A Study Of The Efficacy Of Diclofenac Iontophoresis For Providing Effective Topical Analgesia

S Hariharan, R Ramsewak, D Chen, L Merritt-Charles, C Bridglal

Citation

Abstract
Background & Objectives:
Iontophoresis has evolved as one of the attractive methods for enhanced drug delivery. The purpose of the study was to determine the efficacy of iontophoresis of diclofenac gel in providing topical analgesia.

Methods:
Healthy volunteers were tested using the Iontophor meter. To the right dorsum of the hand of each volunteer, an electrode containing diclofenac gel was applied. No gel was applied to the left dorsum as a control. A current of 0.4 milliamps was applied for ten minutes to the right dorsum. The dorsal surfaces of both hands were tested with an eighteen gauge needle at 0, 5 and 10 minute intervals. The volunteer's response to the pinprick was recorded using the Visual Analogue Scale (VAS).

Results:
48 volunteers were tested. The control group had no significant variation from the overall mean pain score during the time of study. However, the mean pain score of the iontophoresis group decreased with time. Multivariate analysis of repeated measures to determine the effect of iontophoresis on the perception of pain showed statistical significance with respect to decrease in pain scores over time (p<0.001).

Conclusions:
Iontophoresis with diclofenac gel significantly reduces pain for pinprick and may be used as an alternative technique to provide topical analgesia.

INTRODUCTION
Topical pain relief could be achieved by many different methods. Injections in general and especially the placement of intravenous cannulae are often the cause of pain and anxiety for many patients. Anaesthetists are often faced with “needle-phobic” patients and are constantly looking for innovative methods of alleviating the pain of intravenous cannulation. Infiltration of local anaesthetics such as lidocaine is a common method used by many anaesthetists to reduce the pain of intravenous cannulation. However, this involves another injection for the patient. Recent advances in topical anaesthesia include application of EMLA (Eutectic mixture of local anaesthetics), EMLA when applied directly to the skin provides adequate analgesia for the placement of intravenous catheters, but this becomes effective only after approximately 30 to 60 minutes. Iontophoresis is an injection-free technique by which an agent applied for anaesthesia such as a local anaesthetic or a non-steroidal anti-inflammatory drug (NSAID) is administered to the underlying tissues by an ionizing electrical current. Iontophoresis increases the absorption of EMLA and renders it effective for analgesia within five to fifteen minutes. Iontophoresis also increases the degree of pain relief which EMLA provides for insertion of intravenous lines. Numerous studies have proven that the local anesthetic agent lidocaine has a greater effect when used with iontophoresis. NSAIDs such as diclofenac sodium, piroxicam and ketoprofen have also been studied with iontophoresis and have been shown to have increased transdermal absorption. The present study aimed at determining whether iontophoresis of diclofenac gel topically is effective in providing analgesia for pinprick...
sensation, which could be used as an alternative method to relieve pain topically.

METHODS

This study was approved by the Ethics Committee of the University of the West Indies. Approval was also obtained from Ethical Review Committee of the San Fernando General Hospital, Trinidad, where the study was undertaken.

Volunteers either without any systemic disease or with mild systemic illness (American Society of Anesthesiologists Physical Status 1 and 2) were included for the study. We excluded subjects with known hypersensitivity to NSAID, those with altered integrity of the skin in the area where the NSAID was to be applied, pregnant women and those with indwelling devices such as pacemakers.

Subjects were assured of confidentiality and were allowed to withdraw from the study at anytime. There were however, no abandoned tests. Some of the subjects who were approached declined to get tested because of the anxiety associated with the pinprick testing. Forty-eight volunteers were finally enrolled for the study and a detailed written informed consent was obtained from each of them.

All volunteers were tested using the Iontophormeter®. This equipment is manufactured by Life-Tech Inc®, and has a 4.0 max milliampere (mA) output. The equipment includes dual treatment lead wire, red Meditrode® lead wire, black Meditrode lead wire®, test lead wire. The operating current range is 0-4.0 mA in 0.02 mA increments. The accuracy is 3% of setting, worst case. Treatment Dose Range for this meter is 0-150 mA-minutes in 1 mA-minute increments. With respect to drug polarity, drug delivery electrode can assume “+” or “−” for either phase.

Diclofenac was added to the electrode, so that it totally saturated the area. The electrode which was attached to the area of drug application was of similar charge as the drug and was referred to as the active electrode (Drug Delivery Meditrode™). Diclofenac is negatively charged and so was attached to the anode. A second drug free electrode (Return Electrode™) was attached in close proximity to the active electrode. The Return Electrode™ is saturated with buffers, which assumes the opposite polarity to the Drug Delivery Meditrode™ to complete the circuit, in this case the cathode.

