Pharmacologic Management of Trigeminal Nerve Injury Pain After Dental Implant Surgery

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Purpose: Injuries to the trigeminal nerve are a common postoperative complication of dental implant surgery. Usually, the altered sensation and neuropathic pain caused by the nerve injury is temporary, but a permanent neurosensory disorder can sometimes occur. Surgery is commonly used to treat this condition, but the treatment is associated with some complications and a relatively low success rate. This study analyzed the characteristics of pharmacologic management of trigeminal nerve injury pain after dental implant surgery. ***Materials and Methods:*** Eighty-five patients who visited a temporomandibular joint and orofacial pain clinic with a history of trigeminal nerve injury pain after dental implant surgery were enrolled in this study. The pharmacologic management for trigeminal nerve injury pain was evaluated by prescribing a variety of medications for 12 weeks according to the prescription protocol of the study. The patients' pain characteristics, average percentage of pain reduction, and pain relieving factors were investigated prospectively. ***Results:*** Patients who took anticonvulsants and antidepressants for at least 12 weeks reported a mean reduction in pain of 24.8%. Interestingly, patients who experienced an altered sensation and neuropathic pain for more than 1 year also reported a reduction in pain and discomfort, with an average decrease of 17.1%. In addition, it was found that early treatment using medications had a significant effect on reducing the level of pain and discomfort. ***Conclusion:*** These results suggest that pharmacologic management can be used for treating trigeminal nerve injury pain after dental implant surgery. *Int J Prosthodont 2010;23:342–346.*

The orofacial region is the most sensory sensitive area in the human body. Most of its sensory innervation is through three major divisions of the trigeminal nerve: ophthalmic, maxillary, and mandibular. Damage to any of these nerves or their branches can cause sensory disturbances. Usually, the altered sensation and neuropathic pain caused by a nerve injury are temporary, but the nerve injury can sometimes result in a permanent neurosensory disorder.[1,2]

The common causes of nerve injury in dental patients are third molar extraction, an inferior alveolar nerve block, implant surgery, orthognathic surgery, endodontic treatment, and periodontal surgery.[3,4] Currently, there is considerable evidence suggesting that inferior alveolar nerve injury is one of the most common injuries experienced by dental patients after implant surgery.[5]

Currently, there are surgical interventions and nonsurgical treatments, such as behavioral (counseling, yoga, stress management, psychotherapy), physiologic (exercise, sensory reeducation, transcutaneous electrical nerve stimulation), and pharmacologic treatments, for the management of nerve injury.[6]

This study analyzed the characteristics of pharmacologic management of trigeminal nerve injury pain after dental implant surgery of patients referred to a temporomandibular joint and orofacial pain clinic.

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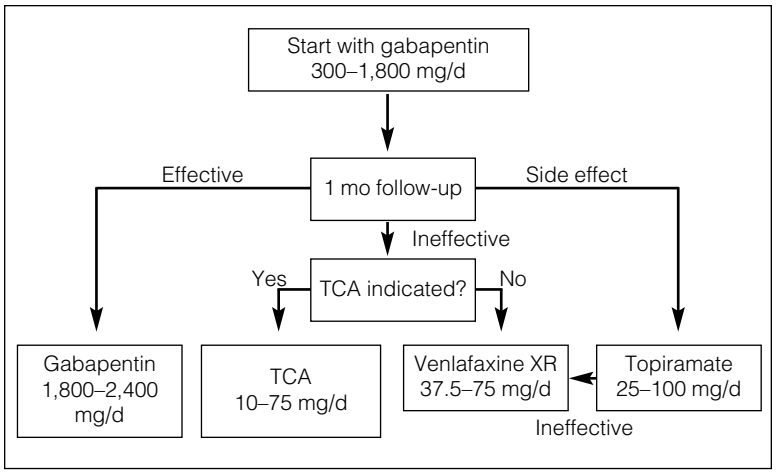
Fig 1 Prescription protocol.



Materials and Methods

Eighty-five patients who presented at the TMJ & Orofacial Pain Clinic, Yonsei University Dental Hospital, Seoul, Korea, complaining of refractory pain or abnormal sensation after dental implant surgery and who agreed to the pharmacologic management protocol of this study were enrolled. Patients with a history or symptoms of major medical illness that could cause possible neurosensory disorders were excluded. All patients were provided with a comprehensive health and jaw function questionnaire to rule out other possible causes of the pain or abnormal sensation.

At the initial office visit, patients were asked to grade the severity of their pain or abnormal sensation on a 10-point visual analog scale and were questioned on the factors affecting pain relief. Patients were then prescribed anticonvulsant or antidepressant medication for 12 weeks according to the prescription protocol of this study (Fig 1).

