

Short Case Report

Ascorbic acid for management of oral surgery pain not responding to conventional medication: case report

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Abstract – Introduction: A 20-year-old female who experienced severe pain during six weeks after dental treatment was followed by oral surgeries. This article focuses on the usage of high dose of oral L-ascorbic acid for pain alleviation which did not respond to conventional pain medication. **Observation:** A female patient complaining about severe pain in tooth number 31 which was measured at every visit she made to the office, using Numerical Rating Pain Scale (NRPS) as the model for registration. **Comments:** Implementation of different types of analgesics along with laser-therapy were not able to reduce patient's ache during forty four consecutive days. Pain relief was only obtained at the next day with L-ascorbic acid supplementation to patient's previous medication. A complete absence of pain was reported by the patient on the seventh day after the ascorbate intake. **Conclusion:** Given to its action of mediating a variety of essential biological and biochemical functions, benefits, low cost, and safety, L-ascorbic acid could be considered by general dentists and oral surgeons as possible pain modulator after oral/dental surgical procedures.

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1]. Minor oral surgeries, including dissection and detachment of periosteum, gingival mucosa, and removal of bone tissue, are procedures associated with frequent postoperative pain and its level can be high [2].

Because postoperative pain is common in those situations mentioned above it can have a significant influence on patient's recovery. The pain management can be often suboptimal and patients return home with ongoing ache. An understanding of patients attitudes, concerns, and previous experiences with postoperative pain is important for improvement of postoperative care, as it is known that adequate pain alleviation is a major element on the postoperative recovery [3].

There are important differences in acute and chronic pain as well as related treatments. Acute pain, which is a symptom, if it is not managed, can lead to chronic pain, which is a disease [4]. Effective analgesia for acute pain is one of the most important protective ways against the development of chronic pain [5].

The chemical compound called (5R)-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydroxyfuran-2(5H)-one is also known as L-ascorbic acid, ascorbate or simply L-ascorbic acid and it is readily distributed in high concentrations into immune cells, has antimicrobial and natural killer cell activities, promotes lymphocyte proliferation, and is consumed quickly during infections, effects indicating a prominent role in immune system regulation [6].

Even though L-ascorbic acid is not a pain medication *per se* it can act as an analgesic in different medical conditions and after surgical therapy. A growing body of scientific evidence support this assertion [7–46].

The objective of this article is to present a case in which a patient had intense and constant pain during several weeks after oral surgery, even when different medicine prescriptions and regimens including antibiotics, non-steroidal drugs and opioids were used. Postoperative pain was only possible to be mitigated after L-ascorbic acid intake.

Observation

A 20-year-old female patient was referred to our OMFS office with severe pain in the anterior lower teeth. Patient was experiencing pain on tooth number 31 and had visited a general dentist who started treatment with tooth trepanation and root

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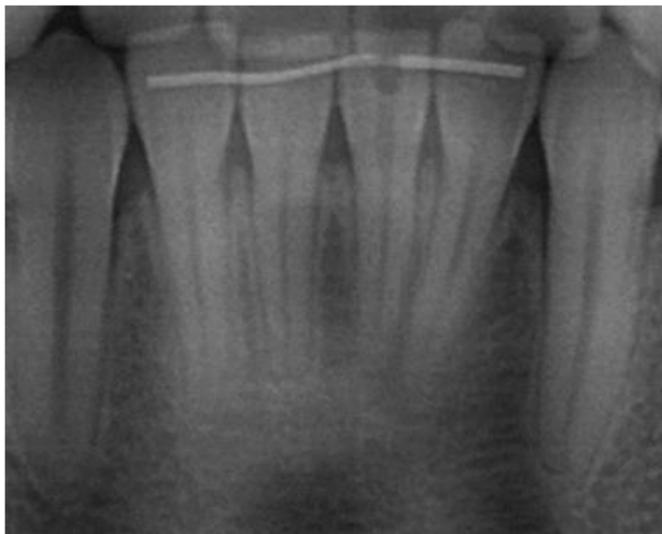


Fig. 1. Periapical X-ray showing preoperative lesion on the apices of teeth 31 and 32.

canal preparation. In spite of pulp extirpation, canal irrigation and insertion of antibiotic paste patient expressed no pain relief. After the second visit to her dentist, the referred tooth was left opened without temporary filling and patient was sent to seek oral and maxillofacial surgery specialty for subsequent treatment.

