Effect Of Vitamin C On Postoperative Pain After Dental Implant Surgery

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Abstract

Dental implant surgery is a minor operation for replacing the tooth by drilling the titanium screw into the jaw bone. Postoperative pain happens because of tissue injury in conjunction with muscle spasms after the surgery. More than 75% of surgery patients suffer from acute pain. Vitamin C is a water-soluble vitamin that has an important role as an enzyme cofactor in human composition. It can reduce and prevent pain after surgery. Nevertheless, the effect of vitamin C on postoperative pain after dental implant surgery is still unknown. The main objective of this study, therefore, is to evaluate the effectiveness of 6oo mg of vitamin C for pain-relieving within the period of 3 days after the dental implant surgery. Twenty selected subjects were inserted with Straumann ® implant (BL, BLT, BLX) at the posterior area of the dental arch. Then, they were randomly divided into 2 groups, namely vitamin C and placebo groups. In the vitamin C group, participants were provided with a 2-daily dose of 600 mg vitamin C for 3 days after dental implant surgery. The other group received the placebo instead. The postoperative pain score, which applied the visual analog scale (VAS), was collected daily in the morning for 3 days after surgery. There were no differences in the participant's age, sex, underlying disease, implant size, implant length, implant torque, and ISQ value ($p > 0.05$). The visual analog score showed that the vitamin C group had a statistically significantly lower postoperative pain score on day 1 after the dental implant surgery ($p = 0.013$) while day 2 and day 3 did not have any statistical significance ($p > 0.05$). Thus, vitamin C can be applied as an additional supplement for postoperative pain relief after dental implant surgery.

***Keywords**: dental implant surgery, vitamin C, Postoperative pain*

1. Introduction

Pain is the subjective feeling that each person recognizes through past experiences. According to Merskey and Bogduk, 1994, the definition of pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk, 1994). Pain can be classified based on pathophysiology. It is separated into nociceptive (pain from injury) and neuropathic pain (nerve damage pain) (Abd-Elsayed and Deer, 2019).

Dental implant surgery originates the nociceptive pain. This postoperative pain initiates from the tissue contusion after surgery. The contusion leads to tissue and surrounding structure inflammation. The site of inflammation will release many endogenous substances such as substance P, an active lipid compound derived from arachidonic acid (Prostaglandins and leukotrienes), histamine, serotonin, and bradykinin (Kehlet and Dahl, 1993). All substances and other byproducts from inflammation activate the peripheral nerve endings and cause electrophysiological alteration that leads to lower the nociceptive threshold and promotes more rapid afferent transport. The afferent transport alterations can lead to the pain after surgery initially through the A-delta fiber, which is the myelinated nerve fiber, that consigns the pain signal to the central nervous system (CNS) (Kehlet and Dahl, 1993). CNS is the area in the brain that process the pain signals. After the interpretation, the CNS will transmit the signal for controlling and activating the C-fiber, which is an unmyelinated nerve, leading to the pain plateauing between 48 to 72 hours after the operation (Bryce et al.,2014). In addition, the nociceptive signal can stimulate the changing in the spinal cord resulting in increasing nociceptive field and hyperexcitability. If this pain pathway can be inhibited, the postoperative pain can be decreased. The endogenous pain pathway that is facilitated through the spinal cord level can be inhibited by controlling the afferent nerve impulse from the brainstem. The transmitters that influence pain relief are norepinephrine, serotonin, and endogenous opioids. Postoperative pain origination is complex due to each patient processing and tolerating pain differently. Variance in VAS scores occurs from many factors such as age, gender, anxiety level, pain expectation, pain disposition, etc (Eli et al., 2003). The patients who

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received dental surgery had pain intensity of around 30 to 70 when applied a visual analog scale of 100 points for pain evaluation. The third molar tooth and retained root removal showed more pain than other operations (Seymour et al., 1983). Based on Kim et al. (2013), the postoperative pain after dental implant surgery is at a moderate level by using a visual analog scale of 10 points for evaluation. The result of this study found that day 1 after surgery had the highest pain score of 4.13 ± 1.37, followed by immediate (1.03 ± 0.83) and day 2 (0.98 ± 0.94) postoperative pain. Besides, many substances can be used as an adjunct to analgesic drugs for pain management such as vitamin (C, D), magnesium, and alpha-lipoic acid (Na et al., 2011; Mijnhout et al., 2010; Carr and McCall, 2017). In this study, vitamin C is focused on.