Of the 85 nerve injury patients, only 47 patients who were prescribed the anticonvulsant or antidepressant medication for more than 12 weeks were analyzed. The patients were divided into four group (before 3 months, 3 to 6 months, 6 to 12 months, and after 12 months) according to the time from injury to taking the first-line medication. All 47 patients were initially prescribed 300 mg of gabapentin and the dosage was gradually titrated up to 1,800 to 2,400 mg for 1 month and reevaluated. Patients who developed side effects or reported inefficacy with gabapentin were prescribed a tricyclic antidepressant (TCA) such as nortriptyline or amitriptyline (10 to 75 mg), topiramate (25 to 100 mg), and venlafaxine XR (37.5 to 75 mg) for the next 2 months.

Results

A total of 47 patients were analyzed in this study (32 women, 15 men; mean age: 47.7 years). Analysis of data was performed using SAS (Statistical Analysis System V9.01, SAS Institute). The mean comparison was completed using the *t* test and analysis of variance.

Table 1 presents the pain-relieving factors associated with trigeminal nerve injury pain after dental implant surgery. Among them, rest or sleep was the main pain-relieving factor reported by patients (44.1%). Other pain-relieving factors reported include warm baths, distraction from the pain, analgesics, and the application of pressure to the pain area.

The relationship between sex and pain reduction is presented in Table 2. There was no significant difference in total pain reduction between men and women ($t = 0.29$, $P = .7717$). The relationship between age and pain reduction is presented in Table 3. There was no significant difference in total pain reduction according to age ($F = 1.52$, $P = .2131$).

Figure 2 shows the relationship between the time of injury to taking the first-line medication and seeing pain reduction. Patients who started pharmacotherapy within 3 months after nerve injury showed a 37.0% decrease in pain on the visual analog scale. The group prescribed medication 3 to 6 months after nerve injury showed a 27.1% reduction in pain. The group prescribed medication 6 to 12 months and more than 12 months after nerve injury showed a 22.2% and 17.1% reduction in pain, respectively.

Table 4 presents the amount of pain reduction according to each prescribed medication. The group taking gabapentin reported a 45.8% reduction of total pain while the gabapentin and TCA group reported a 22.2% decrease.

Table 1 Pain-Relieving Factors

Factors	No. of patients (%)
Rest or sleep	44.1
Warm bath	27.0
Distraction	14.0
Analgesics	4.6
Pressure to pain area	6.9
Miscellaneous	3.4

Table 2 Relationship Between Sex and Pain Reduction

Sex	No. of patients	Total pain reduction (%)
Male	15	24.3
Female	32	26.4
Total	47	25.7

Table 3 Relationship Between Age and Pain Reduction

Age	No. of patients	Total pain reduction (%)
20–29	5	38.0
30–39	5	43.0
40–49	14	24.0
50–59	16	19.1
> 60	7	23.6
Total	47	25.7

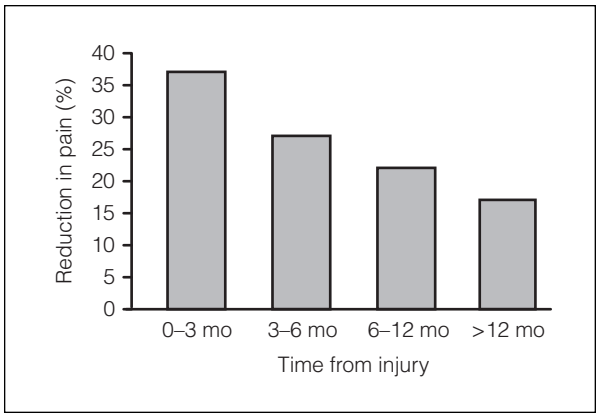


Fig 2 Time from injury to first-line medication and pain reduction.

Table 4 Total Pain Reduction According to Each Medication

Medication	No. of patients	Total pain reduction (%)
Gabapentin	6	45.8
Gabapentin + TCA	25	22.2
Gabapentin + topiramate	3	40.0
Gabapentin (+ topiramate) + venlafaxine XR	13	20.0
Total	47	25.7

TCA = tricyclic antidepressant.

