

ORIGINAL ARTICLE

EVALUATION OF ANTI-INFLAMMATORY EFFICACY OF ASCORBIC ACID AFTER THIRD MOLAR SURGERY

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Background: Abstraction of wisdom teeth or impacted third molar under local anaesthesia is one of the most frequent interventions by an oral and maxillofacial surgeon. The abstraction of the third molar is usually followed by the release of liberation and consequent trismus, pain, and swelling due to the area of the third molar being highly vascularized and rich in loose connective tissue. Objective of the study was to evaluate the anti-inflammatory effect of ascorbic acid following surgical extraction of the third molar. **Methods:** The current study was carried out Armed Forces Institute of Dentistry, Rawalpindi, from October to December 2022. This was a cross-sectional observational study. Fifty participants who required surgical extraction of the impacted third molar were included in the study via non-probability purposive sampling and were segregated equally into two groups, i.e., Group A and Group B, comprising twenty-five participants in each group. Group A received amoxicillin with clavulanic acid (625 mg) thrice a day and metronidazole (400 mg) twice daily. In comparison, Group B received amoxicillin with clavulanic acid (625 mg) thrice daily, ascorbic acid (500 mg) twice daily, and metronidazole (400 mg) twice daily. Both groups received naproxen sodium as per requirement (550 mg). Pain, facial swelling, and C reactive protein concentration were evaluated until the 7th postoperative day. **Results:** There was a reduction in pain and facial swelling in both groups, but in the ascorbic acid group, there was more reduction in pain and facial swelling compared to the control group. However, the difference between the two groups in reducing pain and facial swelling was statistically significant ($p < 0.01$). There was a reduction in CRP in both groups, but in the ascorbic acid group, there was more reduction in CRP 2.35 (1.60–5.30) compared to the control group 2.6 (0.86–5.03). However, the difference between the two groups in reducing C reactive protein concentration was statistically insignificant ($p > 0.05$). **Conclusion:** Our study concluded that ascorbic acid significantly reduced inflammation and C reactive protein, so ascorbic acid should be used as an adjuvant supplement with other conventional drugs.

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INTRODUCTION

Abstraction of wisdom teeth or impacted third molar under local anaesthesia is one of the most frequent interventions by an oral and maxillofacial surgeon. The abstraction of the third molar is usually followed by the release of liberation and consequent trismus, pain, and swelling due to the area of the third molar being highly vascularised and rich in loose connective tissue.¹ Acute inflammation is the primary cause of these signs and symptoms arising from the surgical handling of soft and hard tissues. Many inflammatory reactions occur after oral surgical procedures, which are not restricted to the oral cavity and can be imitated in the soft tissues of the face. Pain and local inflammation patients' reactions after third molar surgery make it difficult to perform routine work. There are also psychological consequences because individuals who have substantial soft tissue swelling avoid social interaction and tend to stay at home.²

During the postoperative period, an acute inflammatory response is a consequence of tissue damage and is accompanied by the repair mechanisms that intercede to restore tissue integrity.³ After the third molar abstraction, one of the postoperative complications associated with it is trismus, as a manifestation of swelling, pain, or both. Some studies have revealed that postoperative pain peaks around 6–8 hours, while postoperative swelling and trismus reach their maximum intensity 24–48 hours after surgery, and all diminish on the 7th postoperative day.⁴ The activated macrophages produce interleukin-1 and interleukin-6, and tumour necrosis factor- α during tissue damage that causes the synthesis of acute phase reactant through the liver.⁵

Determining C reactive protein (CRP) in the blood effectively analyses inflammation and tissue damage. In the acute phase of inflammation, CRP is the most effective. Like other proteins in the acute phase of inflammation, CRP acts as a defense signal in the host's innate immune responses. The range of CRP concentration

in healthy individual fields 0.1–3.9 mg/L depends on the determination method. A rise in CRP occurs four to six hours after injury, and its extreme concentration is noted after twenty-four to seventy-two hours. After surgery, CRP concentration increases twice every eight hours and returns to average concentration after seven days. The infection with gram-negative bacteria has a significant role in inflammation in the oral cavity in case of severe injury. Due to the neoplastic process, the concentration of CRP increases by thousands of folds, reaching a value superior to five hundred milligrams per liter.⁶

Ascorbic acid reduces the response of several proinflammatory biomarkers such as interferon, interleukins, tumour necrosis factor, and some inflammatory biomarkers such as C-reactive protein. It also affects the wound-healing genes by blocking the nuclear factor kappa-light-chain-enhancer of activated B cells and endothelial cells, which are crucial in regulating gene expression during inflammation.⁷

Worldwide, no clinical studies assessed the role of ascorbic acid in reducing the concentration of CRP immediately after surgery and on the 7th day after the third molar surgery. The purpose of the current study is to identify the effect of ascorbic acid on pain, facial swelling, and the concentration of CRP immediately after surgery and on the 7th day after surgical removal of wisdom teeth in the Pakistani population.

