Pharmacologic management of trigeminal nerve injury after endodontic treatment
: A retrospective analysis

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Pharmacologic management of trigeminal nerve injury after endodontic treatment : A retrospective analysis

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ABSTRACT

Pharmacologic management of trigeminal nerve injury after endodontic treatment: A retrospective analysis

Background: Trigeminal nerve injury following endodontic treatment, leading to unpleasant sensations or partial sensory loss in the face or oral mucosa, is uncommon but significant when it occurs.

Objective: This study analyzed the pharmacological management of trigeminal nerve injuries(TNI) in a university-based hospital.

Methods: We conducted a retrospective analysis of 47 patients who visited the Department of Orofacial Pain and Oral Medicine at Yonsei University Dental Hospital, Seoul, Korea, after TNI following endodontic procedures in primary clinics. Both objective tests and subjective evaluations, assessed the extent and duration of sensory injury during the initial visit. The patient's initial symptoms, the presumed cause of TNI, referral delay (time interval between TNI and the first visit to our clinic), and medications were analyzed to determine whether these factors affected the outcomes.

Results: Most patients with TNI experienced dysesthesia with hypoesthesia (70.2%). The mandibular molars were predominantly affected (72.3%), with the inferior alveolar nerve (IAN), lingual nerve (LN), both IAN and LN, and maxillary nerve compromised in 83.0, 12.8, 2.1, and 2.1% of cases, respectively. Causes of TNI included local anesthesia (29.8%), overfilling/over-instrumentation (25.5%), endodontic surgery (17.0%), and unknown factors (27.7%). A shorter referral delay was associated with better outcomes, with an average delay of 8.6 weeks for symptom improvement compared with 44.1 weeks for no change. The medication regimens included steroids, NSAIDs, topical lidocaine, vitamin B complex, Adenosine Triphosphate (ATP), antiepileptics,

antidepressants, and opioids administered alone or in combination, with a mean duration of 20.7 weeks. 53.2% of the patients reported improvement in their symptoms, 27.7% experienced no significant change, and 19.1% had unknown outcomes.

Conclusions: Swift referral to an orofacial pain specialist is recommended for effective recovery in cases of TNI arising from endodontic treatment.

Key words : endodontic treatment, neuropathy, pharmacologic management, trigeminal nerve injury

1. Introduction

Trigeminal nerve injuries (TNI) may occur after several common dental treatments, such as administering a local anesthetic block, tooth extraction, dental implant placement, and endodontic treatment.[1)] While most injuries are transient and resolve independently, TNI can have long-term consequences for patients. Symptoms vary but are potentially severe. Neurosensory deficits resulting from dentoalveolar procedures can affect speech, eating, drinking, smiling, and intimacy. Without early intervention, these injuries may develop into a debilitating neuropathic pain syndrome.[2)] A survey of 2,338 patients found that 7% experienced chronic neuropathic pain after a single endodontic procedure.[3)]

Practically, all endodontic procedures performed near the trigeminal nerve branches can cause nerve injury, including local anesthesia administration, root canal preparation and irrigation, root canal filling, and surgical endodontic treatments.[4)] Many conditions unrelated to endodontic

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[1)] Hillerup, S. (2007). Iatrogenic injury to oral branches of the trigeminal nerve: records of 449 cases. *Clinical oral investigations, 11*, 133-142.

[2)] Yampolsky, A., Ziccardi, V., & Chuang, S.-K. (2017). Efficacy of acellular nerve allografts in trigeminal nerve reconstruction. *Journal of Oral and Maxillofacial Surgery, 75*(10), 2230-2234.

[3)] Klasser, G. D., Kugelmann, A. M., Villines, D., & Johnson, B. R. (2011). The prevalence of persistent pain after nonsurgical root canal treatment. *Quintessence International, 42*(3).

[4)] Garisto, G. A., Gaffen, A. S., Lawrence, H. P., Tenenbaum, H. C., & Haas, D. A. (2010). Occurrence of paresthesia after dental local anesthetic administration in the United States. *The Journal of the American Dental Association, 141*(7), 836-844; Garisto, G. A., Gaffen, A. S., Lawrence, H. P., Tenenbaum, H. C., & Haas, D. A. (2010). Occurrence of paresthesia after dental local anesthetic administration in the United States. *The Journal of the American Dental Association, 141*(7), 836-844; Garisto, G. A., Gaffen, A. S., Lawrence, H. P., Tenenbaum, H. C., & Haas, D. A. (2010). Occurrence of paresthesia after dental local anesthetic administration

treatment, including infectious diseases, trauma, tumors, and idiopathic diseases, have also been suggested as possible origins of altered sensation in the trigeminal nerve branches. These conditions should be considered in the differential diagnosis of nerve injuries related to endodontic treatment.[5)] Therefore, dentists play an essential role in ensuring patients receive timely and appropriate treatment.

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in the United States. *The Journal of the American Dental Association, 141*(7), 836-844; Kim, S., & Kratchman, S. (2006). Modern endodontic surgery concepts and practice: a review. *Journal of endodontics, 32*(7), 601-623; Kim, S., & Kratchman, S. (2006). Modern endodontic surgery concepts and practice: a review. *Journal of endodontics, 32*(7), 601-623; Alves, F. R., Coutinho, M. S., & Gonçalves, L. S. (2014). Endodontic-related facial paresthesia: systematic review. *J Can Dent Assoc, 80*(80), e13; Yatsuhashi, T., Nakagawa, K.-I., MATsuMoTo, M., Kasahara, M., Igarashi, T., Ichinohe, T., & Kaneko, Y. (2003). Inferior alveolar nerve paresthesia relieved by microscopic endodontic treatment. *The Bulletin of Tokyo Dental College, 44*(4), 209-212.

[5)] Divya, K., Moran, N., & Atkin, P. (2010). Numb chin syndrome: a case series and discussion. *British dental journal, 208*(4), 157-160; Rosen, E. (2014). Nerve injury during endodontic surgical procedures. In *Complications in Endodontic Surgery: Prevention, Identification and Management* (pp. 137-151): Springer; Gallas-Torreira, M. M., Reboiras-López, M. D., García-García, A., & Gándara-Rey, J. (2003). Mandibular nerve paresthesia caused by endodontic treatment. *Medicina oral: organo oficial de la Sociedad Espanola de Medicina Oral y de la Academia Iberoamericana de Patologia y Medicina Bucal, 8*(4), 299-303; Givol, N., Rosen, E., Bjørndal, L., Taschieri, S., Ofec, R., & Tsesis, I. (2011). Medico-legal aspects of altered sensation following endodontic treatment: a retrospective case series. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 112*(1), 126-131; Pogrel, M. A. (2007). Damage to the inferior alveolar nerve as the result of root canal therapy. *The Journal of the American Dental Association, 138*(1), 65-69; Tilotta-Yasukawa, F., Millot, S., El Haddioui, A., Bravetti, P., & Gaudy, J.-F. (2006). Labiomandibular paresthesia caused by endodontic treatment: an anatomic and clinical study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 102*(4), e47-e59.