Discussion

Implants are widely used in the dental offices as prosthetic tooth replacements. The nerve injuries following implant surgery, although not common, can lead to chronic pain or altered sensations such as paresthesia, dysesthesia, or anesthesia dolorosa.[5,7] These symptoms are often refractory to conventional analgesics and are a challenge to treat. Sometimes the nerve injury begins a series of neurochemical processes: increased spontaneous activity and ectopic discharge, increased sensitivity to stimuli, change in ion-channel expression, and abnormal neuronal sprouting. The local release of chemical mediators from the primary sensory nerve terminal alters the threshold for the activation of nociceptors (Fig 3).[8]

After tissue trauma, the release of inflammatory mediators sensitizes the Aδ and C fibers peripherally and may initiate the central activation of different mediators including cyclo-oxygenase (COX) enzymes.[2,9] COX enzymes produce prostaglandins that increase the release of neurotransmitters, such as glutamate, which can increase the possibility of activating the N-methyl D-aspartate (NMDA) receptor. Under normal circumstances, this receptor is blocked by magnesium ions. Prolonged or more intense nociceptor activation enhances the risk of NMDA receptor activation and provides an opportunity for synaptic plasticity. Sustained NMDA receptor activation promotes signaling to the nucleus, which culminates in cAMP response element binding (CREB) phosphorylation, multiple gene activation, and long-term synaptic plasticity.[10–12] Therefore, central sensitization is considered to be a partial consequence of NMDA receptor activation. A dysfunction of the NMDA-dependent disinhibition of temporal summation can contribute to central sensitization. Other mechanisms, such as activation of the neurokinin-1 receptor and the production of nitric oxide, have been suggested to play a role in central sensitization.[13]

There are surgical interventions and nonsurgical treatments, such as behavioral, physiologic, and pharmacologic treatments, for the management of nerve injury.[6] Surgical approaches to the treatment of neuropathic pain began 3 decades ago. In such surgeries, the section of damaged nerve or neuroma is excised and replaced with an autogenous vein graft or

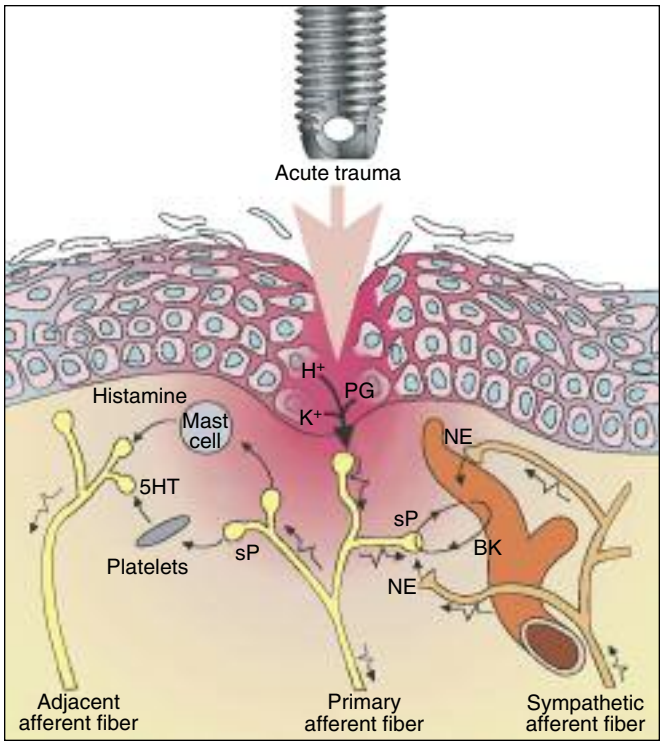


Fig 3 Neurochemical processes in peripheral tissue after acute trauma. H = hydrogen; K = potassium; PG = prostaglandin; NE = norepinephrine; sP = substance P; BK = bradykinin; 5HT = serotonin.

alloplastic tubes.[3] However, it is unclear whether patients with nerve injuries would benefit from early surgical decompression or repair compared to nonsurgical management.[14] Also, secondary injury from surgery may exacerbate and further sensitize an already hyperesthetic nervous system.[15,16] Because the majority of nerves are known to recover spontaneously to some degree, and due to the possibility of further unrecognized damage, conservative pharmacologic management has been suggested. Neuropathic pain conditions are associated with changes in the central nervous system. Moreover, drugs acting on specific ion channels and receptors centrally can be helpful in treating these neuropathic pain conditions. Anticonvulsants and TCAs have been proven to be effective in treating neuropathic pain conditions.

Gabapentin

Gabapentin was used as a first-line medication in this study. Although its mechanism of action is unclear, gabapentin is widely used to treat chronic pain. It is an analog of inhibitory neurotransmitter gama-aminobutyric acid (GABA). The drug binds to specific subunits (α2-δ) of the voltage-sensitive calcium channels in the spinal cord, which may interfere with the transmission of noxious stimuli.[17] The effective dosage for treating neuropathic pain is 1,800 to 2,400 mg/day. Minor side effects reported with this drug include weight gain, somnolence, and dizziness.

Topiramate

This anticonvulsant drug is also effective in treating migraine headaches and neuropathic pain conditions.[18–20] The effective dose for treating neuropathic pain conditions is 25 to 100 mg/day. The reported side effects include weight loss, memory loss, dizziness, and paresthesia. Topiramate was used as a second-line medication in this study. Patients who reported minor side effects with gabapentin, such as weight gain, were transferred to topiramate.

