Alternating Current Iontophoresis for Control of Postoperative Pain

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Control of early postoperative pain entails the use of various medications including acetaminophen, nonsteroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, tramadol, and opioids. However, these medications should be carefully administered in patients with aspirin-exacerbated respiratory disease because some medications may trigger adverse reactions after maxillofacial surgeries. The goal of postoperative pain control in patients with aspirin-exacerbated respiratory disease is to eliminate pain without complications. Local anesthesia is an efficient tool for the control of postoperative pain after maxillofacial surgeries. We utilized a transdermal drug delivery system, iontophoresis by alternating current, in order to develop an alternative technique for administering local anesthetic to control postoperative pain in 2 patients with aspirin-exacerbated respiratory disease. A visual analogue scale was used to objectively measure the severity of pain. A 55-year-old woman who underwent mandibular wisdom tooth extraction and an 18-year-old woman who underwent sagittal split ramus osteotomy of the mandible both complained of pain multiple times. After application of iontophoresis, the visual analogue scale score was reduced to zero and postoperative pain could be controlled. There were no adverse events such as bronchospasm or skin irritation after the application of iontophoresis by alternating current.

Key Words: Transdermal drug transport; Aspirin-exacerbated respiratory disease; Postoperative pain; Maxillofacial surgery.

Aspirin-exacerbated respiratory disease (AERD) is characterized by the combination of asthma, chronic rhinosinusitis and nasal polyps, in addition to hypersensitivity to aspirin and cyclooxygenase-1 (COX-1)-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs).^{1,2} The detailed mechanism of AERD is still unknown and the triggers of AERD are difficult to distinguish from those of the other types of asthma.^{3,4}

Control of postoperative pain is important after oral and maxillofacial surgery. NSAIDs are frequently used to control pain, but are relatively contraindicated in patients with AERD because they strongly inhibit the activity of COX-1.⁴ Patients with AERD usually tolerate alternative drugs, such as highly selective

COX-2 inhibitors, NSAIDs with very weak COX-1 inhibitory properties, and acetaminophen in doses as high as 650 mg; 20% of AERD patients will experience respiratory symptoms to a dosage of acetaminophen 1000 mg.⁵⁻⁷

The opioid class of drugs is another effective medication group to control postoperative pain. The use of large doses of opioids may lead to opioid-induced ventilatory impairment, nausea, and/or vomiting.⁸⁻¹⁰ In patients undergoing maxillofacial surgeries that remodel the upper airway and extra-airway tissues, particularly when they have often undergone intermaxillary fixation, which inhibits maintenance of airway patency and proper drainage, these medications should be carefully administered with appropriate monitoring.¹¹ Weak opioids, such as tramadol, with or without added acetaminophen, are effective for control of dental pain,¹² but their use may be associated with nausea as an adverse effect.¹³ Submucosal application of tramadol in the surgical field has also been shown to reduce postoperative pain after third molar surgery.¹⁴ Management of postoperative pain in patients with AERD requires careful consideration in order to avoid

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Figure 1. Setup and position of electrodes in Case 1. The 2 electrodes were placed far apart on the facial skin on the side of the mandible where the wisdom tooth was extracted. One electrode was placed on the skin in front of the ear; the other was placed on the skin next to the left corner of the mouth.

complications due to administration of analgesics, especially after maxillofacial surgeries.

Local anesthesia is effective in controlling postoperative pain in the field of maxillofacial surgery. Nerve block with bupivacaine can reduce the need for analgesics in mandibular symphyseal fractures.¹¹ In addition, a significant reduction in postoperative pain on the injected side was observed with bupivacaine in third molar surgery.¹⁵ Thus, local anesthesia would be applicable to postoperative management of patients with AERD after maxillofacial surgeries with minimum adverse effect.

Iontophoresis (IOP) is a transdermal drug delivery system that transports charged molecules using low intensity electric current across 2 electrodes that are placed apart from each other on the skin.¹⁶ IOP by direct current (DC IOP) causes skin irritation and electrode polarization.¹⁷ Conversely, IOP by alternating current (AC IOP) causes minimal complications; therefore, it is more suitable than DC IOP for clinical applications.¹⁸ AC IOP (hereafter just “IOP”) medication transport has been one of the clinically applicable methods to control neuropathic pain in some hospitals.^{19,20} In IOP application after maxillofacial surgeries, patients do not need to open their mouth and are able to keep their mouth at rest without disturbing the surgical site. We initially developed this technique to control early postoperative pain in patients with AERD. We first applied IOP with 4% lidocaine after wisdom tooth extraction and sagittal split ramus osteotomy of the mandible (SSRO). Using a visual analogue scale (VAS), we objectively recorded the response to IOP and found that IOP was efficacious in controlling postoperative pain.