Timeliness is a crucial factor for the successful management of TNI.[6] Prompt diagnosis and repair of the trigeminal nerve significantly increases the likelihood of improvement.[7] Surgical intervention to repair TNI should be scheduled within 3 months of the injury, underscoring the importance of a speedy referral.

In this study, we analyzed cases of TNI characterized by unpleasant sensations or partial loss of sensitivity in the facial skin or intraoral mucosa resulting from endodontic treatments. We aimed to evaluate the outcomes of conservative treatment for TNI after endodontic treatment and identify predictors of better recovery.

2. Materials and Methods

2.1. Subjects

This study examined patients who experienced altered sensation due to TNI following endodontic treatment and were treated conservatively at the Orofacial Pain and Oral Medicine Department (OFP) of Yonsei University Dental Hospital, Seoul, Korea. Data were collected from 1 January 2004 to 31 December 2020 and included 47 patients who met the eligibility criteria, comprising 35 women and 12 men: (1) development of neurosensory alterations following root canal treatment (RCT) or endodontic surgery and (2) no history of neurologic discomfort.

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[6] Zuniga, J. R., Mistry, C., Tikhonov, I., Dessouky, R., & Chhabra, A. (2018). Magnetic resonance neurography of traumatic and nontraumatic peripheral trigeminal neuropathies. *Journal of Oral and Maxillofacial Surgery, 76*(4), 725-736.

[7] Bagheri, S. C., & Meyer, R. A. (2014). When to refer a patient with a nerve injury to a specialist. *The Journal of the American Dental Association, 145*(8), 859-861.

2.2. Clinical Assessment

2.2.1 Neurosensory Function and Pain

The diagnostic process relied primarily on patient-reported information, including self-assessment of neurosensory function and patient descriptions of their current sensory state compared to their pre-injury status. Relevant details included the duration of symptoms, pain levels assessed using the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS) with Face Pain Rating Scale (FPRS), information on previous endodontic procedures, specifically affected teeth, regions exhibiting abnormal sensations in the face or oral cavity, prior neuropathy medications and any observed symptom improvements. Additionally, the duration of the injury may be regarded as a delay in professional intervention.

Neurosensory impairment was evaluated using the VAS or NRS for pain and quantitative sensory tests (QSTs), such as pinprick, light touch, two-point discrimination (TPD) and pressure pain threshold (PPT) assessments. These assessments were conducted to determine the boundaries of the regions with abnormal sensations and to diagnose the type of sensory abnormality. Patients who reported a loss of sensation or numbness were diagnosed with hypoesthesia, and patients who reported pain in their daily lives were diagnosed with dysesthesia. All patients demonstrated nerve injury symptoms, hypoesthesia, or dysesthesia, and altered sensations, such as numbness, tingling, and burning in the intraoral mucosa or facial skin within the dermatomes of the maxillary (V2) or mandibular division (V3) of the trigeminal nerve. Patients rated the sensation in the affected region compared to the unaffected side. Although the sensory tests including QST were performed, they were inconsistent and not performed in all patients.

2.2.2 Causes of Nerve Injury

The causes of nerve damage were inferred from the patient's symptoms during endodontic procedures and radiographic images. The onset of pain is linked to traumatic procedures that affect the trigeminal nerve. For instance, patients experiencing sharp pain during anesthesia for an inferior alveolar nerve (IAN) block may experience potential nerve injury from needle puncture. Pain during the injection may indicate chemical nerve damage caused by the anesthetic. A radiographic examination may reveal direct nerve injury stemming from compression by radiopaque materials used in canal obturation or sealing materials when these materials encroach on the IAN canal or mental foramen. As the patient did indicate pain during RCT or endodontic surgery, but there were no symptoms or signs mentioned above, over-instrumentation or chemical damage from antiseptic/antibacterial solutions beyond the apex should be considered as potential causes.

2.2.3 Pharmacotherapy

According to the prescription and medical records, most patients received pharmacotherapy until their symptoms subsided. However, patients with unimproved symptoms or those who missed follow-up visits did not receive pharmacotherapy. When patients did not visit the hospital or records were unavailable, 'unknown outcomes' were documented.

2.3. Data Analysis

Data analysis was carried out using the Statistical Package for Social Sciences (SPSS) and Microsoft Excel. Factors associated with improvement of the nerve injury were assessed using Student's t-test, Fisher's exact test, Kruskal–Walis test, Spearman's Rho, and Kendall's tau-b.c

2. Results

3.1. Overview of TNI cases

A total of 47 patients with TNI underwent endodontic treatment at primary dental clinics. This retrospective study included 12 men (25.5%) and 35 women (74.5%), with a mean age of 45.8 years. Primary dental procedures predominantly involved RCTs (83.0%) and apicoectomies (10.6%). The most frequently treated teeth were the mandibular molars (72.3%).

The patients reported abnormal sensations in various areas, with the lower lip (70.2%) and chin (61.7%) being the most affected areas. The most affected nerves were the IAN (85.1%) and LN (14.9%). The IAN, specifically the mental nerve, was most frequently affected.

The patients described two main types of abnormal sensations: dysesthesia, characterized by neuropathic pain (72.3%), and hypoesthesia, indicating a decrease in sensation (97.9%).

The mean duration of injury, regarded as visiting delays to secondary dental hospitals (OFP), was 22.8 weeks, ranging from 1 to 104 weeks (standard deviation: 28.016). Patients who visited the hospital were classified based on the duration of 4 weeks: those who visited the hospital within 4 weeks (40.4%) and >12 weeks (44.7%) after injury accounted for a large proportion (85.1%).

The presumed causes of TNI were local anesthesia (29.8%), overfilling (23.4%), endodontic surgery (17.0%), over-instrumentation (2.1%), and unknown causes (27.7%).

Almost all the patients (97.9%) received medication for neuropathy at our OFP clinic. The medication regimens included steroids, NSAIDs, topical lidocaine (patch), vitamin B complex, Adenosine Triphosphate (ATP), antiepileptics (carbamazepine, oxcarbazepine, gabapentin, pregabalin, topiramate, and levetiracetam), antidepressants (amitriptyline, nortriptyline, clonazepam, paroxetine, and venlafaxine), and opioids (tramadol) administered alone or in combination.

The duration of medication therapy at the OFP clinic ranged from 1 to 108 weeks, with a mean duration of 20.7 weeks. Following medication therapy, 53.2% of the patients reported improvement

in their symptoms, 27.7% experienced no significant change, and 19.1% had unknown outcomes. A summary of TNI cases is presented in <Table 1>.

