. Comparison of Transdermal Patch with Intramuscular Diclofenac Injection as an analgesic modality following surgical extraction of impacted mandibular third molars. A cross-over efficiency trial. *Int J Sci Stud* 2016; 4: 117-123.
 10. Dastagir F, Balamurugan R. Comparing the analgesic efficacy of diclofenac sodium tablet vs transdermal diclofenac on postoperative third molar extraction pain swelling and trismus. *J Dentomaxillofac Sci.* 2019; 4: 67-70.
 11. Bachali PS, Nandakumar H, Srinath N. A comparative study of diclofenac transdermal Patch against oral diclofenac for pain control following removal of mandibular impacted third molars. *J Maxillofac Oral Surg.* 2009; 8: 167-172.
 12. Bhaskar H, Kapoor P, Ragini. Comparison of transdermal diclofenac patch with oral diclofenac as an analgesic modality following multiple premolar extractions in orthodontic patients. A cross over efficacy trial. *Contemp Clin Dent.* 2010; 1: 158-163.
 13. Krishnan S, Sharma P, Sharma R, Kumar S, Verma M, Chaudhary Z. Transdermal diclofenac patches for control of post-extraction pain. Pilot randomised controlled double-blind study. *Oral Maxillofac Surg.* 2015; 19: 5-12.
 14. Rajeswar SR, Gowda T, Kumar T, Mehta DS, Arya K. Analgesic efficacy and safety of transdermal and oral diclofenac in postoperative pain management following dental implant placement. *Gen Dent.* 2017; 65: 69-74.
 15. Diwan V, Srinivasa ST, Ramreddy YK. A comparative evaluation of transdermal patch with oral diclofenac sodium as an analgesic drug following periodontal surgery a randomized controlled clinical trial. *Indian J Dent Res.* 2019; 30: 57-60.
 16. Murthykumar K, Varghese S. Analgesic efficacy and safety of transdermal and oral diclofenac in postoperative pain management following periodontal flap surgery. *Drug invent today.* 2019; 11: 652-656.
 17. Tejaswi DV, Prabhuji ML, Khaleelahmed S. Comparative evaluation of transdermal diclofenac patch with oral diclofenac as an analgesic modality following root coverage procedures. *Gen Dent.* 2014; 62: 68-71.
 18. Perepa A, Sinha B R, Uppada UK, Kumar S. Diclofenac transdermal patch: Potential ingress to Maxillofacial Surgery. *J Maxillofac Oral Surg.* 2017; 16: 170-174.
 19. Ural SG, Yener O, Sahin H, Simsek T, Aydinli B, Ozgok A. The comparison of analgesic effect of various administration methods of diclofenac sodium, transdermal oral intramuscular in early postoperative period in laparoscopic cholecystectomy operations. *Pak J Med Sci.* 2014; 30: 96-100.
 20. Banning M. Topical Diclofenac Clinical effectiveness and current uses in osteoarthritis of the knee and soft tissue injuries. *Expert Opin Pharmacother.* 2008; 9: 2921-2929.
 21. Alessandri F, Lijoi D, Mistrangelo E, Nicolletti a, Crosa M, Ragni N. Topical diclofenac for postoperative wound pain laparoscopic gynecologic surgery: a randomized study. *J Minim Invasive Gynecol.* 2006; 13: 185-200.
 22. Funk L, Umaar R, Molajo A. Diclofenac patches for postoperative shoulder pain. *Int J Shoulder Surg.* 2008; 2: 47-48.
 23. Agarwal A, Dhiraaj S, Kumar A, Singhal V, Singh U. Evaluation of a Diclofenac transdermal patch for the attenuation of venous cannulation pain. A prospective randomized double-blind placebo-controlled study. *Anaesth.* 2006; 61: 360.
 24. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain meta-analysis. *BMC Family Practice.* 2004; 5: 10.
 25. Predel HG, Koll R, Pabst H, Dieter R, Gallcchi G, Giannetti B et al. Diclofenac Patch for topical treatment of acute impact injuries. A randomized, double-blinded, placebo-controlled multicenter Study. *Br J Sport Med.* 2004; 38: 318-323.
 26. Bruhmann P, Michel BA. Topical diclofenac patch in patients with knee osteoarthritis. A randomized double-blind, controlled clinical trial. *Clin Exp Rheumatol.* 2003; 21: 193-198.
 27. Cranney A, O'Donnell S. Topical Diclofenac improved pain and physical function with no systemic side effects in primary osteoarthritis of the knee. *Evid Based Med.* 2005; 10: 81.
 28. Vaile JH, Davis P. Topical NSAIDs for Musculoskeletal Conditions. A Review of the Literature. *Drugs.* 1998; 56: 783-799.
 29. Charan J, Biswas T. How to calculate sample size for different study designs in medical research. *Indian J Psychol Med.* 2013; 35: 121-126.
 30. Gabka J, Matsumura T. Measuring techniques and clinical testing of an anti-inflammatory agent. *Munch Med Wochenschr.* 1971; 113: 198-203.