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Iontophoresis using a local anesthetic for the treatment of pediatric acute herpetic pain

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Introduction

Acute herpetic pain that is unresponsive to pharmaceutical agents, including nonsteroidal antiinflammatory drugs (NSAIDs) and opiate analgesics, can be treated with neural blockade. In pediatric patients, however, performing nerve blocks is more complicated than in adults, because heavy sedation or general anesthesia is often required. Therefore, pediatric patients with acute intractable herpetic pain require treatments other than nerve blocks. Iontophoresis, a relatively new method whereby a small amount of electrical current, instead of a "needle," is used to drive a drug through the skin, is associated with less pain and anxiety than the application of neural blockade.

We report four pediatric patients with acute herpetic pain who were unresponsive to traditional analgesics but were all successfully treated with iontophoresis using a local anesthetic.

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Materials and methods

This study was performed on four pediatric patients with acute intractable herpetic pain. These four cases are summarized in Table 1. They consisted of three girls and a boy aged from 7 to 14 years (mean, 10 years). Two patients had leukopenia, thrombocytopenia, or both, associated with an underlying malignancy, which had been treated by chemotherapy and immunosuppressants, and thus a nerve block was contraindicated because of the risk of infection or uncontrolled bleeding.

Because of a lack of understanding or cooperation, no reliable pain scores could be obtained except in case 2. A score of 10 corresponds to the maximum intensity of pain before undergoing initial iontophoresis, and a score of 0 corresponds to no pain.

Iontophoresis

The iontophoretic procedures were performed as follows; A cotton pad was soaked with 10ml of 2% lidocaine with 1:80000 epinephrine, 0.625% methylpredonisolone, or sterile 0.9% sodium chloride. The cotton pad was placed over the area to be treated, and then the electrode, measuring 50 × 50mm, was placed over the pad and fixed with a thin, self-adhesive paper sheet. If the area of pain was larger than the electrode, the active electrode was applied only to the spot that was considered to be the center of the most painful area.

Iontophoresis involved the application of a 1mA electrical current to the cathode for 10min to drive the anesthetic through the skin. A physiological salt solution (0.9% sodium chloride) was used as the indifferent solution. In patient 2, who had significant inflammatory changes in the affected skin, methylpredonisolone was administered to the same area after the iontophoretic delivery of the local anesthetic. When methylpre-

Table 1. Demographic data, affected lesions, interval from onset to consultation, underlying malignancies, antineoplastic therapy, administration of acyclovir, analgesics used, and the number of times that iontophoretic procedures were performed in the four pediatric herpetic patients

Case (no.)	Age (yr) sex	Affected lesions	Interval from onset to consultation (days)	Underlying malignancy	Antineoplastic therapy	Administration of acyclovir	Analgesics	No. of iontophoresis treatments
1	9, F	First branch of right trigeminal nerve	4	Glioblastoma of the right frontal lobe	+	+	Mefenamic acid	1
2	14, M	Left second sacral nerve	4	Acute myeloblastic leukemia	+	+	Diclofenac sodium and pentazocine	2
3	7, F	First branch of right trigeminal nerve	3	Medulloblastoma of the cerebellar vermis	+	+	Mefenamic acid	1
4	12, F	Right fifth thoracic nerve	5	—	—	—	NSAID	1

donisolone was administered, the indifferent solution was 0.9% sodium chloride while a cathode electrode was used.

Case reports

Case 1

A 9-year-old girl who had a 2-day history of acute herpes zoster (HZ) of the ophthalmic division of the right trigeminal nerve and complained of severe, constant, burning pain of the ophthalmic, facial, and temporal regions visited the pediatric department of our university hospital. Treatment was started with intravenous acyclovir ($30 mg \cdot kg^{-1} \cdot day^{-1}$), oral mefenamic acid (150mg as needed for pain), and intramuscular hydroxyzine pamoate (25mg as needed for severe pain), but all treatments failed to relieve her pain. Four days after the onset of her acute HZ, she was referred to our pain clinic.

A maculopapular eruption with small vesicles covered the right side of her forehead. She had conjunctivitis, and hypesthesia was also observed on the region of intact skin in the affected area.