Table 1. Summary of nerve injury cases during endodontic treatment

No	Age	Gender	Tooth	Previous treatment	Duration of injury (weeks; Delayed period)	Areas affected	Nerve affected	Neuropathic pain (VAS or NRS)	Abnormal sensation	Medication treatment[a]		Duration of medication (weeks)	Outcome
1	63	M	#46	RCT	1	Lower lip, chin	IAN	0	Hypoesthesia	Only ATP	ATP	12	Improved
2	76	F	#47	Apicoectomy	1	Lower lip	IAN	Not measured	Dysesthesia, hypoesthesia		ATP	8	Improved
3	43	F	#36	RCT (Direct pulp capping)	2	Lower lip, chin	IAN	0	Hypoesthesia		ATP	8	Improved
4	23	M	#37	RCT	2	Chin	IAN	0	Hypoesthesia		ATP	4	Unknown
5	27	F	#47	RCT	4	Tongue	LN	8	Dysesthesia, hypoesthesia		ATP	24	Improved
6	66	F	#46,47	RCT	4	Chin, gingiva	IAN	3	Dysesthesia, hypoesthesia		ATP	12	Unknown
7	56	F	#46	Root resection	101	Lower lip, chin	IAN	5	Dysesthesia, hypoesthesia		ATP	4	Unknown
8	24	F	#35	RCT	1	Lower lip, chin	IAN	Not measured	Dysesthesia, hypoesthesia	Anti-epileptics (gabapentin, pregabalin, levetiracetam, carbamazepine)	Gabapentin 800 mg tid	10	None
9	45	M	#34	RCT	2	Lower lip, chin	IAN	6	Dysesthesia, hypoesthesia		Gabapentin 300 mg tid—ATP	8	Improved
10	66	F	#35	RCT	2	Lower lip	IAN	3	Dysesthesia, hypoesthesia		Gabapentin 300 mg tid—ATP	4	Unknown
11	42	F	#47	RCT	2	Lower lip, chin, gingiva	IAN	0	Hypoesthesia		Steroid—gabapentin 600 mg tid	12	Improved
12	70	F	#33	Apicoectomy	3	Lower lip, chin	IAN	6	Dysesthesia, hypoesthesia		Levetiracetam 1500 mg	4	Unknown
13	16	F	#47	RCT	3	Lower lip, chin, tooth, gingiva	IAN	10	Dysesthesia, hypoesthesia		Gabapentin 400 mg tid	28	Improved
14	74	F	#45	RCT	8	Lower lip, chin	IAN	8	Dysesthesia, hypoesthesia		Gabapentin 500 mg tid—mecobalamin	32	Improved
15	64	M	#37	RCT	10	Chin	IAN	0	Hypoesthesia		Gabapentin 400 mg tid—carbamazepine 400 mg	7	Improved
16	53	F	#47	RCT	12	Lower lip, chin, gingiva, tooth	IAN	6	Dysesthesia, hypoesthesia		Gabapentin 800 mg tid	84	Improved
17	32	F	#37	RCT	16	Lower lip, chin	IAN	7	Dysesthesia, hypoesthesia		Gabapentin 800 tid—pregabalin 150 mg bid—mecobalamin	32	Improved
18	41	F	#47	RCT	23	Lower lip, chin	IAN	0	Hypoesthesia		Gabapentin 300 mg tid	4	None
19	57	M	#23	I&D	32	Upper lip, philtrum	MN	Not measured	Dysesthesia, hypoesthesia		Gabapentin 300 mg tid—ATP	8	None
20	43	M	#41,42,31,32	RCT	39	Teeth	IAN	Not measured	Dysesthesia		Gabapentin 300 mg tid	2	Unknown
21	48	F	#36	RCT	104	Lower lip, chin, gingiva	IAN	8	Dysesthesia, hypoesthesia		Pregabalin 150 mg bid—mecobalamin	8	None
22	40	F	#46	RCT	2	Tongue, lingual gingiva	LN	8	Dysesthesia, hypoesthesia	Anti-depressant (amitriptyline)	Steroid—amitriptyline	11	None
23	37	M	#47	RCT	10	Tongue	LN	4	Dysesthesia, hypoesthesia		Amitriptyline 20 mg	12	Improved
24	55	F	#35	Apicoectomy	32	Lower lip, chin	IAN	0	Hypoesthesia		Amitriptyline 10 mg	1	Unknown
25	65	F	#47	RCT	55	Lower lip	IAN	8	Dysesthesia, hypoesthesia		Amitriptyline 10 mg	12	Unknown

Continued.

No	Age	Gender	Tooth	Previous treatment	Duration of injury (weeks; Delayed period)	Areas affected	Nerve affected	Neuropathic pain (VAS or NRS)	Abnormal sensation	Medication treatment[a]		Duration of medication (weeks)	Outcome
26	46	F	#34,36	re-RCT	1	Lower lip, gingiva	IAN	6	Dysesthesia, hypoesthesia	Anti-depressants/ antiepileptics (amitriptyline, nortriptyline, venlafaxine, paroxetine/ gabapentin, pregabalin, topiramate, carbamazepine)	Tramadol+acetaminophen—amitriptyline 200 mg—pregabalin 300 mg bid	54	Improved
27	46	F	#47	RCT	2	Lower lip, chin, tooth	IAN	Not measured	Dysesthesia, hypoesthesia		Steroid—gabapentin 600 mg tid—amitriptyline 20 mg hs	36	Improved
28	23	M	#45	RCT	5	Tongue	LN	0	Hypoesthesia		Gabapentin 800 mg tid—nortriptyline 30 mg—amitriptyline 50 mg—pregabalin 150 mg bid, vit.B	44	Improved
29	53	F	#44	I&D	12	Lower lip, chin, gingiva	IAN	Not measured	Dysesthesia, hypoesthesia		Topiramate 100 mg—oxcarbazepine 1200 mg—amitriptyline 40 mg—pregabalin 150 mg—lidocaine patch	49	Improved
30	42	F	#37	RCT	14	Lower lip	IAN	5	Dysesthesia, hypoesthesia		Gabapentin 600 mg tid—amitriptyline 20 mg—topiramate 50 mg	13	None
31	41	F	#46	RCT	20	Lower lip, chin	IAN	0	Hypoesthesia		Vit.B—amitriptyline 30 mg—carbamazepine 200 mg	32	Improved
32	41	M	#46	RCT	27	Lower lip	IAN	3	Dysesthesia, hypoesthesia		Amitriptyline 30 mg—gabapentin 600 mg tid	32	Improved
33	29	F	#36	RCT	44	Lower lip	IAN	0	Hypoesthesia		Gabapentin 300 mg tid, amitriptyline 20 mg	7	None
34	47	F	#47	RCT	45	Lower lip, chin	IAN	2	Dysesthesia, hypoesthesia		Gabapentin 800 mg tid—nortriptyline 30 mg	11	Unknown
35	41	M	#46	RCT	48	Lower lip, chin	IAN	7	Dysesthesia, hypoesthesia		Gabapentin 800 mg tid—amitriptyline 20 mg	7	None
36	57	F	#47	RCT	48	Lower lip	IAN	0	Hypoesthesia		Gabapentin 300 mg tid—amitriptyline 10 mg—carbamazepine 400 mg	13	None
37	49	M	#44	Apicoectomy	70	Lower lip	IAN	2	Dysesthesia, hypoesthesia		Amitriptyline 10 mg—gabapentin 600 mg tid	10	None
38	28	M	#37	re-RCT	2	Lower lip, chin, tooth, gingiva	IAN	7	Dysesthesia, hypoesthesia		Gabapentin 1200 mg tid—venlafaxine 75 mg—paroxetine 40 mg—amitriptyline 20 mg	48	Improved
39	22	F	#47	RCT	3	Lower lip, chin	IAN	Not measured	Dysesthesia, hypoesthesia		Gabapentin 1200 mg tid—amitriptyline 30 mg—nortriptyline 30 mg—venlafaxine 75 mg—tramadol+acetaminophen	52	Improved
40	43	F	#34	RCT	4	Lower lip, chin	IAN	10	Dysesthesia, hypoesthesia	Anti-depressants/ antiepileptics/ benzodiazepine (clonazepam)	Tramadol+acetaminophen—gabapentin 300 mg tid—amitriptyline 20 mg—clonazepam 0.5 mg—oxcarbazepine 1200 mg—paroxetine 20 mg	62	Improved
41	52	F	#46	RCT	28	Tongue	LN	4	Dysesthesia, hypoesthesia		Nortriptyline 40 mg hs—pregabalin 75 mg bid—clonazepam tid	12	None
42	53	F	#36	Apicoectomy	40	Lower lip	IAN	7.5	Dysesthesia, hypoesthesia		Gabapentin 300 mg tid—nortriptyline—clonazepam	108	Improved
43	42	F	#47	RCT	55	Chin	IAN	Not measured	Dysesthesia, hypoesthesia		Gabapentin 500 mg tid—amitriptyline 30 mg, clonazepam	12	None
44	55	F	#36	RCT	2	Lower lip, chin, tongue	LN, IAN	0	Hypoesthesia	Benzodiazepine (clonazepam)	Clonazepam 1 mg—ATP—vit.B	12	Improved
45	50	F	#47	re-RCT	7	Tongue	LN	4	Dysesthesia, hypoesthesia		Clonzepam 0.5 mg—ATP	4	Improved
46	38	F	#45	RCT	20	Lower chin, cheek	IAN	10	Dysesthesia, hypoesthesia		Clonazepam 0.5 mg bid	4	Improved
47	29	F	#46	RCT	104	Chin	IAN	0	Hypoesthesia	-	x	0	None