At patient's first visit to our office severe and constant pain for over one week was reported with a grade 8 in the Numerical Rating Pain Scale (NRPS) used for pain quantification.

Clinical examination showed minor swelling in the anterior lower buccal gingiva but pathological response to vitality test on tooth number 32 and extreme pain after percussion on teeth numbers 31 and 32. Periapical X-ray of the lower anterior teeth revealed apical lesion on both apices (Fig. 1).

After discussion with the patient about all possible therapeutic alternatives, surgical therapy consisting in apicoectomy was proposed. The elected surgical procedure would follow root canal treatment of teeth numbers 31 and 32. Consent form was read and signed. Prior surgery both teeth were endodontically treated.

On the day of the surgery, under local anesthesia, an incision was performed on the region of teeth numbers 31 and 32. Apices of those teeth were resected with piezosurgery (Fig. 2).

Periapical lesion was curetted and the material send for histological examination. The whole procedure was uneventful and painless. Surgical site was abundantly rinsed with Chlorhexidine solution and 0.9% saline solution. A gelatine sponge (Gelastyp[®] –Sanofi-Aventis, France) was inserted into bone defect and the wound primarily closed with 4.0 supramid suture. Postoperative medication consisted of Amoxicillin 1000 mg every 8 hours/daily and Metamizole (liquid form) 750 mg every 8 hours/daily for pain. Cooling pad was given to patient and she was oriented how to properly administer it.

The histological result showed normal bone tissue with no specific fibrous content.

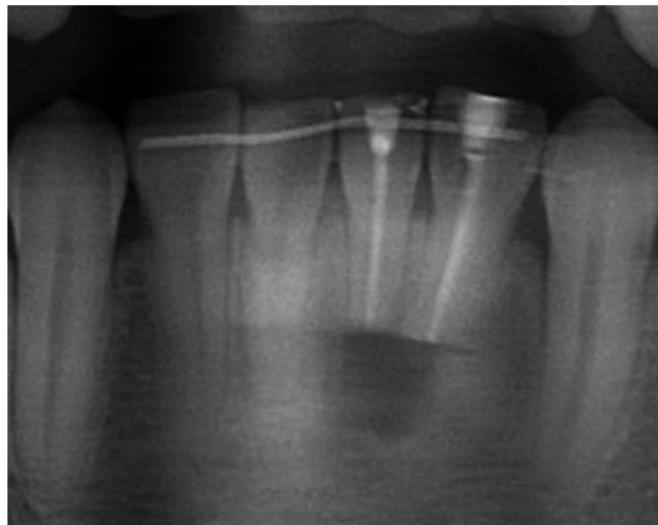


Fig. 2. Postoperative X-Ray after root treatment and apicoectomy of teeth 31 and 32 performed with piezosurgery.

At the next follow up, one day after the surgery, no complications were observed at the surgical site but the patient had the same severe pain (NRPS – grade 8). The pain medication was changed to Novalminulfon and dosage increased to 750 mg taken four times/daily. Five days later, patient returned to scheduled appointment complaining of no pain relief. The NRPS numbered 8. Intraorally there were no clinical signs of exacerbated inflammation, no swelling or erythema of the mucosa. Nine days later patient visited our office without any pain relief with NRPS numbering 8. Three ml of a long-lasting local anesthetic (Bupivacaine 0.5%) was injected in the region of teeth numbers 33 to 41. Because complete absence of pain was reported around ten minutes after the local analgesic infiltration, neuropathic pain of central origin was excluded. Ibuprofen 600 mg to be taken three times/daily was prescribed as an additional pain medication in an attempt to obtain a summation effect.

