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ANALGESIC EFFECT OF INTRAVENOUS ASCORBIC ACID VERSUS ACELCOFENAC POST-TRANSALVEOLAR EXTRACTION: A CASE–CONTROL STUDY

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ABSTRACT

One of the most important aspects of postsurgical care is finding an efficient way for the management of pain. Third molar extractions/surgical impaction is one of the most frequent surgical procedures in dental hospitals, and it is most often associated with postoperative complications like severe pain, oedema and reduced mouth opening. This study was aimed to evaluate the efficacy of 2 g intravenous

(IV) vitamin C compared to 100 mg aceclofenac on postsurgical pain, swelling and trismus after the surgical removal of third molars. A total of 101 patients were recruited for the study, and theywere divided into two treatment groups; group A (n = 51) received 2 g IV vitamin C and group B (n = 50) received 100 mg aceclofenac. Pain intensity, facial swelling and mouth opening were assessed till day 3 post-surgically. Statistical analysis of pain intensity revealed that IV vitamin C performed slightly better but not significantly different (p>0.05) from aceclofenac group at the end of day 3. No significant difference for facial swelling and mouth opening between the two treatment protocols was seen (p>0.05). Our results concluded that both treatment groups were overall similar in analgesic efficacy, postoperative oedema and reduction in mouth opening. It was also determined that the method devised administering 2 g IV vitamin C intravenously was well suited to the treatment of postoperative pain, swelling and trismus following the surgical extraction of impacted third molars.

Keywords: *third molar extraction; IV vitamin C; aceclofenac; post-surgical pain; trismus; facial swelling*

Third molar extraction/surgery is a multibillion dollar industry that generates significant amount of money in general dental practice, especially for oral and maxillofacial surgeons.[1] Considerable controversy associated with third molars is the prophylactic removal of respective teeth. No scientific studies suggested or supported the early/prophylactic extraction of third molars to prevent future disease, but still it continues to be promulgated by the professionals.[2,3] As a matter of fact, no more than 12% of the impacted teeth have associated pathology, which is similar in terms of incidence to appendicitis (10%) and cholecystitis (12%).[4]

Evidence from research suggested that wisdom teeth removal has immediate negative effect on patient's quality of life (QoL), that is, working and social lives. In a study by Colorado-Bonnin et al., where they evaluated QoL, patients took an average of 1.6 days off work, with over one-third of patients stating that the surgery had affected their performance at work.[5] Rodrigues et al. in their systematic review and meta-analyses assessed the impact of third molar removal on patient's QoL. Their findings revealed that the highest negative impact on QoL was observed on the first day postoperatively, and then, gradually it decreased over a period of time, with physical pain as the most scored domain.[6]

Although third molar removal was considered a relatively common procedure, it is an invasive procedure and has many postoperative complications. They include (1) pain, which occurs as a consequence of surgery due to reasonable damage to gums and bone, (2) swelling, (3) bruising, (4) trismus or limited mouth opening along with difficulty in eating and (5) sensitivity and alveolitis.[7] Typical postoperative pain begins within 1 to 3 hours following surgery, ranging from moderate to severe in intensity. An estimated 63.5% of the patients experience severe pain at some point of time on the first day and requires the use of analgesics.[8]

Pharmacological management of postoperative pain following the surgical removal of third molars is one of the most significant advances in oral surgery over past decades.[9] Literature has advocated the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the management of postoperative pain, and they are known for their wide usage for pain relief in dentistry.[10] Ibuprofen is the commonly prescribed NSAIDs and has been subjected to much research regarding its efficiency in postoperative dental pain.[11] Combination analgesia is often recommended for

the relief of severe pain, and the analgesic effect of combining drugs has been well documented. Daniels et al. in their study compared the efficacy of combination analgesic (ibuprofen and paracetamol) and found that its analgesic effect was superior to either of the drugs alone or other combination analgesics.[12] Derry et al. in a recent Cochrane review compared the combined drug (paracetamol plus ibuprofen) with placebo or the same dose of oral ibuprofen alone using the postoperative dental pain model. They concluded that combination drug provided better analgesia than either drug alone.[13]

Aceclofenac, an NSAID, is reported to be an effective and superior analgesic in the treatment of moderate-to-severe acute pain resulting from third molar surgery, compared to diclofenac.[14,15] Chunduri et al. conducted a comparative study testing the analgesic effect of aceclofenac with diclofenac and concluded that aceclofenac is superior and showed tolerability profile compared to diclofenac.[14]