The dorsal surfaces of both hands of each volunteer were cleaned with alcohol swabs before the procedure. To the right dorsum, an electrode containing diclofenac gel was applied. No gel was applied to the left dorsum to serve as a control. A return electrode was then applied to the right forearm and both electrodes were connected to the meter. A current of 0.4 milliamps (mA) was applied for ten minutes for a total dose of 4 mA. The dorsal surfaces of both hands were tested with an 18-gauge needle for pin-prick sensation. The volunteer’s response to the pinprick was recorded using the Visual Analogue Scale (VAS). Data were recorded at three time intervals namely zero minute, five minutes and ten minutes following iontophoresis.

Descriptive analyses of the data were done. Multivariate analysis of repeated measures was done to analyse the pain scores. Statistical significance was fixed at the level of p<0.05. Data were analysed using Statistical Package for Social Sciences (SPSS) version-8 software.

RESULTS

Forty-eight volunteers were tested and Table 1 shows the demographic data.

**Figure 1**

Table 1: Demographic data

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.58</td>
</tr>
<tr>
<td>Range</td>
<td>37.3 ± 9.9</td>
</tr>
<tr>
<td>Gender (n) (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (39.6)</td>
</tr>
<tr>
<td>Female</td>
<td>29 (60.4)</td>
</tr>
</tbody>
</table>

Table 2 shows the pain scores of the control and iontophoresis groups at the three time intervals. The minimum pain score was 0 and the maximum score was 7 in both the groups. The control group demonstrated no significant decrease in the mean pain score over time. However, the mean pain score decreased over time in the group who had iontophoresis. The mean pain score of the iontophoresis group decreased from 4.0 at zero time to 2.9 at
five minutes, and to 2.3 at ten minutes. This is illustrated in Figure 1.

**Figure 2**
Figure 1: Decrease of pain scores over time

![Figure 1: Decrease of pain scores over time](image)

**Figure 3**
Table 2: Pain Scores in Different Groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (0 min)</td>
<td>1</td>
<td>7</td>
<td>4.08 (1.69)</td>
</tr>
<tr>
<td>Iontophoresis (0 min)</td>
<td>1</td>
<td>7</td>
<td>4.08 (1.69)</td>
</tr>
<tr>
<td>Control (5 min)</td>
<td>0</td>
<td>7</td>
<td>4.04 (1.76)</td>
</tr>
<tr>
<td>Iontophoresis (5 min)</td>
<td>1</td>
<td>6</td>
<td>2.98 (1.42)</td>
</tr>
<tr>
<td>Control (10 min)</td>
<td>1</td>
<td>7</td>
<td>4.00 (1.66)</td>
</tr>
<tr>
<td>Iontophoresis (10 min)</td>
<td>0</td>
<td>7</td>
<td>2.35 (1.3)</td>
</tr>
</tbody>
</table>

Multivariate analysis of repeated measures (general linear model) was performed to determine the effect of iontophoresis on the perception of pain. There was a statistically significant decrease in pain scores over time in the group who had iontophoresis (p<0.001). This is depicted in Table 3.

**Table 3: Multivariate analysis of the effect of iontophoresis**

<table>
<thead>
<tr>
<th>Effect</th>
<th>F</th>
<th>df</th>
<th>Error df</th>
<th>Significance 'p' value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIME</td>
<td>27.614</td>
<td>2</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TREATMENT</td>
<td>45.223</td>
<td>1</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIME × TREATMENT</td>
<td>23.034</td>
<td>2</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

F: Statistical value obtained by multivariate analyses

There were no significant complications associated with the procedure of iontophoresis. Although approximately half of the volunteers complained of mild tingling or burning at the iontophoresis site, this was very trivial and was not a major discomfort to cause any of the participants to discontinue the testing. In addition, at the end of the testing period, all tingling and burning sensations disappeared.

**DISCUSSION**

Fear for injection is almost a universal phenomenon and there have been many methods recommended to alleviate pain during injections. Although it may be argued that a single injection may not have a major undesirable effect, there is no doubt that painful stimuli during injections may produce long-term effects, such as chronic pain syndromes, especially in young patients. Patients are often more satisfied with their doctors when they are treated by methods having minimal or no pain. Children will be less fearful of doctors as well as medical procedures if pain is addressed correctly. If medical procedures are not associated with pain, then there may be greater compliance with routine regimens such as immunization.

A common method is to apply EMLA before injections, which is probably the easiest and most convenient way to reduce pain during injections. However, the time of onset of action of the drug is prolonged and the absorption is also varying. There have been some measures to enhance the absorption and shorten the onset time by some investigators,
which include the application of iontophoresis.