Abbreviation: IAN, inferior alveolar nerve; LN, lingual nerve; MN, maxillary nerve; RCT, Root canal treatment.
[a]Medication: It is the maximum dose of each drug, not simultaneous.

3.2. Causes of Nerve Injury

The causes of TNI included local anesthesia (29.8%), overfilling/over-instrumentation (25.5%), endodontic surgery (17.0%), and unknown factors (27.7%) <Fig. 1>.

A. Local anesthesia: 14 patients (29.8%) reported pain during local anesthesia, which was attributed to mechanical or chemical damage. Twelve patients received IAN block anesthesia, one infiltrative anesthesia, and one intra-pulpal anesthesia. In 11 cases, the patients described severe sharp pain, often resembling a pinprick or electric shock during the needle stick. Three patients reported experiencing pain when the anesthetic agent was injected. Notably, two patients were administered articaine (block, one patient; infiltration, one patient).

B. Overfilling: 11 patients (23.4%) exhibited specific radiographic evidence of extrusion of the root canal filling material beyond the apex. Radiopaque substances, including calcipexes (6 cases), vitapexes (2 cases), and unknown materials 3 cases), were observed extending past the apex. In certain cases, excess sealer, which is one of the unknown constituents, is extended along the IAN canal within the mandible.

C. Over-instrumentation: 1 patient (2.1%) reported severe pain during instrumentation preceding root canal filling, where nerve injury may be attributed to either direct injury through instrumentation beyond the apex into the neurovascular bundle or chemical nerve injury due to the extravasation of irrigants such as sodium hypochlorite. In this specific case, over-instrumentation was the primary concern, as there was no evidence of ecchymosis suggestive of chemical injury in the patient.

D. Endodontic surgery: 8 patients (17.0%) reported pain after the surgical procedure, mainly associated with apicectomy, root resection, and incision and drainage. Apicoectomy is the most frequently identified cause of endodontic surgical injuries due to its frequent use in endodontic treatment.

E. Unknown: 13 cases (27.7%) lacked any definitive event or radiographic evidence of nerve injury, with all cases involving block anesthesia administration except one. Following treatment, patients reported dysesthesia or hypoesthesia of the facial skin within the dermatome of the mandibular division (V3) of the trigeminal nerve (Mn. molar, 9 cases; Mn. premolars, 2 cases; Mn. molar and premolar, 1 case; Mn. incisor, 1 case).

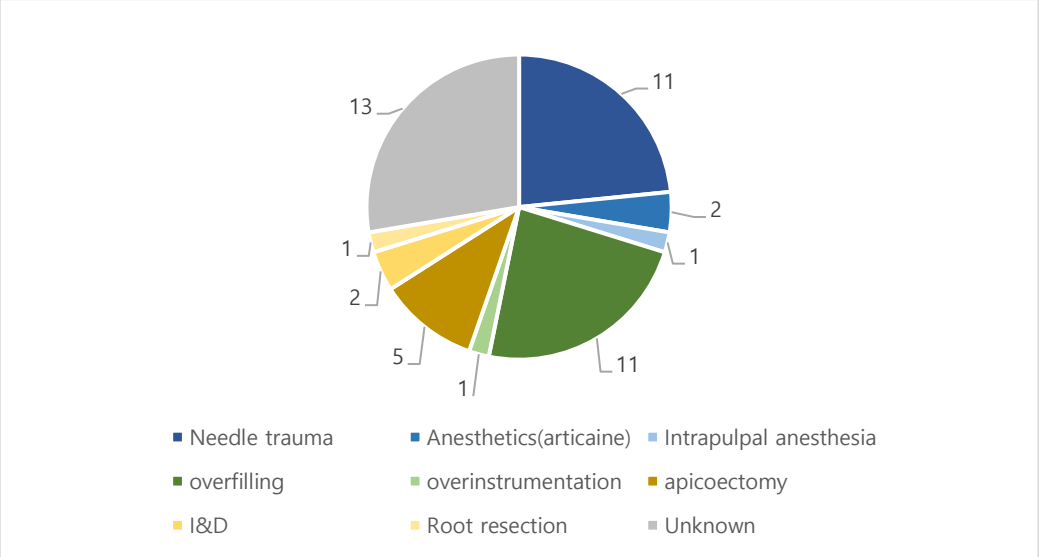

Figure 1. Causes of Nerve Injury

3.3. Analysis of affected nerve branch depending on the causes of TNI

The damaged nerves were analyzed according to the cause of TNI <Table 2>. These were as follows: IAN, 83.0%; LN, 12.8%; (IAN + LN), 2.1% and MN, 2.1%. Most injuries were caused by local anesthesia (29.8%), overfilling (23.4%), and endodontic surgery (17.0%). IAN injuries were caused by overfilling (28.2%), direct needle trauma (15.4%), apicoectomy (12.8%), and others. The LN injuries were caused by needle trauma (66.7%) or articaine use (33.3%).

Table 2. Causes of nerve injury and the affected nerve

	Local anaesthesia (29.8%)					Endodontic surgery (17.0%)				
	Needle trauma (IAN block anaesthesia)	Articaine	Intrapulpal	Overfilling (23.4%)	Overinstrumentation (2.1%)	Apicoectomy	I&D	Root resection	Unknown (27.7%)	Total (%)
IAN	6	1	1	11	1	5	1	1	12	39 (83.0)
LN	4	1	0	0	0	0	0	0	1	6 (12.8)
IAN+LN	1	0	0	0	0	0	0	0	0	1 (2.1)
MN	0	0	0	0	0	0	1	0	0	1 (2.1)

Abbreviations: I&D, incision and drainage; IAN, inferior alveolar nerve; LN, lingual nerve; MN, maxillary nerve.