Vitamin C, known to be ascorbate or ascorbic acid, is an essential component for collagen synthesis, and it also plays a vital role in the immune function by improving the absorption of non-heme iron.[16,17] It is evident from literature that pain is a symptom of vitamin C deficiency, and such pain was completely resolved within a week or two following a supplementation of vitamin C.[18] It is believed that the anti-nociceptive effects of vitamin C is mainly based on its antioxidant properties by scavenging a wide range of ROS. Various studies proved the effectiveness of vitamin C in patients with postherpetic neuralgia, zoster-associated neuralgia and rheumatoid arthritis when infusions of higher concentrations were administered.[19–21] Recent research has indicated a positive impact of high-dose vitamin C on cancer and chemotherapy-related QoL.[22] Cameron and Campbell reported a number of cases suffering from severe cancer-related pain, and when they were administered a high-dose of oral and intravenous (IV) vitamin C, mild to complete amelioration of pain was observed.[23] Jeon et al. assessed the effect of IV vitamin C on postoperative pain scores during the first 24 hours after laparoscopic colectomy. Infusion of vitamin C at higher concentrations produced significantly lower pain scores following surgery.[24] So far, no studies are available in literature testing the effect of IV vitamin C in the reduction of pain after the third molar surgery. Owing to its role in the management of pain post-surgically, we designed this clinical study to examine the effect of IV vitamin C (3 g) and aceclofenac (100 mg) on postoperative lower third molar extraction. And also, we evaluated their role in the reduction of postoperative swelling and trismus among both groups.

PATIENTS AND METHODS

Patients who attended the Department of Oral Medicine and Radiology with painful impacted third molars in the lower arch and required surgical removal of the same were included in this study. This study was conducted between December 2018 and April 2019, and all the subjects participated were above 18 years of age. The study protocol and informed consent were approved by the research and ethics committee of the institute (BCDS/Dean/2018/605(A)). This was a single-centre double-blinded double arm interventional study. A written informed consent was obtained from each patient after detailed explanation of the study protocol. Patients who had a history of corticosteroid use over a period of last two months, any history of thromboembolic events, current use of anti-inflammatory drugs, pregnant or lactating women were excluded from the study.

All the patients were then allocated into two groups: Group A and Group B. The patients, surgeon and examiner were blinded to test and control medications. Group A (n = 51) consisted of patients who received 2 g IV ascorbic acid twice daily for 3 days which was administered

post-surgically. Group B (n = 50) patients were given 100 mg oral aceclofenac twice daily for 3 days post-extraction. The preoperative data collected from each patient included demographic data (age and sex), type of impaction, location of impaction, degree of impaction and an orthopantomograph (OPG).

Operative Procedure

Each patient underwent a mandatory systemic examination and an assessment of medical risk status with emphasis on renal stones and iron overload estimation. Intravenous cannula was placed on the left arm within the cuboidal vein. The patency of the vein was felt for all patients before procedure. Impacted third molar location was assessed clinically and radiographically for the proximity to the nerve bundle. Transalveolar extraction was carried out under regional anaesthesia atraumatically. For patients in group A, intravenous ascorbic acid 2 g was given immediately after extraction followed for 8 hours through the cannula. The injections were prescribed for 3 consecutive days, each day amounted for 4 g. All patients had the liberty to withdraw from the study at a point when they felt that the pain was intolerable and an NSAID was prescribed. For patients in group B, NSAID in the form of oral aceclofenac 100 mg was prescribed for all patients twice daily for 3 days post–extraction, and all participants were followed up for 3 days. Suture removal was carried out on the 5th day postoperatively.

All the patients were assessed preoperatively and postoperatively for trismus, any possible swelling anteroposteriorly and superoinferiorly, and pain by the same examiner using the same methods. The entire procedure and methodology was exclusively devised and tailored for this study.

Pain Measurement

Pain intensity for each patient was evaluated using the visual analogue scale (VAS). VAS has got a horizontal line of 10 mm, which indicates 0 mm stands for "no pain" and 10 mm stands for "severe pain." Patients were asked to mark on the horizontal line the point that best represents their pain perception. Assessments were made on each consecutive day following the surgical extraction.

Measurement of Facial Width Swelling

Facial swelling was measured preoperatively using a measuring tape. The outer contour of the cheek was measured using the method described by Amin and Laskin.[25] All the measurements were recorded by a single examiner, taken thrice, and the average was recorded in centimetres (cm). Post-surgically the measurements were carried out on day 2 and day 3.