Vitamin C (L-ascorbic acid) is a water-soluble vitamin that takes the part of enzyme cofactors in human composition. This vitamin can not be synthesized in the body due to a lack of L-gluconolactone (GLO) (Linster and Schaftingen, 2006), which is an enzyme that alters glucose to vitamin C (Kohlmeier, 2013). Introducing vitamin C into the human body requires dietary sources that mostly originate from plants (Linster and Schaftingen, 2006). For the vitamin C pharmacokinetics, vitamin C that is provided orally will be transported both through active and passive channels using the specific pathways. It is separated into 2 forms, which are ascorbate and dehydroascorbic acid form (Lykkesfeldt and Tveden-Nyborg, 2019). The first form is transported both through active and passive processes. The active diffusion way passes through the sodium-dependent vitamin C transporters (SVCT-1) into the intestinal epithelium (Tsukaguchi et al., 1999). The dehydroascorbic acid form will pass via GLU1 and GLU3 transporters. After that, both forms of vitamin C will be sent to plasma by using GLU1 and GLU2 in the basolateral membrane (Lindblad et al., 2013). Generally, vitamin C concentration in human plasma is about 50-80 mM while the tissue concentration is lesser, which is approximately 0.5-10 µM. The normal range of plasma vitamin C concentration is not over 80 µM because it can be excreted rapidly via the kidney. In addition, the average oral dose, 200 mg of vitamin C, can be completely absorbed while the larger doses have less efficacy and lower absorption is on the contrary. Based on Levine et al. (1996), 500 mg and 1250 mg of vitamin C can be absorbed in less than 75% and 50% respectively. Furthermore, vitamin C has a short half-life of approximately 2 hours after consumption. Medical professionals, thus, recommend that vitamin C should be administered in small doses more frequently during the day. According to Padayatty and Levine (2001), the dose that humans must intake for a day to prevent vitamin C deficiency symptoms is 50 to 60 mg; however, the dosage for pain relief, remains controversial. Nevertheless, the studies about complex regional pain syndrome (CRPS), which is the chronic pain developed after an injury, surgery, or heart attack, provided the dose of vitamin C from 200 mg to 1500 mg per day to the patient. The study by Zollinger et al. (2007) found that vitamin C doses that are equal to or more than 500 mg can dwindle the CRPS incidence effectively. Moreover, the patients who received surgery desire higher vitamin C supplements of more than 500 mg. Based on Shukla (1969), vitamin C concentration in plasma will be diminished sharply in 3 to 6 days after surgery. The adverse events of vitamin C are rare. A dose of more than 2000 mg per day is not suggested due to the side effects such as diarrhea, stomach upset, flushing, headache, fatigue, and skin rash (Schlueter and Johnston, 2011).

About vitamin C and pain, vitamin C is still controversial for pain-relieving. However, it is found that vitamin C has effective antioxidant, anti-inflammation, neuroprotective, and neuromodulation properties (Carr and McCall, 2017). In antioxidant properties, it can eliminate the reactive oxygen species and prevent the surrounding tissues and cells from oxidative destruction (Carr and Frei, 1999). In a situation that has excessive oxidative stress, vitamin C which plays an important role in many enzyme cofactors inside the human body still has the ability in the situation due to its potent antioxidant capacity. Moreover, vitamin C also decreases the expression of inflammatory markers such as C-reactive proteins and pro-inflammatory cytokines (tumor necrosis factor, interferon, and interleukins) (Mikirova et al., 2012).