Local lidocaine anesthesia administered by iontophoresis to the right-hand side of her forehead had an immediate analgesic effect. Complete relief of her pain lasted 5h after iontophoresis was performed. Thereafter, she needed no additional treatment other than oral mefenamic acid for the right ophthalmic pain, which only occasionally flared up. Her pain was thus entirely abolished within 3 days.

Case 2

A 14-year-old boy developed severe constant pain on the left buttock and on the dorsal side of the leg and was diagnosed as having acute HZ of the left 2nd sacral nerve. He was initially treated with intravenous acyclovir ($22 mg \cdot kg^{-1} \cdot day^{-1}$), oral diclofenac sodium (25mg), and intramuscular pentazocine (15mg). The insufficient analgesic effect of these measures resulted in a referral to the pain clinic 4 days after the onset of his acute HZ.

Erythema around a maculopapular eruption with vesicles of various sizes covered the left buttock and the dorsal side of his thigh. Somatosensation of the intact skin in the affected area was normal.

Lidocaine was iontophoresed to the most painful spot in his left buttock, and subsequently iontophoresis with methylpredonisolone was performed. The pain was satisfactorily reduced by one administration of iontophoresis, and the analgesic effect lasted approximately 9h. The pain scores before and after iontophoresis were 10 and 2, respectively. However, since the pain gradually increased and he needed oral diclofenac sodium (25mg) three times a day, iontophoresis was performed a second time using the same combination 2 days after the first procedure. His pain was further reduced by the second procedure (the pain score decreased from 7 to 2), and thereafter

he needed no further analgesics and the pain was completely abolished within 2 days.

Case 3

A 7-year-old girl who had a 3-day history of acute HZ of the ophthalmic division of the right trigeminal nerve was referred to the pain clinic. She complained of severe constant facial and ophthalmic pain. Treatment with intravenous acyclovir ($30\,mg \cdot kg^{-1} \cdot day^{-1}$) and oral mefenamic acid (150 mg as needed for pain) resulted in insufficient analgesic effect and loss of appetite due to the persistent pain.

Erythema and a maculopapular rash with small vesicles and partly crusted lesions covered the right side of her forehead. She had conjunctivitis. A somatosensary examination of the affected area was not successful due to her lack of cooperation.

After iontophoretic delivery of lidocaine to the right side of her forehead, the patient no longer complained of pain, and the pain disappeared completely within a few days.

Case 4

A 35-kg, 12-year-old, previously healthy girl was diagnosed as having acute HZ of the right 5th thoracic nerve and was referred to our pain clinic. She had a 5-day history of HZ and complained of severe right chest pain with simultaneously developing skin eruptions. The physical examination found no abnormality except for hypesthesia on the region of intact skin in the affected area.

Although epidural block or intercostal nerve block was indicated, iontophoretic administration of lidocaine to the most painful spot in her anterior chest resulted in complete pain relief, and she needed no further treatment. Therefore no nerve block was performed.

Discussion

Although there is little information on the exact occurrence of HZ and postherpetic neuralgia (PHN) in childhood, it has been well documented that the incidence of HZ in children is lower than that in adults, and the occurrence of PHN is less frequent in pediatric patients than in aged patients [1,2]. There are still no epidemiologic data whatever regarding the actual rate of complications, such as pain associated with pediatric HZ.

It seems that most pediatric herpetic pain can be well controlled by analgesics and is relieved in a short period of time. In some pediatric cases, however, persistent pain that is resistant to drug management with traditional analgesics results in sleep disturbance or loss of appetite, and in a few cases PHN may even develop, although none of the 183 pediatric patients (aged below 16) diagnosed as having herpes zoster has developed PHN in our hospital in the past 10 years.

Although a variety of techniques have been advocated in an effort to treat acute herpetic pain, no effective treatment has been established because of a poor understanding of the clinical and neurophysiological features of pain in HZ [1–3].

Since Colding [4] reported the effect of regional sympathetic block in the treatment of herpes zoster, sympathetic nerve blockade has been commonly recommended for the treatment of acute herpetic pain. In addition, in pediatric cases, Elias et al. [5] reported that acute intractable herpetic pain was successfully treated with repeated stellate ganglion blockade. Nakayama et al. [6], in a study of 22 patients who developed HZ after bone marrow transplantation, reported that 3 of 9 patients who complained of painful lesions required treatment with epidural neural blockade.