Measurement of Mouth Opening (Trismus),

Mouth opening was measured by the maximum interincisal distance recorded using digital vernier callipers. All the patients were made to sit upright in the chair and also made sure that the orbitomeatal line was parallel to the floor. The reference points used were the incisal edge of the maxillary central incisor and the incisal edge of the mandibular central incisor at the maximal mouth opening available. All the measurements were repeated thrice and the average of those was measured in millimetres (mm).

Statistical Analysis

Data were analysed using statistical software, that is, Statistical package for Social Sciences (SPSS) for windows (Version 20.0, Chicago, IL, USA). Differences between the groups were analysed using one-way analysis of variance (ANOVA). Tukey's test for pairwise comparison was performed when ANOVA indicated significant differences. The level of statistical significance was set at $p<0.05$.

RESULTS

Table 1 presented the results of pain intensity and mouth opening both preoperatively and on successive days postoperatively between the treatment groups. For group A, the mean pain scores on

TABLE 1. Patients assessment of pain, mouth opening between treatment groups at different time intervals.

		Group IV Vitamin C	Group Aceclofenac	p
Pain score- Visual Analog Scale				
	Pre- op	5.96	6.24	0.558
	Day 1	5.7	5.5	0.532
	Day 2	3.37	3.07	0.274
	Day 3	1	1.04	0.809
	p	***0.000****	***0.000****	
Mouth opening/ Trismus				
	Pre- op	41.14	36.38	***0.000****
	Day 1	37.76	35.84	0.098
	Day 2	22.33	22.48	0.865
	Day 3	33.31	32.8	0.550
	P	***0.000****	***0.000****	

**Statistically significant (p<0.05).*

consecutive days were significantly lower with increase in time interval (p<0.05). The result of Tukey's post hoc test revealed that there was no statistical significance in the mean pain scores between the preoperative period and day 1 (p=0.866). For group B, results of the ANOVA test show that the mean pain scores on consecutive days exhibited significant reduction in pain intensity (p<0.05). Post hoc test showed that there is no statistically significant difference between the preoperative period and day 1 (p=0.118). Results from independent *t*-test show that there was no statistically significant difference between treatment groups (p>0.05) for all time intervals. Figure 1 compared pain intensity between the two treatment groups.

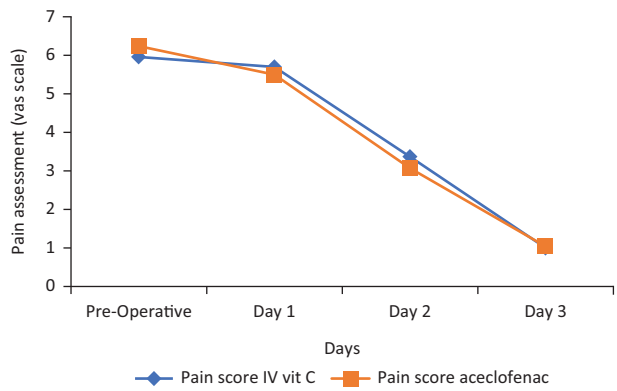

FIG 1. Comparison of subjective pain in IV Vitamin C and Aceclofenac groups.

For mouth opening, results of the ANOVA test show that there was a significant difference (p<0.05) between consecutive days for group A, with the mean mouth opening of 41.14 cm preoperatively and 33.31 cm on day 3. Also, significant difference between consecutive days was obtained for group B (p<0.05). Results from independent *t*-test revealed that there was no statistically significant difference between treatment groups (p>0.05) for all time intervals except preoperatively, that is, p<0.05. Figure 2 compared mouth opening between the two treatment groups.

Although no significant differences were observed between the treatment groups with respect to pain scores and mouth opening, the pain scores for group A were lower (1 mm on day 3) than those of group B (1.04 mm on day 3). Similarly, better mouth opening was observed in group A compared to group B on day 3.

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Table 2 presents facial swelling anteroposteriorly and superoinferiorly on postoperative days 2 and 3. For group A, the mean measurement of swelling anteroposteriorly was significantly lower than (p=0.049) that of group B. The mean measurement of swelling superoinferiorly showed no significant difference on consecutive days for either of the groups. Independent *t*-test shows that there is significant difference between groups on day 2 for swelling anteroposteriorly and on day 1 for swelling superoinferiorly (Table 2). Figures 3 and 4 showed a comparison of swelling, anteroposteriorly and superoinferiorly, for both treatment groups.