Vitamin C also takes an important role as a cofactor in various neurotransmitter syntheses such as catecholamine, dopamine, and serotonin neurotransmitter. It, therefore, is related to neuromodulation (Harrison and May 2009). Vitamin C supports dopamine β-hydroxylase enzyme creation that transforms dopamine into norepinephrine (May et al., 2013). Besides, vitamin C promotes the synthesis of dopamine passed through the tetrahydrobiopterin cycle by up-regulating the tyrosine hydroxylase (the rate-limiting enzyme of dopamine) (May et al.,2012) and also relates to serotonin formation passing through this cycle.

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Due to the excessive number of neurotransmitters, it presents that serotonin and norepinephrine reuptakes are inhibited, which leads to effective pain control. Based on Bornstein et al. (2013) who compared deficiencies of vitamin C and normal animals, the result showed that deficiency animals had a norepinephrine concentration lower than control. Thus, vitamin c stimulated more endogenous transformation of these neurotransmitters, which conducts less pain in some patients.

Similarly, vitamin C is crucial to endomorphin-1 and -2 synthesis (amidated neuropeptide) because one of the enzymes, which is peptidyl glycine α-amidating monooxygenase (PAM), is a vitamin C-dependent enzyme (Prigge et al., 2000). This enzyme alters glycine-extended peptide to peptidyl (2-hydroxyglycine) by using its peptidyl glycine α-hydroxylating monooxygenase (PHM) domain. After that peptidyl is changed to amidated products by the other domain called a peptidyl α-hydroxyglycine α-amidating lyase (PAL) (Carr and McCall, 2017). The action area of Endormorphins is mainly in CNS and immune tissue (Bodnar and Richard, 2018). They have analgesic and anti-inflammatory properties. According to Horning (1975), nervous tissue where mono-amine, neurotransmitter and amidated neuropeptide synthesis showed that it has the highest vitamin C concentration. Moreover, it has another amidated peptide hormone called calcitonin. Calcitonin is used for osteoporosis and other bone disease treatment. It also has analgesic properties on bone pain in many diseases such as bone malignancy, Paget's disease, CRPS, and acute vertebral fracture (Mehta et al., 2003). This amidated neuropeptide requires PAM for changing to the mature hormone. It is seen that vitamin C is also important for calcitonin synthesis.

Vitamin C has been mentioned in various studies about its ability in pain management. However, the study that focuses on postoperative pain, especially in dentistry is rare. Therefore, this study will emphasize the effect of vitamin C and postoperative pain in the dental field.

2. Objective

This study's objective is to assess the effect of vitamin C on postoperative pain after a dental implant surgery by applying a visual analog scale (1-to-10 point scale) as a primary outcome.

3. Materials and Methods

3.1 Study design and patient selection

This study is a randomized controlled clinical trial that was conducted in the Faculty of Dentistry, Chulalongkorn University. The study consisted of 20 patients in total. All of the participants were selected following the inclusion and exclusion criteria that will be mentioned below.

3.2 Sample

The volunteers who were enrolled had the age over 18 years old. All of them had to require a single or two dental implants at the posterior area (premolar and molar area) in the maxilla or mandible. Before dental implant surgery, the bone in the surgery area had to heal from a tooth extraction in not less than 2 months. Besides, it must be sufficient in bone quantity and quality for dental implant insertion without guide bone regeneration, and the implant stability quotient (ISQ) value was not less than 50 on the day of surgery (day 0). The participants had to have good cooperation during the entire process of the study. For the exclusion criteria, the research excluded volunteers who had systemic diseases that affected the healing process such as diabetes (FBS more than > 200 mg/dL or HbA1c > 9%), and osteoporosis. Moreover, the patients who were pregnant, smoked (more than 5 cigarettes per day), or had a problem in cooperation were kept out and the history of bone pathology (cyst and tumor) at the dental implant area, intraoperative and postoperative complications (infection, excessive bleeding, and astray implant position) were also considered as inappropriateness.