In pediatric patients, however, since it is often impossible to obtain the required level of cooperation to perform the necessary series of safe and successful nerve blocks, general anesthesia or heavy sedation is required [7]. Moreover, in patients with leukopenia, thrombocytopenia, or both, invasive techniques such as nerve blockade, which involve the subcutaneous injection of a local anesthetic, are contraindicated because of the risk of infection or uncontrolled bleeding.

As a simple and less invasive method of achieving substantial pain relief in HZ or PHN, laser irradiation [8], the application of powdered aspirin in chloroform to the affected skin [9], transcutaneous electrical neurostimulation (TENS) [1], topical application of a eutectic mixture of local anesthetics (EMLA) [10], and the iontophoretic method [11,12] have been previously proposed. However, there are still few reports on the application of iontophoretic techniques to the treatment of acute herpetic pain. There are differences in the analgesic mechanisms of these measures. It is thought that the analgesic potency of the iontophoretic application of local anesthesia is almost as high as that of subcutaneous injection of local anesthetic [13]. Since EMLA is not available in Japan and seems to be less effective than iontophoresis [14], we selected an iontophoretic procedure for the treatment of intractable herpetic pain. The theoretical basis for iontophoretic local anesthesia is to interrupt the nociceptive input by blocking the somatic nerves. It is hypothesized that blocking of the sympathetic nerve fibers, thus eliminating the sympathetic activity that may sensitize peripheral nociceptors in the affected regions, might be involved in the mechanism of the analgesic effect of this technique.

Although intravenous lidocaine infusion is analgesic [15], the analgesic effect of iontophoretic lidocaine in this study might not have been due to the systemic reaction of the drug. In addition, the analgesic level of the plasma lidocaine concentration in intravenous infusion is considered to be higher than that in iontophoretic lidocaine administration [16], even though no plasma lidocaine concentrations were measured in this study.

The analgesic effect of local infiltration with hydrocortisone has also been reported in a small series of patients with PHN [17]. If iontophoretic delivery of glucocorticoid had the same effect as local infiltration of the agent, it might play some role in the analgesic mechanism in the relief of acute herpetic pain as well. Moreover, although we used methylpredonisolone as an antiinflammatory drug in case 2, in which significant inflammatory lesions of the affected area were observed, the pharmacological effect of the glucocorticoid might have not only inhibited the inflammatory nociceptive input to the central nervous system, but also suppressed the ectopic neural discharge originating in the affected peripheral nerves [18].

The adverse side effects associated with iontophoretic delivery are minimal. Erythema may develop at the location of the dispersive pad but resolves within 24h without treatment. All other adverse side effects are related to the delivered drug. In this study no adverse side effects due to the delivered drugs were seen.

To our knowledge, there have been no previous reports on the successful treatment of pediatric acute herpetic pain by means of iontophoresis using local anesthetics with or without glucocorticoids. Although the mechanism of the dramatic analgesic effect of iontophoresis reported here remains unknown, and the analgesic benefits could be related to a placebo effect, the rapid, complete, and long-lasting analgesic effect of the iontophoretic method might be associated with the unknown mechanisms underlying the facts that most herpetic pains in children are relieved in a short period of time, and the development of postherpetic neuralgia is less frequent in younger patients [2].

After peripheral tissue or nerve injury, a pathological process involving nociceptor sensitization and neuroma formation sometimes develops, and it is likely to contribute to the pathological pain present at the early stage of injury. However, recent evidence indicates that changes in the function of the central nervous system, i.e., central neuroplasticity, which are induced by noxious stimuli or tissue injury, may play a significant role in the development of persistent pain during or after healing of the damaged peripheral tissue [19]. The generation of this plasticity might possibly be prevented by blocking the noxious inputs. In our study it might have also contributed to the satisfactory outcome, in which the blocking of the noxious stimuli by iontophoretic local anesthesia was initiated in the early stages of this disease.

Although there is a possibility that the outcome of this study may also be related to the natural history of pediatric HZ, which spontaneously improves in most patients, intractable pediatric herpetic pain still needs to be relieved in some way.

In conclusion, the procedure of iontophoresis using local anesthetic was found to be effective, less invasive, safe, and simple to carry out for the treatment of pediatric acute herpetic pain that proved to be resistant to traditional analgesics, and this technique is considered to deserve further trials in such patients.

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