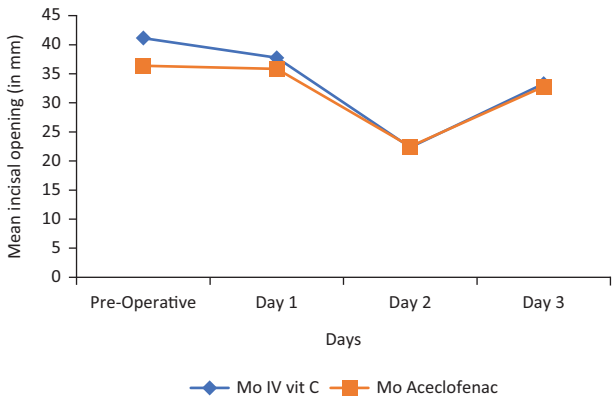

FIG 2. Comparison of mouth opening (in mm) in IV Vitamin C and Aceclofenac groups.

DISCUSSION

Third molar extraction is the most common surgical procedure carried out by oral and maxillofacial surgeons in dental clinic setups worldwide. Although this surgical procedure was considered to be secure and with low morbidity, the risk of complications always exists. Such complications include constant pain and swelling, haemorrhage, dry socket, dentoalveolar fracture, paraesthesia due to the involvement of

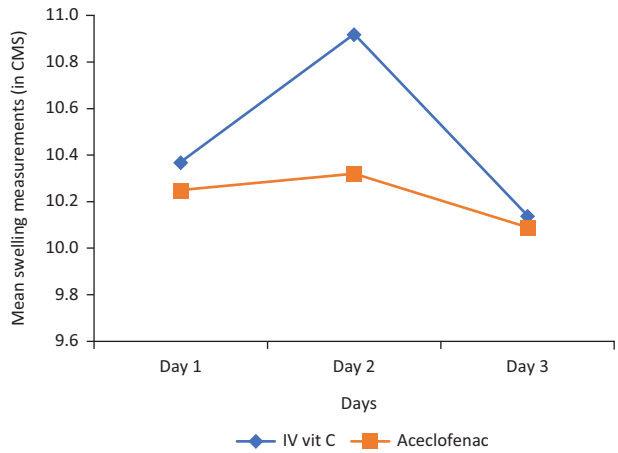

FIG 3. Comparison of facial swelling (anteroposterior) IV Vitamin C and Aceclofenac groups.

TABLE 2. Patients assessment of facial swelling between treatment groups at different time intervals pre and post surgically.

		Group IV Vitamin C	Group Aceclofenac	p
Swelling- Anteroposterior				
	Day 1	10.37	10.25	0.636
	Day 2	10.92	10.32	**0.017***
	Day 3	10.14	10.09	0.911
	p	**0.049***	0.701	
Swelling- Superoinferior				
	Day 1	10.37	10.68	**0.017***
	Day 2	10.53	10.7	0.615
	Day 3	10.49	10.61	0.388
	P	0.744	0.911	

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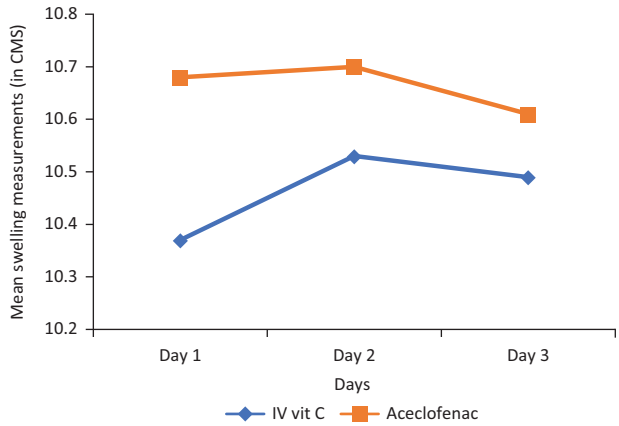

FIG 4. Comparison of facial swelling (Superoinferior) IV Vitamin C and Aceclofenac groups.

inferior alveolar or lingual nerve, jaw fracture, and so on.[26] It has been reported in literature that the complication rates following third molar surgeries varied between 2.6% and 30.9%.[27] Pain, swelling and difficulty in mouth opening are the more commonly reported unpleasant experiences by the patients. Owing to the increased attention towards the management of post-surgical pain in hospital settings, the quest towards the development of newer analgesics with more potency and fewer adverse effects was never ending.