3.3 Intervention

All of the participants were informed of the research objective, procedures, risks, and benefits of the treatment before beginning the therapy. The oral examination and X-ray (dental CT) were done for all patients. After that, the dental implant fixtures were inserted in each patient under the local anesthesia (2%

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Mepivacaine with 1:100,000 epinephrine) by dental professionals who were blinded to the group of the patients. A full mucoperiosteal flap was done in the middle of the edentulous area and attended to both adjacent teeth. The dental implant fixture that was inserted following its protocols was a Straumann bone level implant (BL, BLT, and BLX). The diameter of the fixtures was not less than Ø4.0 and the length was not less than 8 mm. The ISQ was collected in each implant before inserting the healing abutment and closing the flap with the vicryl 4-0. After the surgery, the participants were divided into 2 groups by using block randomization. The first group was indicated to consume 600 mg of vitamin C 3 days after dental implant surgery by dividing it into 2 doses (300 mg) for taking in the morning and evening. The second group received the placebo instead. The placebo consisted of calcium carbonate and sucrose and was coated with carnauba wax under the license of the Faculty of Pharmaceutical Science, Chulalongkorn University instead. Figure 1 below presents this entire research procedure. Furthermore, both participant groups received paracetamol 500 mg for pain-relieving consumption every 4 to 6 hours and Amoxicillin 500 mg or Clindamycin 300 mg (if allergic to Amoxicillin) for 7 days.