TCAs

Patients who did not respond well to gabapentin and topiramate were prescribed TCAs (third-line medications). Secondary TCAs (nortryptyline and desipramine) are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine). The effective dosage used was 10 to 75 mg/day. The reported side effects were sedation, anticholinergic effects, and orthostatic hypertension.

Venlafaxine XR

Patients contraindicated for TCAs were prescribed a serotonin and norepinephrine reuptake inhibitor (venlafaxine XR). Venlafaxine XR inhibits serotonin reuptake at lower doses, and both serotonin and norepinephrine reuptake at higher dosages. The effective dosage in

treating neuropathic pain ranges from 37.5 to 75 mg/day. Although pharmacologic methods are an inexpensive and more conservative treatment for chronic neuropathic pain, many side effects have been reported with these drugs. These include somnolence, dizziness, and anticholinergic effects such as dry mouth, constipation, urinary retention, and increased risk of cardiovascular diseases.[21,22]

Conclusions

These results suggest that pharmacologic management can be used for treating trigeminal nerve injury pain after dental implant surgery. In addition, patients started with pharmacotherapy early after nerve injuries showed better results. Patients treated with anticonvulsants and antidepressants within the first 3 months showed the maximum reduction in pain. Despite these encouraging results, caution should be taken when drawing strong conclusions regarding the analgesic properties of these medications in implant surgery patients. In addition, this study was limited to a small group of patients and there were no placebo controlled clinical trials. Since more than one medication was used in one patient, it is difficult to measure the analgesic efficacy of each medication. A further placebo controlled clinical study covering a larger number of subjects is needed to properly estimate the effect of pharmacologic management of trigeminal nerve injury pain after dental implant surgery.

References

1. Shenkman Z, Findler M, Lossos A, Barak S, Katz J. Permanent neurologic deficit after inferior alveolar nerve block: A case report. Int J Oral Maxillofac Surg 1996;25:381–382.
2. Woolf CJ, Mannion RJ. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. Lancet 1999;353:1959–1964.
3. Robinson PP, Loescher AR, Yates JM, Smith KG. Current management of damage to the inferior alveolar and lingual nerves as a result of removal of third molars. Br J Oral Maxillofac Surg 2004; 42:285–292.
4. Sandstedt P, Sörensen S. Neurosensory disturbances of the trigeminal nerve: A long-term follow-up of traumatic injuries. J Oral Maxillofac Surg 1995;53:498–505.
5. Delcanho RE. Neuropathic implications of prosthodontic treatment. J Prosthet Dent 1995;73:146–152.
6. Meyer RA, Ruggiero SL. Guidelines for diagnosis and treatment of peripheral trigeminal nerve injuries. Oral Maxillofac Surg Clin North Am 2001;13:383–392.
7. Juhl GI, Jensen TS, Norholt SE, Svensson P. Central sensitization phenomena after third molar surgery: A quantitative sensory testing study. Eur J Pain 2008;12:116–127.
8. Dickenson A. The neurobiology of chronic pain states. Anaesth Intensive Care Med 2008;9:8–12.
9. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52:77–92.
10. Bleakman D, Alt A, Nisenbaum ES. Glutamate receptors and pain. Semin Cell Dev Biol 2006;17:592–604.
11. Kemp JA, McKernan RM. NMDA receptor pathways as drug targets. Nat Neurosci 2002;5(suppl):1039–1042.
12. Parsons CG. NMDA receptors as targets for drug action in neuropathic pain. Eur J Pharmacol 2001;429:71–78.
13. Zimmermann M. Pathobiology of neuropathic pain. Eur J Pharmacol 2001;429:23–37.
14. Gregg JM, Zuniga JR. An outcome analysis of clinical trials of the surgical treatment of traumatic trigeminal sensory neuropathy. Oral Maxillofac Surg Clin North Am 2001;13:377–381.
15. Ziccardi VB, Steinberg MJ. Timing of trigeminal nerve microsurgery: A review of the literature. J Oral Maxillofac Surg 2007:65: 1341–1345.
16. Evans GR. Peripheral nerve injury: A review and approach to tissue engineered constructs. Anat Rec 2001:263:396–404.
17. Sihoe AD, Lee TW, Wan IY, Thung KH, Yim AP. The use of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients. Eur J Cardiothorac Surg 2006;29:795–799.
18. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to mechanism of drug action. Pain 1999;83:389–400.
19. Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. Pain 1997;73:123–139.
20. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain 2007;132:237–251.
21. Finnerup NB, Otto M, Jensen TS, Sindrup SH. An evidence-based algorithm for the treatment of neuropathic pain. MedGenMed 2007;9:36.
22. Raiteri M. Functional pharmacology in human brain. Pharmacol Rev 2006;58:162–193.