Figure 2. Setup and position of electrodes on the mandible in Case 2. One electrode was placed on the skin in front of the ear; the other was placed on the skin next to the corner of the mouth of the patient who underwent sagittal split ramus osteotomy of the mandible (SSRO).

METHODS

In accordance with the Declaration of Helsinki, we obtained written and informed consent from the patients for the publication and the performance of general anesthesia, perioperative management, premedications, and IOP application for pain relief.

AC IOP Application

Initially, we did not administer any medications after the patients returned to the ward. Instead, we started applying IOP from the time the patients complained of pain after returning to the ward. We used a clinical electrical device for IOP (LASPER; Sankyo Electric Co., Japan). The electrode was made of cotton and a copper wire mesh. The 2 electrodes were soaked in 4% lidocaine and were placed apart on the facial skin, in such a way that the operative site was between the electrodes (Figures 1 and 2); after fixing the electrodes with surgical tape, a pulsed AC voltage (1 V; 50 Hz) was applied for 30 minutes or 60 minutes as described in previous reports, a level which does not induce complications.^{19,20}

Measurement of Severity of Pain

To measure pain perception, we asked the patients to rate the severity of pain on a standard VAS scale (100-mm horizontal line with the left end of the line

Figure 3. Trend in visual analogue scale (VAS) and the period of iontophoresis by alternating current (AC IOP) application and Rikkosan administration (arrow) after wisdom tooth extraction.

corresponded to a scale of 0 mm marked as “no pain,” and the right end corresponded to a scale of 100 mm marked as “most severe pain”).

CASE 1

A 55-year-old woman was scheduled for a difficult deep left mandibular wisdom tooth extraction in close proximity to the inferior alveolar nerve under general anesthesia. She was diagnosed with AERD at 28 years old and hyperthyroidism, now controlled, and hyperlipidemia at 55 years old. She was prescribed theophylline, procaterol hydrochloride, and inhaled salmeterol xinafoate and fluticasone propionate. Her asthma has been controlled for the past 5 years.

Management of general anesthesia: The patient received premedication with salmeterol xinafoate and fluticasone propionate. Induction of anesthesia was performed with 100% oxygen and sevoflurane. Fentanyl citrate at 50 µg and a muscle relaxant, vecuronium bromide at 6 mg, were administered intravenously before tracheal intubation. Intravenous hydrocortisone sodium phosphate 100 mg and fentanyl citrate 100 µg, as well as propitocaine hydrochloride-felypressin, for local anesthesia, were administered during the operation. Anesthesia maintenance was uneventful with 1.5 to 2.5% sevoflurane and 33% air/oxygen. Return of neuromuscular function was confirmed, and the tracheal tube was successfully removed and did not induce bronchospasm. The patient was brought back to the ward thereafter.

Control of postoperative pain (Figures 1 and 3): IOP was applied 90 minutes after the patient returned to the ward for a reported VAS of 30. Application of IOP with 4% lidocaine for 30 minutes reduced the VAS to 0. At 165 minutes, IOP application for 60 minutes with a reported VAS of 20 lowered the VAS to 0. At 325 minutes, the patient complained again of pain with a reported VAS of 35. Rikkosan, a traditional Japanese medicine (Kampo) that is known to relieve oral pain,²¹ was administered orally (Figure 3, arrow), but it did not relieve the pain. With persistent pain of the same severity, the patient asked to relieve the pain immediately. IOP was applied for 30 minutes at 330 minutes, which relieved the pain and reduced the VAS to 0.

CASE 2

An 18-year-old woman was scheduled for SSRO under general anesthesia. The patient was diagnosed with asthma when she was 16 years old and received formoterol fumarate hydrate. The last asthmatic attack occurred after administration of aspirin for pain relief for mechanical tooth movement during preoperative orthodontics.