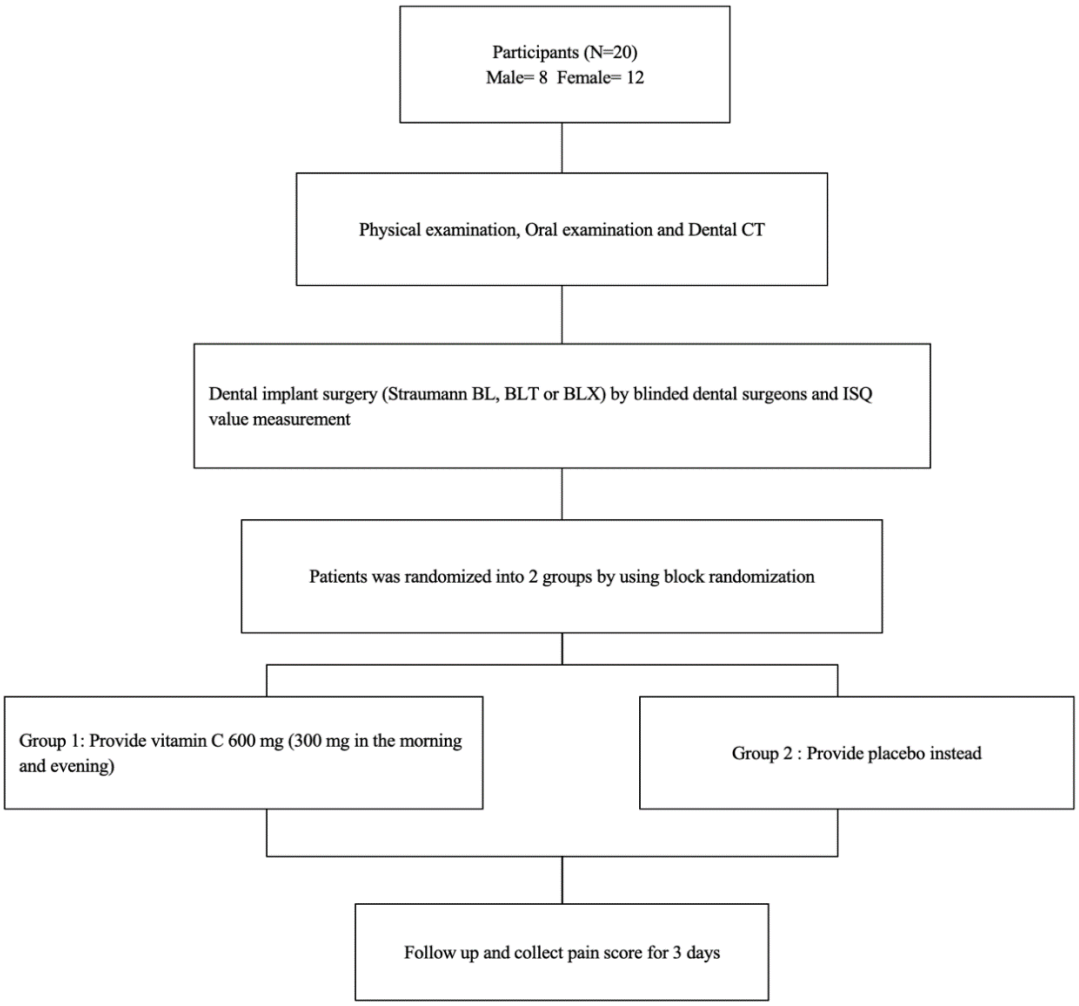

Figure 1 Research procedure

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3.4 Outcomes

The primary outcome of this study was collected about the pain by applying a visual analog scale (0 to 10 scale point, 0 = no pain and 10 = the most pain). The data collection sheet was provided to the participants for recording the pain score in the morning for 3 days after surgery.

3.5 Statistical analysis

The statistical analysis was performed by applying IBM SPSS software version 22. A comparison in pain scores between the vitamin C and no vitamin C group was calculated using the Mann-Whitney U test. The statistically significant was computed at P-value ≤ 0.05 (the confidence level of 95%).

4. Result and Discussion

4.1 Result

Demographic data

Participants who had eligibility for the study were enrolled in a total number of 20. 40% of the participants were male and 60% were female. The mean age of participants in the placebo group was 55.40 ± 14.16 while the vitamin C group was 59.60 ± 16.97. Both groups' age range was between 26 to 88 years old. The underlying diseases that participants had were hypertension and dyslipidemia. Twenty participants were operated on by dental surgeons, with two implants in the placebo group and one implant in the vitamin C group in the posterior maxilla and the others in the posterior mandible area. The implant type that was applied in the research was a bone level implant (BL, BLT, and BLX) of the Straumann implant system. The placebo group used Staraumann® BL (n=5) more than the other two types while Staraumann® BLT was applied the most in the vitamin C group (n=4). Implant diameter used mostly in both groups (n=6 in the placebo group and n=4 in the vitamin C group) was Ø4.8, followed by Ø4.0 in the placebo group (n=4) and Ø4.1 in the vitamin C group (n=3). For implant length, 8 mm was mainly in the placebo group, followed by 10 mm. In the vitamin C group, on the contrary, 10 mm was the most applicable, followed by 8 mm and 12 mm respectively. Implant torque and ISQ value were the other factors that were focused on. The implant torque of placebo and vitamin C groups was 31.50 ± 12.70 and 29.50 ± 12.57 in order. The ISQ value collected on the surgery day was evaluated on 2 sites of the dental implant (buccal and mesial). The buccal side's ISQ values were 70.20 ± 7.71 in the placebo group and 68.80 ± 9.61 in the vitamin C group. ISQ values at the mesial side were 71.00 ± 7.70 in the placebo group and 70.40 ± 9.42 in the vitamin C group. All of the demographic data, in addition, were not statistically significant at a 95% confidence level (Table 1).

Postoperative pain

Postoperative pain had a statistically significant difference between placebo and vitamin C groups on the day one after dental implant surgery. The placebo group pain score presented the mean score as 3.90 ± 2.60 while the vitamin C group's mean score is 1.50 ± 2.12. On day 2 after surgery, the pain score of the vitamin C group was 0.55 ± 1.301, which was lower than the placebo group's pain score (1.00 ± 1.05). The score on day 3 has a similar trend to the day 2 data in which the pain score of the placebo group (1.10 ± 1.91) was greater than the vitamin C group (0.45 ± 1.01). However, there was no statistical difference between groups on day 2 and day 3 after dental implant surgery at P-value ≤ 0.05 (Table 2).