One week after, Bupivacaine infiltration, patient returned. Pressure pain and percussion symptoms on surgery site were minimal but patient referred no change in the pain status, recording a NRPS grade 8. Antibiotic and analgesic therapies were continued for another week and new appointment for surgical revision was planned. At this point, patient underwent surgical revision under local anesthesia. After flap elevation, material for microbiological test and tissue probe for histological examination were taken. Prior to wound closure with 4.0 supramid suture, bone defect was curetted and copiously irrigated with 0.9% saline solution. Exacerbated inflammation, exudation or other pathological findings were not observed intraoperatively. Antibiotic was then changed to Cefuroxime 500 mg taken two times/daily and Ibuprofen 800 mg taken three times/daily. The microbiological and histological results added no important information. These exams showed only resident microorganisms which were sensible to Amoxicillin and Cefuroxime, plus normal reparative tissue.

On the next follow up, two days after surgical revision, pain was still persistent with NRPS grade 8. After injection of 3 ml of Bupivacaine 0.5% for a temporary symptomatic relief, new pain regimen was given which consisted of Tramadol 75 mg taken four times/daily. The next infiltration of Bupivacaine 0.5% was scheduled for two days later. On this next visit laser-therapy applied to surgical site was included. The laser-therapy protocol consisted of Diodlaser 810 nm with an intensity of 1.6 W and 300 J per session. On the next day the same pain treatment was performed. The patient did not report any pain reduction when laser treatment was added.

A week after surgical revision, a month after apicoectomy, and forty four days after the first surgical procedure, patient was still reported the same severe pain with NRPS grade 8. She referred pain relief for no more than three hours after taking pain medication. At this point, intake of L-ascorbic acid 1000 mg three times/daily was recommended for a period of ten days.

The next visit, forty eight hours later, patient expressed the first relative pain reduction with NRPS grade 5–6. After three more days of L-ascorbic acid intake pain improvement was significant with NRPS grading 4. Two days later, after a phone call, patient informed that she was completely pain free.

On a six months follow up patient referred no soreness at all in the surgical area.

Comments

Potential mechanism of action

Although there is no consensus as to the analgesic mechanism by which L-ascorbic acid could be acting, there are at least three potential theories accordingly with Carr *et al.* [7]: (a) action as a potent antioxidant; (b) role as a cofactor for the synthesis of catecholamine neurotransmitters; and (c) potential role of L-ascorbic acid in the synthesis of amidated opioid peptides.

- Action as a potent antioxidant – L-ascorbic acid serve as an antioxidant and scavenges reactive oxygen species and protect cells from oxidative damage. It also exhibits anti-inflammatory properties and decreases markers of inflammation such as C-reactive protein and pro-inflammatory cytokines [7]. Reactive Oxygen Species (ROS) are a number of reactive molecules and free radicals derived from molecular oxygen. They are well known for their role in mediating both physiological and pathophysiological signal transduction [8]. Based on literature data, the ROS has been elucidated as a factor in the generation of pain, especially persistent, recurrent, or neuropathic. The ascorbic acid protects the cells and tissues, including the nerves from oxidative stress and damage through scavenging a wide range of ROS [9–11].
- Role as a cofactor for the synthesis of catecholamine neurotransmitters – L-ascorbic acid can be a cofactor for the synthesis of catecholamine neurotransmitters and is involved

in neuromodulation. It is important for the conversion of dopamine into norepinephrine and alleviate the synthesis of dopamine. L-ascorbic acid also takes part in the biosynthesis of the serotonin. Both serotonin and norepinephrine reuptake inhibitors show efficacy in control of pain [7].

- Potential role of L-ascorbic acid in the synthesis of amidated opioid peptides – Currently unexplored analgesic mechanism of L-ascorbic acid involves the potential role in the synthesis of amidated opioid peptides as a cofactor for the enzyme peptidylglycine α -amidating mono-oxygenase (PAM). PAM is the only known enzyme in humans capable of amidating the carboxy-terminus of peptide hormone precursors, a post-translational modification which is essential for their subsequent stability and/or biological activities. A number of amidated neuropeptides have potent opioid activity [7].

Acute and chronic pain can be debilitating for patients, particularly if not adequately alleviated by conventional analgesics. There is increasing scientific evidence indicating that L-ascorbic acid can exhibit analgesic properties in some clinical conditions, thus potentially mitigating suffering and improving patient's quality of life [7].