Management of general anesthesia: We gave the patient formoterol fumarate hydrate 2 hours before she was brought to the operating room. Anesthesia was induced with 100 mg propofol, 100% oxygen, 3% sevoflurane, and 0.5 µg·kg⁻¹·hr⁻¹ remifentanyl. Vecuronium bromide 6 mg was administered intravenously. Tracheal intubation was uneventful. Hydrocortisone sodium phosphate 200 mg and fentanyl citrate 200 µg were administered during the operation. Anesthesia maintenance was uneventful with 1.5 to 2.5% sevoflurane, 33% oxygen, and 0.1 to 0.5 µg·kg⁻¹·hr⁻¹ remifentanyl. At the end of the operation, 1% lidocaine with epinephrine was injected by infiltration to the surgical site to relieve pain after its emergence. The patient was extubated with no complications, and she was brought back to the ward thereafter.

Control of postoperative pain (Figures 2 and 4): For a reported VAS of 22, IOP was applied 75 minutes after the patient returned to the ward. Application of IOP with 4% lidocaine for 30 minutes reduced the VAS to 0. Nine hours and 35 minutes later, the patient complained of pain and the reported VAS went up to 40. Repeat IOP application for 30 minutes effectively reduced the pain to a VAS of 0 (Figure 4). Thereafter, there was no recurrence of pain and no further need for IOP. We observed no complications.

Figure 4. Trend in visual analogue scale (VAS) and the period of iontophoresis by alternating current (AC IOP) application after sagittal split ramus osteotomy of the mandible (SSRO).

DISCUSSION

We demonstrated that application of AC IOP with 4% lidocaine effectively reduced and controlled pain in AERD patients after wisdom tooth extraction and SSRO. Further statistical analysis is required to confirm the efficacy of IOP. However, IOP may be a useful tool to control postoperative pain, particularly for patients in whom asthma may be triggered by the use of certain medications.

With this in mind, Rikkosan was a likely candidate medicine to control pain without complications. However, it was not so effective in controlling postwisdom tooth extraction pain in Case 1. In such a situation, IOP was the alternative method that effectively relieved pain.

The VAS scores recorded from the patients were not high (40 mm or less) and IOP was effective in alleviating this degree of pain in our patients. In both cases, the site of the operation was the mandible. The efficacy of IOP for pain after maxillary surgery, such as Le Fort I osteotomy, will be examined in the future in patients with AERD.

In these reported cases, placement of the electrodes enabled coverage of almost the entire surface of the skin that covered the mandible (Figures 1 and 2), excluding the chin. Wisdom tooth extraction and SSRO likely injures superficial tissues near the skin surface, but also the mandibular periosteum and bone, particularly in the SSRO osteotomy sites. The response of our patients to the treatment implied that 4% lidocaine was able to penetrate tissues deeper than the skin. Draper et al.²² showed that 2% lidocaine with epinephrine can be delivered up to 5 mm deep to the surface of the skin when administered via IOP and that passive delivery occurs for at least 50 minutes after the active delivery

has terminated. It has been demonstrated that the anesthetic effects of lidocaine IOP are greater with added epinephrine than without epinephrine.²³ We delivered 4% lidocaine without epinephrine following the procedure described in previous clinical reports,^{19,20} but have never examined the extent of penetration into the tissue of the mandible. We were able to control pain after SSRO; however, 5 mm below the surface of the skin was so shallow that it would be difficult to relieve pain without delivery of lidocaine to deeper tissues. It has also been reported that lidocaine induces nerve growth factor (NGF) in human fibroblast cells.²⁴ In the present case, it may have been possible that lidocaine induced NGF and other factors in the skin and in the deeper tissues to relieve pain. The exact mechanism will be investigated in the future.

We applied a pulsed AC voltage (1 V; 50 Hz) for 30 minutes or 60 minutes in these cases because this pulse duration does not cause local complications and has been demonstrated as being effective for controlling neuropathic pain in some hospitals.^{19,20} In the rat, it has been shown that lidocaine is transported through living rat skin in a voltage- and time-dependent manner and that pulsed AC voltage (20 V; 1 KHz) delivers lidocaine more effectively.²⁵ Further analysis will be required to improve the efficiency of lidocaine delivery for clinical applications while assuring no complications occur.

In conclusion, we demonstrated that AC IOP of 4% lidocaine was effective for controlling mild to moderate mandibular surgical pain in the early postoperative period.