3.4. Analysis of factors associated with symptom improvement

Excluding nine patients with unknown outcomes, we examined the factors influencing symptom improvement in 25 patients who experienced improvement and 13 patients whose symptoms did not change.

The location of the previously treated teeth and the patient's age were not associated with the outcomes (Fisher’s exact test: $p>.05$).

We classified the altered sensations following endodontic treatment into two categories: Hypoesthesia with dysesthesia and hypoesthesia alone. This study investigated the relationship between the causes of TNI and the types of sensory abnormalities, as well as the correlation between pharmacological treatment and subsequent symptom improvement. The objective was to elucidate the factors that influence the prognostic outcomes of pharmacological interventions in cases of nerve damage. Our analysis measured the extent of improvement for each cause, as shown in Table 3.

Table 3. Comparison of the symptom relief in causes of nerve injury and abnormal sensation

	Local anaesthesia (14)			Overfilling (11)				Endodontic surgery (8)				
	Needle trauma	Articaine	Intrapulpal	Vitapex	Calcipex	Unknown	Overinstrumentation (1)	Apicoectomy	I&D	Root resection	Unknown (13)	Total / improved patients (%)
Dysesthesia/improved patients (%)	3/8 (37.5%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	2/4 (50%)	1/2 (50%)	-	2/4 (50%)	1/2 (50%)	0/1 (0%)	6/10 (60%)	18/34 (53%)
Only hypoesthesia/ improved patients (%)	3/3 (100%)	1/1 (100%)	-	0/1 (0%)	1/2 (50%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	-	-	2/3 (67%)	7/13 (54%)
Total/improved patients (%)	9/14 (64%)			5/11 (45%)			0/1 (0%)	3/8 (38%)			8/13 (62%)	25/47 (53%)

Abbreviation: I&D, incision and drainage.

Overall, we found a similar improvement rate between patients experiencing both hypoesthesia and dysesthesia (53%) and those experiencing only hypoesthesia (54%). Considering the presumed cause of injury, we observed varying rates of improvement. Cases related to local anesthesia showed the highest improvement rate, followed by those associated with overfilling and surgical treatment. However, these differences were not statistically significant (Fisher's exact test, $p = .768 > .05$). Additionally, there was no correlation between the cause of TNI and duration of medication use among patients who improved (Kruskal– Wallis test: $p > .05$).

However, we found a significant relationship between the time it took for patients to visit the OFP clinic and their treatment outcomes (Mann–Whitney test: $p < .05$). Patients who experienced symptom improvement had an average delay (duration of injury) of 8.6 weeks, whereas those with no change in symptoms had a delay of 44.1 weeks <Figure 2>.

Patients with nerve damage were categorized into four groups based on the duration of their injuries. The largest group consisted of 21 patients (44.7%) who presented after 12 weeks, followed by 19 patients (40.4%) who presented within 4 weeks, 4 patients who presented between 9 and 12 weeks, and 3 patients who presented between 5 and 8 weeks. Among the patients who visited within 4 weeks, 13 out of 19 exhibited symptom improvement(68.4%); however, only 5 out of 21 patients

who delayed their visit for more than 12 weeks demonstrated symptom improvement(23.8%). The rate of symptom improvement significantly decreases after 12 weeks(3 months) <Table 4>.

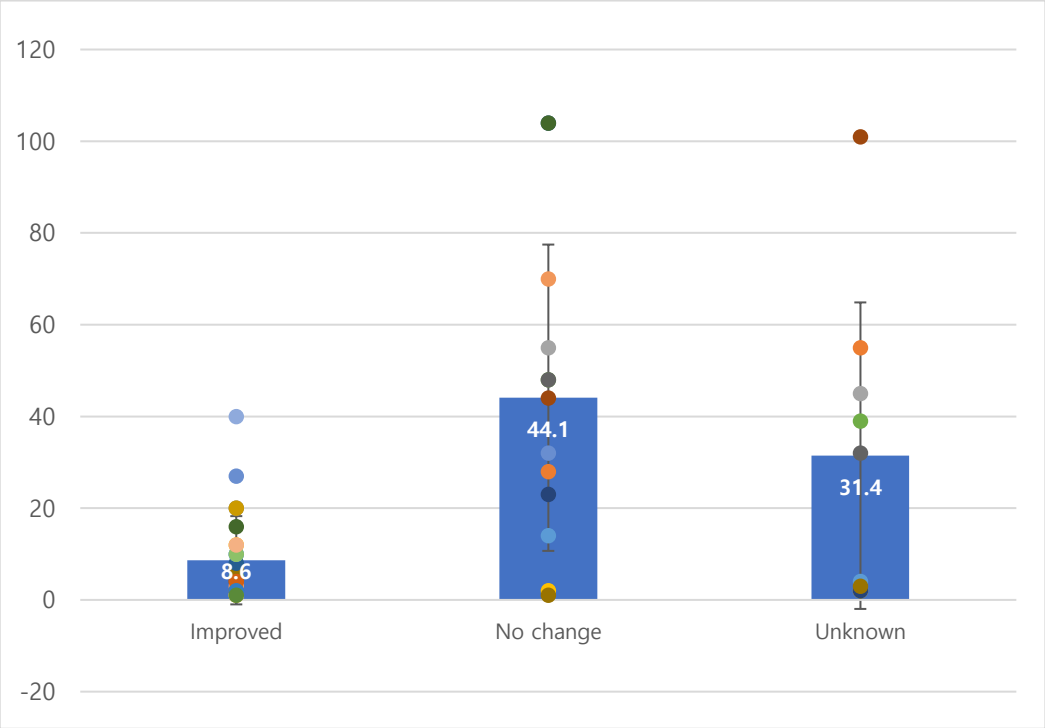

Figure 2. Patient distribution of duration (weeks) in three groups before pharmacologic management by a specialist ($p < .05$)

Table 4. Rate of improvement depending on duration of nerve injury period

Duration of injury(week)	Improvement (%)	No change	Unknown	Total
≤4	13 (68.4%)	2	4	19
5-8	3 (100%)	0	0	3
9-12	4 (100%)	0	0	4
12<	5 (23.8%)	11	5	21

Our analysis also explored the relationship between the duration of injury and the medication period at the OFP clinic. Although a longer duration of injury tended to be associated with a longer medication period in the improved group, the relationship was not statistically significant (Spearman's rho: ro=.179, p>.05).

Conversely, we found a statistically significant positive correlation between the duration of injury and recovery time in patients who showed improvement (Spearman's rho: r= .52, p= .008<.05), as illustrated in <Figure 3>. The recovery time is the sum of the duration of the injury and the medication period at the OFP clinic.