MATERIAL AND METHODS

The current study was conducted in the Department of Oral Surgery, Armed Forces Institute of Dentistry (AFID), in collaboration with the Department of Pharmacology, Army Medical College (AMC), Rawalpindi, Pakistan, from October to December 2022. Ethical approval was taken from the Ethics Review Committee of AMC, the National University of Medical Sciences (ERC/ ID/ 255), and AFID. This was a cross-sectional observational study. A sample size of 50 was calculated using the World Health Organization sample size calculator, with twenty-five participants in both groups.

Patients fulfilling the inclusion criteria were included through non-probability purposive sampling. Then participants were segregated equally into two groups: Group A (n=25) received amoxicillin with clavulanic acid (625 mg) thrice daily and (400 mg) metronidazole twice daily for five days. This was considered a control group. Group B (n=25) received amoxicillin with clavulanic acid (625 mg) thrice daily, metronidazole (400 mg) twice daily for five days, and ascorbic acid 500 mg thrice daily for seven days. This was considered a test group. Both groups received naproxen sodium (550 mg) as per requirements. Both males and females with ages more than 18 years requiring third molar surgery with one-third impacted tooth were included in our study. Pregnant or lactating

women, periapical and periodontal disease, and any comorbid conditions such as diabetes and hypertension were excluded from this study.⁸ All participants were counselled preoperatively, and informed consent was taken from each participant. Demographic details like age, gender, and body mass index were recorded. The concentration of CRP was determined immediately after the surgery (CRP 1) and the seventh day after the surgery (CRP 2). Moreover, the difference (Δ CRP) between CRP 1 and CRP 2 (Δ CRP) was also determined. The rate of Δ CRP was evaluated as the difference between CRP 2 and CRP 1 and expressed as a number using the following formula:⁶

$$\Delta \text{CRP} = \text{CRP 2} - \text{CRP 1}$$

The pain was evaluated by using a Visual Analogue Scale with "0 mm" showing "no pain" and "10 mm" showing the "worst possible pain" at different time intervals: T0 (immediately after surgery as a baseline), T1 (24 hours postoperatively), T2 (48 hours postoperatively) and T3 (72 hours postoperatively). Facial swelling was assessed using a six-point VAS, where 0 shows "no swelling," and 5 shows "extreme severe swelling" at different time intervals: T0 (24-48 after surgery as a baseline), T1 (72 hours after surgery) and T2 (7th day after surgery).^{9,10} A statistical interpretation was performed by using SPSS 25. Qualitative variables like gender, pain, and facial swelling were presented as percentages and frequencies and examined using Pearson's Chi-Square test. For non-parametric data, the Mann-Whitney U test was applied like CRP and was expressed as the median and interquartile range (IQR). The confidence interval of 95% was used, and the significance level was set at $p \leq 0.05$.

RESULTS

There was a reduction in CRP in both groups, but in the ascorbic acid group, there was more reduction in CRP 2.6 (0.72–6.31) compared to the control group 2.5 (1.60–5.30). However, the difference between the two groups in reducing C reactive protein concentration was statistically insignificant ($p > 0.05$), presented in Table-1. The severity of facial swelling was reduced in both groups. However, ascorbic acid observed a better response than the control group presented in Table-2. There was a statistically significant difference in the frequency of pain between study groups ($p < 0.001$), shown in Table-3.

Table-1: Comparison of CRP between the control group and study groups

	Group A (n=25)	Group B (n=25)	p-value
	Median (IQR)	Median (IQR)	
CRP 1 $\mu\text{g/mL}$	2.3 (0.60–8.70)	6.2 (1.67–13.70)	0.056 [#]
CRP 2 $\mu\text{g/mL}$	2.6 (0.72–6.31)	2.5 (1.60–5.30)	0.600 [#]
Δ CRP 2–CRP 1	0.0 (-6.20 -2.12)	-1.10 (-5.45 -0.700)	0.290 [#]

[#] = Insignificant (p value > 0.05)

Table-2: Comparison of the facial swelling between the control and study group

	Group A (n=25)	Group B (n=25)	p-value
Baseline			
	n (%)	n (%)	0.141#
None	1 (4%)	1 (4%)	
Slight	0 (0%)	0 (0%)	
Mild	0 (0%)	1 (4%)	
Severe	0 (0%)	4 (16%)	
Very Severe	4 (16%)	1 (4%)	
Extremely Severe	20 (80%)	18 (72%)	
At 72 hours			
None	1 (4%)	1 (4%)	0.126#
Slight	0 (0%)	2 (8%)	
Mild	1 (4%)	4 (16%)	
Severe	8 (32%)	12 (48%)	
Very severe	6 (24%)	3 (12%)	
Extremely Severe	9 (36%)	3 (12%)	
At 7 th day			
None	4 (16%)	13 (52%)	0.025*
Slight	4 (16%)	7 (28%)	
Mild	9 (36%)	3 (12%)	
Severe	5 (20%)	2 (8%)	
Very Severe	1 (4%)	0 (0%)	
Extremely Severe	2 (8%)	0 (0%)	

* = significant (p value ≤ 0.05), # = insignificant (p value > 0.05)