REFERENCES

1. Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res.* 2011;3:3–10.
2. Choi JH, Kim JH, Park HS. Upper airways in aspirin-exacerbated respiratory disease. *Curr Opin Allergy Clin Immunol.* 2015;15:21–26.
3. Hekking PP, Bel EH. Developing and emerging clinical asthma phenotypes. *J Allergy Clin Immunol Pract.* 2014;2:671–680.
4. Sakalar EG, Muluk NB, Kar M, Cingi C. Aspirin-exacerbated respiratory disease and current treatment modalities. *Eur Arch Otorhinolaryngol.* 2017;274:1291–1300.
5. Morales DR, Lipworth BJ, Guthrie B, Jackson C, Donnan PT, Santiago VH. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: meta-analysis of controlled clinical trials. *J Allergy Clin Immunol.* 2014;134:40–45.
6. Settiple RA, Schrank PJ, Simon RA, Mathison DA, Christiansen SC, Stevenson DD. Prevalence of cross-sensitivity

with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol*. 1995;96:480–485.

7. Laidlaw TM, Israel E. Aspirin-exacerbated respiratory disease. In: Bochner BS, ed. UpToDate. Available at: <http://www.uptodate.com/contents/aspirin-exacerbated-respiratory-disease>. Accessed February 28, 2017.

8. Moss J, Rosow CE. Development of peripheral opioid antagonists' new insights into opioid effects. *Mayo Clin Proc*. 2008;83:1116–1130.

9. Macintyre PE, Loadman JA, Scott DA. Opioids, ventilation and acute pain management. *Anaesth Intensive Care*. 2011;39:545–558.

10. Smith HS, Laufer A. Opioid induced nausea and vomiting. *Eur J Pharmacol*. 2014;722:67–78.

11. Mesgarzadeh AH, Afsari H, Pourkhamne S, Shahamfar M. Efficacy of bilateral mental nerve block with bupivacaine for postoperative pain control in mandibular parasymphysis fractures. *J Dent Res Dent Clin Dent Prospects*. 2014;8:172–175.

12. Medve RA, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. *Anesth Prog*. 2001;48:79–81.

13. Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N; Protocol TRP-CAN-1 Study Group. Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol*. 2004;31:2454–2463.

14. Gönül O, Satılmış T, Bayram F, Göçmen G, Sipahi A, Göker K. Effect of submucosal application of tramadol on postoperative pain after third molar surgery. *Head Face Med*. 2015;11:35.

15. Nayyar MS, Yates C. Bupivacaine as pre-emptive analgesia in third molar surgery: randomized controlled trial. *Br J Oral Maxillofac Surg*. 2006;44:501–503.

16. Roustit M, Blaise S, Cracowski JL. Trials and tribulations of skin iontophoresis in therapeutics. *Br J Clin Pharmacol*. 2014;77:63–71.

17. Ledger PW. Skin biological issues in electrically enhanced transdermal delivery. *Adv Drug Delivery Rev*. 1992;9:289–307.

18. Reinauer S, Neusser A, Schauf G, Hölzle E. Iontophoresis with alternating current and direct current offset (AC/DC iontophoresis): a new approach for the treatment of hyperhidrosis. *Br J Dermatol*. 1993;129:166–169.

19. Yamazaki Y, Shibaji T, Takahashi T, et al. The effect of 4% lidocaine AC iontophoresis for postherpetic neuralgia. *J Japanese Soc Study Chronic Pain*. 2007;26:137–140.

20. Ando Y, Yamazaki Y, Niimi T, Tomizawa D, Kawashima M, Shimada M. A case report: pain control of persistent trigeminal neuralgia using a combination of AC iontophoresis, acupuncture treatment, and Kampo medicine. *Japanese J Orofacial Pain*. 2010;3:49–54.

21. Matsushita A, Fujita T, Ohtsubo S, Kumamoto E. Traditional Japanese medicines inhibit compound action potentials in the frog sciatic nerve. *J Ethnopharmacol*. 2016;178:272–280.

22. Draper DO, Coglianese M, Castel C. Absorption of iontophoresis-driven 2% lidocaine with epinephrine in the tissues at 5 mm below the surface of the skin. *J Athl Train*. 2011;46:277–281.

23. Wakita R, Oono Y, Oogami S, Hayashi S, Umino M. The relation between epinephrine concentration and the anesthetic effect of lidocaine iontophoresis. *Pain Pract*. 2009;9:115–121.

24. Matsumura T, Kubota K, Sakamoto K, Fukayama H. NGF is induced by lidocaine in human skin fibroblast cells in vitro. *Masui*. 2016;65:288–290.

25. Haga H, Shibaji T, Umino M. Lidocaine transport through living rat skin using alternate current. *Med Biol Eng Comput*. 2005;43:622–629.