4.2 Discussion

Patients who received dental implant surgery have intense postoperative pain, particularly in the first 24 hours (Li et al., 2014). The pain usually lasted 1 to 3 days after surgery. Thus, pain management after dental implant surgery is a challenge. The main point of postoperative management is to minimize the pain intensity and lead to faster wound healing. One substance that has the effect of reducing pain is vitamin C. This study examined the analgesic effect of 600 mg of vitamin C orally in patients who undergo dental implant surgery in the posterior maxilla or mandible.

In this study, participants were provided with paracetamol 500 mg and amoxicillin 500 mg or clindamycin 300 mg (if patients had an amoxicillin allergy). Vitamin C is the supportive substance that only

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the patients in the vitamin C group received. Although the patients received analgesic and antibiotic drugs, the researcher gave them to both groups equally. In addition, paracetamol is affected lastly in 4 to 6 hours in the human body (Bannwarth and Pe´hourcq, 2003). The patients were asked for collecting the VAS score in the morning and the effect of paracetamol's latest dose (consuming at night) vanished in the patient body and the next dose still did not consume. Most of the studies about vitamin C and pain management applied vitamin C as an adjunctive substance with analgesic drugs for reducing postoperative pain. Pisalsitsakul et al. (2022) studied oral vitamin C and dental extraction. This study compared the control (No vitamin C group) and 2 vitamin C groups (600 mg and 1500 mg). All patients in the study were also provided acetaminophen 500 mg for pain relief. Only 2 vitamin C groups received vitamin C 600 mg and 1500 mg, respectively. The result showed that the group that received 600 mg of vitamin C had a significantly lower pain score from day 1 to day3 than the control (Pisalsitsakul et al., 2022). The study of Ayatollahi et al. (2016) also found that using vitamin C 3 mg IV as a supplement after uvulopalatopharyngoplasty with tonsillectomy can significantly reduce the pain severity in 6, 12, and 24 hours postoperative pain. Furthermore, the vitamin C group had a significantly different time interval of analgesic drug request, time for the first analgesic dose, and pethidine dose (Ayatollahi et al., 2017).

Table 1 Demographic data

	Placebo group	Vitamin C group	P-value
Age	55.40 ± 14.16	59.60 ± 16.97	0.622
Sex			
• **Male**	5 (50.00)	3 (30.00)	0.374
• **Female**	5 (50.00)	7 (70.00)	
Underlying disease			
• **Yes**	2 (20.00)	2 (20.00)	1.000
• **No**	8 (80.00)	8 (80.00)	
Area of surgery			
• **Posterior maxilla**	2 (20.00)	1 (10.00)	1.000
• **Posterior mandible**	8 (80.00)	9 (90.00)	
Implant type			
• **BL**	5 (50.00)	3 (30.00)	0.796
• **BLT**	1 (10.00)	4 (40.00)	
• **BLX**	4 (40.00)	3 (30.00)	
Implant diameter			
• **4.0**	4 (40.00)	2 (20.00)	
• **4.1**		3 (30.00)	0.324
• **4.8**	6 (60.00)	4 (40.00)	
• **5.0**		1 (10.00)	
Implant length			
• **8 mm**	6 (60.00)	3 (30.00)	0.218
• **10 mm**	4 (40.00)	6 (60.00)	
• **12 mm**		1 (10.00)	
Implant torque	31.50 ± 12.70	29.50 ± 12.57	0.796

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	Placebo group	Vitamin C group	P-value
ISQ value			
• **Buccal**	70.20 ± 7.71	68.80 ± 9.61	0.850
• **Mesial**	71.00 ± 7.70	70.40 ± 9.42	0.912