Table-3: Comparison of pain between the control and study group

Pain	Group A (n=25)	Group B (n=25)	p-value
Baseline			
Mild	4 (16%)	4 (16%)	0.291#
Moderate	2 (8%)	6 (24%)	
Severe	19 (76%)	15 (60%)	
At 24 hours			
None	0 (0%)	0 (0%)	0.001*
Mild	2 (8%)	13 (52%)	
Moderate	8 (32%)	8 (32%)	
Severe	15 (60%)	14 (56%)	
At 48 hours			
None	0 (0%)	1 (4%)	< 0.001*
Mild	4 (16%)	17 (68%)	
Moderate	12 (48%)	7 (28%)	
Severe	19 (76%)	0 (0%)	
At 72 hours			
None	0 (0%)	3 (12%)	0.001*
Mild	10 (40%)	20 (80%)	
Moderate	11 (44%)	2 (8%)	
Severe	4 (16%)	0 (0%)	

* = significant (p value ≤ 0.05), # = insignificant (p value > 0.05)

DISCUSSION

One of the most common procedures worldwide is third molar surgery in oral and maxillofacial surgery departments, leading to postoperative complications including pain, facial swelling and trismus.¹¹ Our aim in this study was to determine the CRP concentration, pain and facial swelling of ascorbic acid following surgical removal of the third molar.

To the best of our knowledge, this was our first study in which the effect of ascorbic acid on CRP after third molar surgery was evaluated. Worldwide

two studies have been conducted in which the effect of vitamin C on chronic periodontitis was assessed. Still, the result of vitamin C is considered in combination with other drugs. Our study found that there was a reduction in CRP concentrations in both groups, but there was more reduction in CRP concentration in the ascorbic acid group when compared with the control group. However, both groups had a statistically insignificant difference in CRP concentration. In our study, there was a statistically significant difference in reducing the severity of pain and facial swelling between both groups.

Similar to our findings, a study conducted by Rasperini *et al.* revealed that intake of multivitamins reduced the CRP concentration after three months of therapy compared with baseline. However, there was a statistically insignificant difference between both groups.¹² In contrast to our findings, there was a study carried out by Penmetsa and his friends in which the role of orthoboon (glucosamine sulfate + collagen + vitamin C) on CRP before and after non-surgical periodontal therapy was evaluated and concluded that the mean CRP levels were reduced significantly in orthoboon group.¹³ Contrary to our findings there was another study carried by Amaliya *et al.* in which the effect of vitamin C in combination with calcium threonate and citrus flavonoids supplementation on CRP was evaluated. This study revealed that vitamin C combined with calcium threonate and citrus flavonoids decreased the CRP level, and there was a statistically significant difference before and after supplement administration ($p < 0.001$).¹⁴

Recently, a study conducted by Gonzalez-Serrano and his colleagues in 2021, showed that the application of propolis extract, nano vitamin C and E reduced the severity of pain and incidence of dry sockets.¹⁵ A study by Pribadi *et al.* showed that taking (320 mg) of vitamin C supplement for three months reduced gingival bleeding by increasing collagen formation.¹⁶ Another study by Chaudhary *et al.* demonstrated that injectable vitamin C decreased pain intensity and gingival inflammation.¹⁷ Recently study conducted by Gadge and his colleagues showed that taking vitamin C supplements decreased postoperative pain after dental implant surgery.¹⁸ Another study by Mukherjee and Gowda showed that taking ascorbic acid (500 mg) reduced postoperative pain, pocket depth and clinical attachment loss in periodontal flap surgery.¹⁹

The improvement in the parameters mentioned above, i.e., reducing the intensity of postoperative pain, facial swelling and CRP concentration, was achievable because ascorbic acid has anti-inflammatory and anti-nociceptive properties. Ascorbic acid plays an important role in inflammation by decreasing the inflammatory cytokines such as interleukin 1 and 6, tissue necrosis factor α and proinflammatory cytokines such as C-reactive protein. The anti-nociceptive properties of ascorbic acid are due to the antioxidant effect of scavenging the reactive oxygen species.^{7,10}

Hence different studies support our findings as ascorbic acid has an ameliorating effect on pain and facial swelling as it is an antioxidant and anti-inflammatory agent, and its use is associated with fewer adverse effects. Hence it is safe and can be prescribed to patients for oral surgery as an adjuvant with other drugs.

The small sample size is a limitation of the current study. In our future work, we will take a large sample size with the expectation of elaborating the benefits of this treatment scheme to the patient on an extensive community basis.

CONCLUSION

We conclude that intake of ascorbic acid (500 mg) reduces postoperative pain, CRP concentration, and facial swelling in patients after surgical abstraction of the third molar. We recommend using ascorbic acid as an adjuvant supplement after the third molar surgery for better therapeutic outcomes.

Disclaimer: None

Conflict of Interest: None

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AUTHORS' CONTRIBUTION

MF: Conceived, designed, collected data and did statistical analysis with interpretation & manuscript writing. KF: Project supervision right from its conception, and evaluated manuscript for important intellectual content. SA, MN, FFG: Did review and final approval of the manuscript; responsible for accuracy and integrity of data. CMU: Supervised the entire project in the hospital, revised the manuscript critically for final publication

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