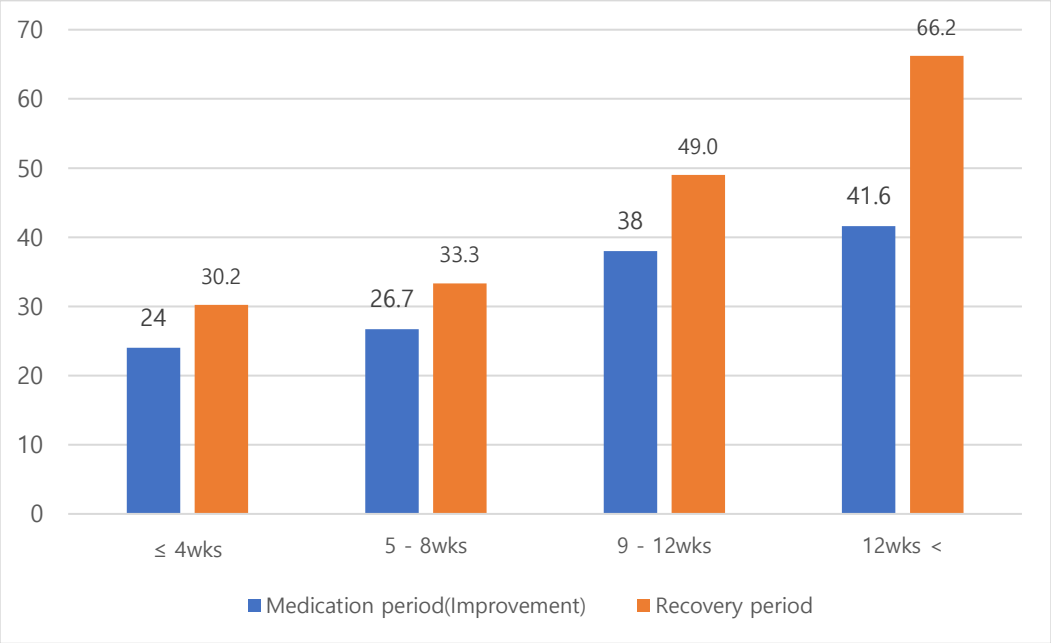

Figure 3. Medication and recovery period for symptom relief in improved group depending on Duration of injury

Before visiting the OFP clinic, the improvement in symptoms of patients who received pharmacological treatment for nerve damage at a primary clinic and those who did not are shown in

the <figure 4> below. In the primary clinic, patients who received pharmacological treatment following nerve damage demonstrated a higher rate of symptom improvement compared to those who did not receive medication. Nonetheless, this difference was insignificant and there was no statistically significant difference.

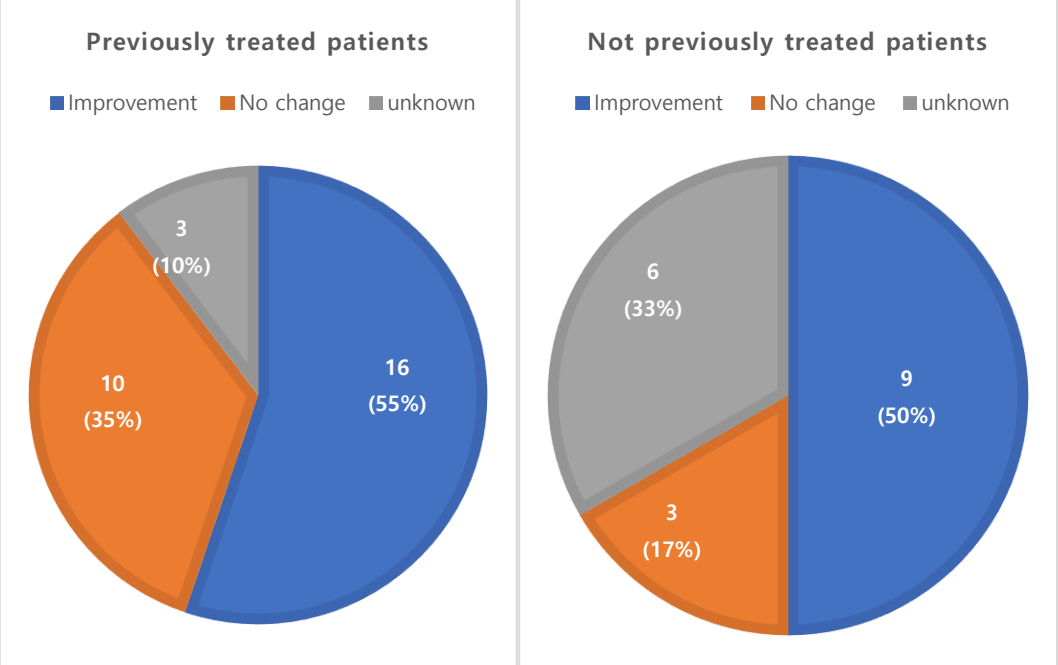

Figure 4. Rate of improvement with/without previous pharmacotherapy

However, limitations related to retrospective studies prevented the identification of specific drugs administered in primary clinics. In addition, the presence of "groups with unknown improvements" has led to restrictions on the accurate analysis of these associations.

4. Discussion

This study was conducted to assess the recovery rate of TNI following endodontic treatment and to identify the key influencing factors. Patients commonly present to our clinic complaining of hypoesthesia accompanying dysesthesia. None of the patients experienced worsening symptoms, and half (53.2%) reported improved sensation. A critical finding from our analysis was the association between the duration from injury to the first visit to our clinic and the treatment outcome. Patients seeking prompt medical attention exhibit better recovery. However, in a study of patients who experienced TNI during dental implant placement, only a limited number (16%) exhibited improved sensation, whereas the majority (70%) remained stationary. Further research is needed to determine the prognosis of TNI according to the dental procedures.3 In this study, the diagnostic process relied primarily on patient reported information, including self-assessment of neurosensory function and patient descriptions of their current sensory state compared to their pre-injury status. Neurosensory impairment was evaluated using the VAS or NRS for pain and QSTs, such as pinprick, light touch, two-point discrimination (TPD), and pressure pain threshold (PPT) assessments. Most patients complaining of numbness (39/46) showed hypoesthesia in mechanical sensory tests (light touch or two-point discrimination), and some patients complaining of pain in daily lives showed hyperalgesia in pain detection tests (pin-prick or PPT) or allodynia for light touch. However QSTs were not consistently performed on all patients, and the type of QST and exminers were different. This is a reason it is difficult to expect the high reliability of QSTs performed in this study. Due to the limitation of the retrospective study, the most consistent and common tool for measuring sensory impairment was patients' symptoms of numbness and pain rating scales. In this study, the visual analogue scale (VAS) or numeric rating scale (NRS) with face pain rating scale (FPRS) was used as a measure for pain intensity. It is known that there is a significant correlation between the VAS and the NRS.19 VAS and NRS are measures of pain intensity, which are known to have a high sensitivity, the ability of the scale to detect change. Since they are used through interviews or questionnaires,

information on the patient's subjective pain intensity can be obtained.[8] However, the pain rating scales have limitations in a multi-dimensional evaluation, and it is known that serial VAS measurements can have a variability of up to 20%.[8] It is suggested that a multi-dimensional evaluation scale for neuropathic pain such as the Short-Form McGill Pain Questionnaire (SF-MPQ) is required.[9] On the other hand, QST has been applied to many studies of the functional changes in the sensory fibres of peripheral nerves as a neurophysiological examination method.[10] It has the advantage of being able to classify the affected area and find out the abnormality of various sensations such as temperature, pressure, touch, and pain. As the American Academy of Neurology evaluated the clinical utility, efficacy, and safety of QST, the authors concluded that QST is a potentially useful tool for measuring sensory impairment for clinical and research studies.[11] However, in a 2022 re-affirmed report, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) noted QST should not be used as a sole method for diagnosis of pathology. The AAN pointed out that Quantitative Sensory Testing (QST) presents technical challenges in examination methodology, reproducibility, and psychophysical factors, all of which constrain the objectivity of test outcomes. Additionally, the authors observed that QST is