One of the more recent applications to anaesthesia, iontophoresis was first studied by Veralti in 1947 and later in the century by Leduc. The process of iontophoresis involves the application of a current to a transdermally applied ionizable drug in order to increase its absorption through the skin. When such a drug dissolves in water, it separates into positive and negative ions. If an electric current passes through the ionized solution, the ionized substances carry the electric current from the positive electrode to the negative electrode. Usually, the iontophoretic substances consist of medications such as anti-inflammatory steroids and local anaesthetics. This applied current causes the drug to be deposited further into the tissues than by simple transdermal application. The degree of iontophoresis is proportional to the applied current density. Iontophoresis is facilitated by the use of water-based preparations, such as Diclofenac Gel, since these preparations are easily ionized. However, iontophoresis is limited to an extent by the hydrolisis of water, and the generation of hydrogen ions which lead to decreased delivery rates, tissue acidosis and electrolyte dissolution. Some formulations have added buffers which reduce the problem of free hydrogen ions. The electrical polarity of the drug delivery electrode determines whether the positive or negatively ions pass into the tissues below. Thus iontophoresis has the advantage over simple transdermal application of drugs, by that it increases the absorption of a drug intensifies and prolongs the action and the drug delivery rate may be adjusted by varying the applied current.

Diclofenac and other NSAIDs act by inhibiting the mediators of the inflammatory response to injury such as the prostaglandins. These mediators are usually released only when the tissue is injured and hence theoretically diclofenac should not have any analgesic effect when applied topically to non-inflamed surface. A possible explanation for the enhancement of the analgesic effect of the NSAID by iontophoresis is that iontophoresis itself may stimulate an inflammatory response and during testing the pinprick activates local inflammatory mediators. Iontophoresis may also increase the penetration of the diclofenac into the skin and underlying tissues and thereby increasing the anti-inflammatory effect. As a consequence, there may be an increase in the analgesic effect.

Another possible explanation is that iontophoresis may act similar to transcutaneous electrical nerve stimulation (TENS), and may inhibit the transmission of pain through A-beta fibres, establishing a “gate control”. Gamma amino benzoic acid (GABA) has been proposed as the neurotransmitter for this mechanism of action. Regardless of the exact mechanism of action of the iontophoresis enhancing the effect of the diclofenac, the present study found that it does provide sufficient analgesia for intravenous cannulation.

Pain as an experience may be influenced by many subjective and emotional factors making it difficult to exactly quantify the sensation- the so-called problems of “algesimetry”. One of the most common methods to evaluate pain is the application of Visual Analogue Score (VAS). This score allows the quantification of pain, with a scale from one to ten, with one being the least pain possible and ten the worst pain. The VAS was chosen to evaluate pain in the present study, because it is simple and user friendly. Although the VAS may be described an inconsistent scoring system (one patient’s three may be another patient's one) this is inherent with any other measurement of pain.

The major limitation of the present study is the possible introduction of bias by the volunteers and the investigator. Uniform experimental conditions were achieved in order to eliminate bias as far as possible. These conditions included:

1. Single investigator collected all the data to avoid inter-observer variability
2. The same size of needle was used on all volunteers, as different needle sizes are associated with different intensities of pain.
3. Similar sites on the dorsal surfaces of both hands were used as the testing areas to allow for similar dermatome distribution and pain pathways.
4. The same concentration and dosage of drug was used on all volunteers
5. All the electrodes were of the same size.

The other limitation may be the feasibility of the application of iontophoresis in day-to-day clinical practice. The equipment is expensive and requires basic hands-on training. It is more difficult to use than simply applying EMLA or infiltrating with a local anaesthetic.

NSAID iontophoresis may be useful in patients with known hypersensitivity to local anaesthetics.
Iontophoresis has been proven to be effective in providing anaesthesia for small surgical procedures and dermatological procedures which may usually require local or regional anaesthesia. As a needle free technique it may contribute to the multimodal approach to providing analgesia to patients. It has been evaluated in delivering local anaesthetics for paediatric office-based anaesthesia procedures. It has also been used in urological procedures and laser treatment of port-wine stains.

NSAID iontophoresis may also be further evaluated for possible applications to other areas such as the ICU, emergency departments and pain clinics, where it has been used for pain relief.

Thus iontophoresis is a novel method which has the potential of application in various areas of the field of topical drug delivery. The present study has attempted to establish yet another mode of efficient drug delivery which could be safely applied in clinical practice for topical pain relief.

CORRESPONDENCE TO
Seetharaman Hariharan Lecturer in Anaesthesia and Intensive Care Faculty of Medical Sciences The University of the West Indies Eric Williams Medical Sciences Complex Mount Hope TRINIDAD West Indies Telephone/ Fax: 1 868 662 4030 E-mail: uwi.hariharan@gmail.com

References
Author Information

Seetharaman Hariharan, MD
Anaesthesia and Intensive Care Unit, Faculty of Medical Sciences, The University of the West Indies

Reanata Ramsewak, DM
Anaesthesia and Intensive Care Unit, Faculty of Medical Sciences, The University of the West Indies

Deryk Chen, FRCA
Anaesthesia and Intensive Care Unit, Faculty of Medical Sciences, The University of the West Indies

Lorna Merritt-Charles, FRCA
Anaesthesia and Intensive Care Unit, Faculty of Medical Sciences, The University of the West Indies

Charlie Bridglal, FRCA
Anaesthesia and Intensive Care Unit, Faculty of Medical Sciences, The University of the West Indies