There are a number of studies showing the positive effects of ascorbic acid on the pain experience after different surgical procedures. In surgical patients the L-ascorbic acid requirement is increased, and the potential advantage of supplementation is to increase the plasma and tissue levels of L-ascorbic acid and thus reduce oxidative stress. Trauma and surgery are known to significantly deplete L-ascorbic acid concentrations [12].

According to Carr *et al.* the administration of L-ascorbic acid intraoperatively reduced postoperative pain without increased side-effects in patients undergoing uvulopalatopharyngoplasty and tonsillectomy [13]. A number of randomized controlled trials have investigated the effect of L-ascorbic acid supplementation on the incidence of complex regional pain syndrome (CRPS) in wrist and ankle surgery patients. They showed a decreased incidence of CRPS in the patients receiving L-ascorbic acid, with the doses ≥ 0.5 g/day being the most efficacious [14]. Based on the results of a study published in 2017, L-ascorbic acid might be associated with improvement of functional status after posterior lumbar interbody fusion (PLIF) surgery [15]. Jeon *et al.* reported the effect of high dose intravenous supplementation of L-ascorbic acid on postoperative pain control after laparoscopic colectomy [16]. Laflı Tunay *et al.* reported preoperative oral administration 2 g L-ascorbic acid led to a reduction in pain scores, total morphine consumption, supplemental analgesic requirement after major abdominal surgery compared with placebo [17].

There are certain published data for ascorbic acid used as pain modulator not only after surgeries, but also in various acute and chronic conditions and in cancer patients.

A randomized placebo-controlled crossover trial carried out with one hundred thirty three patients with osteoarthritis of the hip or knee joint showed reduced pain following consumption of 1000 mg/day calcium ascorbate (Calcium salt

of ascorbic acid) for two weeks as determined by the visual analogue scale ($P < 0.008$). The observed decrease in pain was less than half than that reported for non-steroidal anti-inflammatory drugs [18].

Patients with painful Paget's disease of the bone were treated with high doses of ascorbic acid (3000 mg/day). Of these patients, 50% experienced reduction of pain within a period of five to seven days after commencing the vitamin therapy. In 20% of these patients the pain was completely abolished [19]. Nabzyk *et al.* [advocated that L-ascorbic acid administration may have a variety of beneficial effects as reducing pain in other conditions – acute burn injury and in the treatment of cancer [20]. Two prospective studies of patients with advanced cancer who were administered high dose of L-ascorbic acid intravenously have shown significant decrease in pain (over 30%) [21,22]. Decrease in postoperative morphine consumption was also reported by other authors [13,16,23]. Even complete reduction in morphine requirement was observed in a patient with terminal cancer treated with high dosage L-ascorbic acid infusion for palliative care [24]. Cameron and Campbell published cases of complete amelioration of osseous pain in patients with bone metastases. The patients were treated orally and intravenously with L-ascorbic acid and the results advocated the use of L-ascorbic acid for improvement in pain experience [25].

Günes-Bayir *et al.* reported similar pain reduction results after ascorbic acid application in patients with radiotherapy-resistant bone metastases [26].

Two case reports and a cohort study from Schencking *et al.* described clinical improvement and relief of pain for patients with acute herpes zoster exacerbation who received L-ascorbic acid [27,28]. Double-blind placebo-controlled study revealed that the duration of pain caused by labial herpes was shortened by 51%, when patients were administered 1 g/day of L-ascorbic acid together with bioflavonoids [29]. Ascorbate treatment also resulted in a better efficacy than placebo in pain modulation in post herpetic neuralgia (PHN) and intravenous ascorbate helps relieve spontaneous pain in PHN [30,31].

Animal experiments also advocate the implementation of L-ascorbic acid. An intraperitoneal injection of Ascorbic acid (400 mg/kg), thirty minutes before morphine self-administration, produced a significant decrease in twelve days self-administration of morphine [32]. A mouse experiment demonstrated that neuropathic pain induced by peripheral injury and the acute pain response to formalin could be inhibited by a combination of Vitamin E and L-ascorbic acid. Hence, supplementation or treatment with both Vitamins might be an option for patients suffering from specific pain states [33]. Another article revealed the results of interactions between ascorbic acid and tramadol or morphine in mice. The results showed that the interaction effects on antinociception may be synergistic or additive, depending on the level of effect [34].