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susceptible to various extraneous influences and could be prone to misinterpretation and misuse. The study by Martín et al. suggested that Quantitative Sensory Testing (QST) and imaging may play a more important role in the diagnosis of orofacial neuropathies when performed together.[12] Pain is entirely subjective, so it is what the patient says it is.19 In this perspective, self-reported pain intensity can be the 'gold standard' for measurement (Dworkin et al. 2005).[13] However, it is also needed to use other tools for the diagnosis of pain, such as multi-dimensional questionnaires for subjective pain evaluation, consistent QSTs, and imaging in future studies. In our study, 97.9% of the 47 patients had injuries to either the IAN or the LN after endodontic treatment. In clinical practice, the mandibular division is the most vulnerable to injury compared with the ophthalmic and maxillary divisions.[14] Unlike the other two trigeminal nerve divisions, the mandibular nerve also contains motor or efferent fibres to innervate the muscles that are attached to the mandible, travelling directly to tissues.[15] The lingual nerve has frequent variations from osseous, fibrous, or muscular irregularities in the region of the infratemporal fossa. Therefore, the mandibular nerve, including the lingual nerve, is bound to be relatively vulnerable to entrapment and irritation by dental procedures as a result of its anatomical location and frequent variations.[15] Analysis of the specific teeth affected revealed that many cases (93.6%) occurred in the mandibular molars or premolars. This propensity for injury arises from the proximity of the IAN canal and mental foramen to the tooth apex. While there have been slight discrepancies among previous studies, recent research employing cone-beam

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computed tomography (CBCT) scans suggests that the root apex of the mandibular second premolar (70%) is closest to the mental foramen, followed by the first premolar (18%), and then the first molar (12%).[16] Another study examining the distance of the second molar from the IAN canal found that in 54.8% of CBCT scans, the distance was ≤3 mm.28 Furthermore, LN injuries have a worse prognosis than IAN injuries.[17] The LN is situated within the connective tissue, making it more susceptible to injury during dental procedures and challenging to repair. Therefore, it is imperative for clinicians to carefully assess the distance between the nerve and the tooth apex using radiography before commencing any dental procedures. Nerve injuries resulting from endodontic procedures have various causes, including mechanical, chemical, thermal, and ischemic damage. Patients experiencing injury due to local anesthesia showed a relatively favorable prognosis, with 64.3% of the 14 patients experiencing symptom improvement. Conversely, injuries attributed to overfilling, endodontic surgery, and over-instrumentation exhibited improvement rates of 45.5 (5/11), 37.5 (3/8), and 0% (0/1), respectively. However, it is crucial to acknowledge the limitations of data in this study (small number of subjects). Other studies have indicated that 91% of patients with altered sensation resulting from the extrusion of root canal filling materials demonstrate full or partial recovery over time.[18] Nerve damage caused by local anesthesia typically manifests as severe, sharp pain during mandibular nerve block injections.[19] Notably, the recovery rate in such cases is generally high,

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although local anesthesia-related nerve injury remains one of the most common types of nerve damage during dental procedures. Therefore, clinicians should exercise caution and vigilance when administering local anesthesia, particularly during IAN blocks. Additionally, there is some debate surrounding the safety and neurotoxicity of articaine compared with other local anesthetics. The high lipid solubility and rapid metabolism of articaine, attributed to its thiophene portion and ester hydrolysis component, may result in 20–21 times greater neurotoxicity than lidocaine.[20] Therefore, it is advisable to consider infiltration anesthesia as the preferred option when using articaine, although prior studies have not provided conclusive evidence suggesting that 4% of articaine causes more nerve damage than 2% of lidocaine.[21] Mechanical nerve injury can occur because of improper instrumentation of the root canal, potentially enlarging the apical constriction. This can lead to direct neural damage, neurovascular bundle compression, ischemic damage, or chemical injury. Neurotoxic chemical effects may also result from the leakage of endodontic irrigants and sealants

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into the IAN canal or mental foramen.[22] These substances can be highly neurotoxic and cause permanent nerve injury and severe neuropathic pain, often because of their high pH levels.[23] To mitigate these risks, clinicians should exercise caution to avoid excessive pressure during instrumentation, irrigation and canal filling. Clinicians should conduct postoperative radiography to confirm whether filling materials have extruded into the nerve canal. When root canal filler extrusion into the nerve canal is confirmed, material removal via re-RCT or surgery should be considered. Treatment options for nerve injury-induced neuropathy include topical analgesia, systemic analgesia,

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and surgical interventions.[24] However, it is essential to exercise caution owing to the potential complications associated with surgery, making it a last-resort option despite the substantial improvements reported by patients who underwent surgical intervention.[24] In cases involving the microsurgical repair of IAN injuries associated with endodontic treatment, the study included 23 patients, 17 (73.9%) of whom reported painful sensations during their initial consultation. Functional sensory recovery (FSR) was achieved in 10 of the 21 patients at the 1-year mark following surgical intervention.[25] This notable improvement was reflected in the reduction of pain levels from an initial average of 4.86 to 2.76 ($p = .001$), with no discernible impact from other variables. However, it is essential to acknowledge that immediate surgical repair of a damaged IAN is relatively uncommon owing to challenges in defining the extent of injury and limited accessibility, often resulting from a closed wound. However, the possibility of complications caused by invasive surgery cannot be ignored. Therefore, the primary consideration should be pharmacotherapy, which may involve the use of antiepileptics as well as low-dose antidepressants that are particularly effective in alleviating neuropathic pain. Lopez et al. reported a case in which complete resolution of paresthesia and pain control was achieved through a nonsurgical approach involving prednisone and pregabalin, underscoring the potential efficacy of this management strategy when the extruded root filling material contacts the inferior alveolar nerve.[26] Additionally, patients who report prolonged