The role of vitamin C or ascorbic acid, which is a six-carbon lactone in the management of orthopaedic pain, virus-associated pain (postherpetic neuralgia), cancer-1related pain and so on, has been widely discussed.[28] However, its role in the management of postoperative dental pain was not evaluated so far. This clinical study was aimed to assess the clinical effect of IV ascorbic acid and aceclofenac (cox-2 inhibitor) on pain, swelling and trismus following the surgical extraction of third molars.

In this clinical study, approximately 48.5% of patients reported severe baseline pain intensity preoperatively. A total of 30.6% reported severe baseline pain intensity at day 1 following the surgical removal of impacted third molar. At the end of day 1 of the postoperative period, there was no statistically significant difference between the analgesia produced by IV ascorbic acid and by aceclofenac. And on remaining days, the pain relief was almost similar in both groups. However, on day 3 of the postoperative period, even though there was no significant difference between the groups, the mean pain score of patients receiving IV vitamin C was slightly lesser than those receiving aceclofenac. Contrary to our findings, in a study by Jyothsna et al., it was observed that the peak analgesic effect of aceclofenac was produced at the end of 8 hours of postoperative period.[15] In another study, immediate pain after surgery using VAS was severe in 47.2% patients and 15.2% of patients have experienced severe pain even after a week following surgery.[29] Therefore, in terms of pain intensity, our results suggested that IV vitamin C performed slightly better but not significantly different from aceclofenac group at the end of day 3.

From the results, we observed that the reduction of mouth opening was seen in both treatment groups. This was particularly marked on the second postoperative day. The difference in the mean interincisal distance between the treatment groups was not statistically significant ($p>0.05$) in the postoperative period, that is, day 1, day 2 and day 3, respectively. Similar pattern of reduction in mouth opening on day 1 following surgery and further improvement on day 5 were observed in the group treated with aceclofenac in the study conducted by Yasin and Tawfiq.[30] Similar to pain intensity, both IV vitamin C and aceclofenac have performed similarly for the treatment of trismus/mouth opening with significant improvement of the same in the postoperative period.

Postoperative swelling or oedema is mainly due to the combined action of inflammatory mediators and also phospholipids released from ruptured cell membranes, which turns into prostaglandins and other metabolites causing pain and swelling.[31] Quantifying postoperative oedema

accurately is difficult owing to the three-dimensional nature with an irregular, convex surface.[32] In this study, measurement of the swelling was recorded both anteroposteriorly and superoinferiorly. Due to diffusion of swelling in different planes, the examiner of study felt difficult to measure accurately, and therefore, measurements were made in triplicate and their average was recorded. It was noted that postoperative swelling (anteroposteriorly) reduced in both groups with increase in postsurgical period from day 1 to day 3. Statistically significant difference was observed for IV vitamin C group ($p<0.05$). Superoinferiorly, no statistically significant difference was observed in both groups ($p>0.05$).

Excellent safety profile has been reported in phase I studies for IV vitamin C alone and when used in combination with chemotherapy. Reported side effects for IV vitamin C include nausea, dizziness, dry mouth, perspiration and weakness.[33] A study by Mikirova et al. reported that the optimal gram doses of IV vitamin C should be between 5 and 25 g.[34] In this study, no reports of any serious intolerance and adverse events were obtained for both treatment groups.

This study effectively demonstrated the analgesic effect of ascorbic acid on intravenous injection although it has few shortcomings. The serum levels of ascorbic acid for all patients were not measured pre- and post-procedures. Enhanced analgesic effect could have been anticipated with increasing doses of ascorbic acid injections. The dose was restricted to only 2 g in this study. However, the positive effect of IV vitamin C and its analgesic effect could pave way for more interventional trials with increasing doses for various surgical procedures. This could reduce the side effects arising from the usage of non-steroidal anti-inflammatory agents in situations involving compromised renal functions and platelet as well as peptic ulcer disorders.

CONCLUSION

This study was an attempt to evaluate and compare the efficacy of IV vitamin C and aceclofenac in controlling the postoperative complications following third molar surgery. Our results demonstrated that there was no statistical difference between the two groups, indicating that IV vitamin C 2 g and aceclofenac 100 mg were overall similar in analgesic efficacy, postoperative oedema and reduction in mouth opening. To prove and substantiate the safety and efficacy of IV vitamin C in painful conditions following surgical extractions, clinical studies with adequate sample size and sound methodologies are needed.

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