This study result showed that, by applying visual analog scale (VAS score), pain scores were statistically significantly lower in the vitamin C group as compared with the placebo group 24 hours after the dental implant surgery, while 48 and 72 hours after surgery showed no statistical difference. According to Mohammed et al. (2015), a study found that the vitamin C use rate was increased when the wound was in an inflammation state (Mohammed et al., 2015). Furthermore, the level of vitamin C was lower than normal at approximately 42 percent during the period of the first 3 days after the operation (Ringdorf et al., 1982). In the same way, based on Sukla cited in Ringdorf et al. (1982), the research showed that the plasma level of vitamin C in patients who were provided 500 mg of vitamin C was dropped promptly within 3 to 6 days after abdominal surgery. In 6 to 9 days after surgery, the decreasing level was at a slower rate (Sukla cited in Ringdorf et al.,1982). Therefore, it is clearly seen that vitamin C was used in the human body, especially in injury or postoperative circumstances. Besides, Zollinger et al. (2007) investigated that oral vitamin C 500 mg daily for 50 days can prevent orthopedic surgery patients from complex regional pain syndrome (CRPS). The research from Byun et al. (2011) found that intravenous 2.5 g of vitamin C can relieve post-herpetic neuralgia that cannot be treated with analgesics and nerve block methods.

Table 2 Postoperative pain in both vitamin C and No vitamin C groups

	Placebo group			Vitamin C group			P-value
	Mean ± SD	[95% Conf. Interval]		Mean ± SD	[95% Conf. Interval]		
		Upper bound	Lower bound		Upper bound	Lower bound	
Day 1	3.90 ± 2.60	5.76	2.04	1.50 ± 2.12	3.02	- 0.02	0.013
Day 2	1.00 ± 1.05	1.75	0.25	0.55 ± 1.301	1.48	- 0.38	0.179
Day 3	1.10 ± 1.91	2.47	- 0.27	0.45 ± 1.01	1.17	- 0.27	0.487

In this study, 600 mg of the vitamin was applied for 3 days. Fukushima and Yamazaki (2010) recommended that patients who undergo uncomplicate surgery require 500 mg or more of vitamin C per day. Similarly, Tanaka and Molnar (2007) also suggested that small to moderate operations can be provided with 500 to 1000 mg of vitamin C by dividing it into 2 doses. Moreover, 500 mg of vitamin C can be reduced postoperative oxidative stress after surgery in a patient with uncomplicated gastrointestinal surgery (Fukushima and Yamasaki, 2010).

The side effects of vitamin C normally are diarrhea, stomach upset, flushing, headache, fatigue, and skin rash. It usually happens to the patients who have been receiving vitamin C of more than 2 grams per day and in long-term use (Winter, 2008). In this study, no patients were having side effects from vitamin C administration.

The limitation of this study was that the vitamin C serum level could not be collected because the process of vitamin C serum level collection was invasive. Moreover, the dietary control of each participant was also difficult. However, before the research process began, the participants were informed about high vitamin C dietary and advised to avoid consumption. Generally, recommended dietary allowances (RDAs) for vitamin C was 90 mg in male and 75 mg in female (Bendich, 2001). The vitamin C supplement dose that

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this research provided to participants was approximately 8 times higher than the dose which the participants got from their daily diet. Therefore, even if the participants forgot to avoid the high vitamin C dietary, the vitamin C they got did not exceed the therapeutic dose required for minor surgery (Tanaka and Molnar, 2006).

5. Conclusion

Providing patients with 600 mg of vitamin C after dental implant surgery resulted in decreasing the pain score when using the visual analog scale, especially on day 1 after the surgery. No side effects of vitamin C were discovered. This study should be useful for the patients who undergo dental implants and other uncomplicated surgeries as an additional supplement with analgesic drugs. Further study is needed in the larger sample number and comparing the pain score in each patient by applying the mean difference for analysis. The number of analgesic drug usage reductions after applying vitamin C as an adjunct to analgesic drugs in dental surgery also has to be studied. Besides, the mechanism of vitamin C and pain as mentioned in the introduction is still in the in-vitro studies. Therefore, the study for evaluating the effectiveness of vitamin C in reducing pain as the main substance in the clinical experiment has to be investigated more.

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