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symptoms following trigeminal nerve injury may also experience secondary issues, including eating disorders (43%), speech difficulties (38%), depression (37%), relationship problems (14%), and adverse effects on employment (13%), as reported by Pogrel et al. in 2011.[27] In this case, antidepressants used for chronic pain were prescribed to 46.8% (22/47) of patients. This shows that neuropathy caused by nerve injury negatively affects patients' quality of life and psychological health for a long time. Therefore, it is crucial to consider the potential effect of psychosocial factors on neuropathy, particularly in patients with chronic symptoms. Neuropathic pain is characterized by chronic pain resulting from damage or disease affecting the somatosensory nervous system. Additionally, chronic inflammation can exacerbate pain as inflammatory mediators impact pain-sensitive nerve endings, lowering neuronal excitability thresholds and heightening firing rate sensitivity. This process contributes to both peripheral and central sensitization.[28] In this study, three patients visiting within 2 weeks after injury were prescribed steroids and diagnosed with acute inflammatory pain during their initial visit. After a short period, they were prescribed antiepileptics and antidepressants, as it turned into chronic pain. It is known that corticosteroids play both direct and indirect roles in reducing the production and release of cytokines. It is attained by inhibiting Phospholipase A2 and consequently suppressing the arachidonic acid metabolic pathway. Moreover, corticosteroids enhance the inhibition of transcription factors (e.g., NK-κB), leading to reduced expression of pro-inflammatory genes.[29] However, when used for chronic pain syndromes

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associated with localised joint, nerve, or disc disease, functional improvements are less common, and alternative drugs are often preferred.[30] As a result, most patients with neuropathic pain were mainly prescribed antiepileptics and antidepressants diagnosed in this study. Recently, TNI treatment has been aimed at holistic management, and it has not changed to consider surgical intervention only when decompression and debridement are required in cases of mechanical invasion to nerve canal. Renton et al. suggested a management strategy for iatrogenic TNI. They recommended surgical removal of tooth or overfilling material, only within 30 h. After that, conservative treatment is recommended first, because of risks from surgical complications.[31] In this study, the majority of patients who came to the university-based hospital were delayed by more than a week after symptoms, leading to the implementation of conservative treatment as the standard approach. Some case studies exhibited minimal impact; for instance, after RCT, approximately 10% of patients meet the criteria for experiencing pain 6 months post-treatment, which is typically of mild to moderate intensity, lasting approximately 10 days per month, and causing minimal disruption to daily activities.[32] However, another subset of cases can be quite intense, with an average VAS pain score of 7.2.[33] This highlights the controversial nature of the TNI outcomes and the need for

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further research to understand and manage these variations effectively. Notably, permanent central and peripheral nervous system changes can manifest within 3 months of nerve injury. This study underscores the critical importance of early referral, as it reveals a statistically significant correlation between a prolonged delay in treatment by a neuropathic pain expert and a diminished likelihood of symptom improvement, which is particularly evident after 12 weeks (approximately 3 months). Moreover, when comparing the duration of injury between the improved and unimproved groups, a significant difference emerged, with the improved group experiencing symptoms for an average of 8.6 weeks, compared to 44.1 weeks in the unimproved group. This extended duration of injury (i.e. delayed time) was directly correlated with a longer recovery period in patients showing improvement, a correlation supported by statistically significant findings (Spearman's rho: $r= 0.52$, $p= .008<.05$).

This study strongly emphasises the 'time', which indicates the delay from injury to treatment by a specialist. Potential for more favourable treatment outcomes when neuropathy is promptly addressed. Clinicians must maintain a vigilant stance and adhere to the established treatment principles. In cases of nerve damage, medication-based interventions for acute injuries, such as corticosteroids, should be promptly administered. Furthermore, healthcare providers must recognise that early and appropriate referrals to neuropathic pain experts can significantly influence the prognosis of neuropathy treatment. However, this study had several limitations, including the relatively small sample size of patients who experienced nerve injury due to endodontic treatment. The participants' presentations did not exhibit regular patterns, necessitating non-parametric analyses. As a retrospective study, it depended on medical records, and there was a lack of detailed information on functional limitations and the degree of symptom improvement after treatment.

5. Conclusions

This study emphasises the significance of early recognition and management of TNI during endodontic treatment. Although infrequent, TNIs can severely affect the daily lives of patients by causing sensory disturbances and discomfort. Our research identified the potential causes of TNI by analysing factors related to symptoms and prognosis, such as local anaesthesia administration and surgical procedures. In conclusion, this study provides valuable insights into TNI afterThis study emphasises the significance of early recognition and management of TNI during endodontic treatment. Although infrequent, TNIs can severely affect the daily lives of patients by causing sensory disturbances and discomfort. Our research identified the potential causes of TNI by analysing factors related to symptoms and prognosis, such as local anaesthesia administration and surgical procedures. In conclusion, this study provides valuable insights into TNI after endodontic treatment and highlights the need for meticulous techniques to reduce the risk of injury. Timely referral to specialists within 90 days of injury was associated with better outcomes. Medication therapy tailored to individual symptoms is promising for symptom improvement. Overall, this study underscores the importance of preventive measures, prompt referrals, and comprehensive care for mitigating the impact of TNI and enhancing patient well-being. Future studies with larger sample sizes and more standardized assessments could further enhance our understanding of this complex condition.

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Abstract in Korean

근관치료 후 발생한 삼차신경 손상에 대한 약물치료 : 후향적 분석

배경: 근관 치료 후 발생한 삼차신경 손상(TNI)은 드물지만 얼굴이나 구강 점막에서 감각부전 또는 감각저하를 유발할 수 있다.

목적: 본 연구는 근관치료에 의한 삼차신경 손상을 주소로 대학병원에 내원한 환자들에 대한 약물 치료 사례들에 대해 분석하고자 하였다.

방법: 연세대학교 치과대학병원 구강내과를 방문한(2004 년~2020 년) 47 명의 환자를 대상으로 후향적 분석을 실시하였다. 근관 치료 후 발생한 TNI 주소로 내원한 환자들은 초진 시 실시된 객관적인 감각신경검사 및 환자들의 주관적 증상 평가를 통해 감각 손상의 정도와 기간을 평가하였으며, 초기 증상, TNI 의 원인, 신경손상 후 경과 기간, 그리고 시행된 약물 치료를 분석하여, 이러한 요인들이 치료 경과에 미치는 영향을 분석하였다.

결과: TNI 환자의 70.2%가 감각저하(hypoesthesia)를 동반한 감각부전(dysesthesia)을 경험하였으며, 하악 대구치 치료 후 가장 많이 발생하였다(72.3%). 손상의 원인은 국소 마취(29.8%), 근관충전재의 과충전, 근관치료 시 과도한 기구 사용(25.5%), 치근단 수술(17.0%) 순으로 나타났으며, 원인 불명(27.7%)의 사례들도 포함되었다. 손상 후 경과된 기간과 증상호전의 연관성이 있는 것으로 나타났는데, 증상이 호전된 환자군의 평균 경과 기간은 8.6 주, 증상이 호전되지 않은 환자군은 44.1 주로, 통계적으로 유의미한 차이를 보였다. 약물 요법으로는 스테로이드, 비스테로이드성 항염증제(진통소염제), 국소 리도카인, 비타민 B 복합체, 아데노신 삼인산염(ATP), 항경련제, 항우울제 및 오피오이드 등이 처방되었으며, 평균 약물 복용기간은 20.7 주였다. 이 중 환자의 53.2%가 증상이 호전되었으며,

27.7%는 차도가 없었다.

결론: 근관 치료로 인한 삼차신경 손상 발생 시, 구강안면통증 전문가에 대한 신속한 의뢰를 통한 전문적인 약물치료는 효과적인 회복에 기여할 수 있다.

핵심되는 말 : 근관치료, 신경병증, 약물치료, 삼차신경 손상