Chaitanya *et al.* concluded that L-ascorbic acid had its potential role in antinociceptive effect and postoperative pain

relief [35]. In addition the authors concluded that future trials were needed to further explore the potential effect on postoperative pain following tooth extractions, treatment of oral ulcers, and the optimal doses and routes of administration. Korean authors Lee *et al.* reported that insufficient intake of dietary ascorbic acid was associated with increased periodontal pain and L-ascorbic acid could be beneficial for pain modulation [36]. A publication in American Journal of Dentistry reported that 4000 mg/day dosages of L-ascorbic acid is associated with rapid recovery after tooth extraction [37]. Another study presented a growing body of evidence that indicated supplemental L-ascorbic acid might be beneficial in speeding healing following tooth extraction and in reducing the likelihood of alveolgia and other complications [38]. Chaitanya *et al.* determined that the method of administering 2000 mg IV L-ascorbic acid intravenously was well suited to the treatment of postoperative pain, swelling and trismus following the surgical extraction of impacted third molars [39]. A study in its summary concluded that because of the reduction in L-ascorbic acid concentration after surgery and the modest evidence for L-ascorbic acid's antinociceptive effect and role in postoperative pain relief, further clinical trials were warranted to determine its potential effect on postoperative pain, as well as its optimal doses and routes of administration [40].

L-ascorbic acid dose and its safety features

In healthy humans, circulating levels of ascorbate are typically in the range of 50–70 $\mu\text{mol/l}$, whereas levels $< 23 \mu\text{mol/l}$ are considered marginally deficient (or hypovitaminosis C) [41]. The optimal dose of ascorbic acid to fully saturate plasma and tissues in healthy adults is 500 mg [42]. That is more than the common recommended (60–100mg) to prevent deficiency diseases. At oral doses of 200 mg, the steady-state plasma concentrations are $\approx 80 \mu\text{mol/l}$. As doses exceed 200 mg, relative absorption decreases, urine excretion increases and the fraction of bioavailable ascorbate is reduced [43].

Levine and coworkers have shown that oral L-ascorbic acid uptake becomes less efficient as the dose increases due to saturation of the transporters. Although an oral dose of 200 mg L-ascorbic acid is completely absorbed, at doses of 500 mg and 1250 mg L-ascorbic acid, $< 75\%$ and $< 50\%$ of the Vitamin dose is absorbed [44]. For the maximum tolerated oral dose of 3000 mg every four hours, pharmacokinetic modeling predicted peak plasma L-ascorbic acid concentrations of 220 $\mu\text{mol/l}$ [45].

It seems that trauma and surgery patients need greater doses of L-ascorbic acid. Long *et al.* (2003) [46] demonstrated that up to 3000 mg/day ascorbate was required to restore plasma levels of critically ill patients to normal (*i.e.* 68 $\mu\text{mol/l}$). Generally, evidence that even doses of at 1.5 g/kg ascorbic acid as infusion exhibit a favorable safety profile and are well tolerated can be found in available scientific publications [47,48]. Based on the L-ascorbic acid levels proposed by these

above mentioned studies the authors decided to prescribe 3000 mg daily for this patient, staying within a safety margin with an effective result though.

Conclusions

The practical importance and optimal efficacious doses of ascorbic acid for treating postoperative pain as a single medication and/or in combination with analgesics is unknown but even with modest effects it may be worth of further research.

Given to its potential benefits, low cost, and safety, and considering the limitation of this paper and need for further research, L-ascorbic acid supplementation could be considered by oral surgeons and general dentists as possible pain modulator after oral/dental surgical procedures.

Regarding that the ascorbic acid intake may not be the only component explaining the disappearance of the pain, the temporality of the events can bring new insights into the possible relationships between ascorbic acid and analgesia to the scientific community.

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