대한물리치료학회지 제10권 제1호
The Journal of Korean Society of Physical Therapy
Vol. 10, No. 1 pp 1~6, 1998.

Effective Concentration of Procaine Solution for Iontophoresis[§]

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〈Abstract〉

The purpose of this study was to determine the effective concentration of procaine iontophoresis for durarion of cutaneous local anesthesia. Forty-five healthy students with an age range of 19 to 34 years(21±2.7), were participated in this study. The subjects were randomly assigned into 5 groups. Each 9 subjects received iontophoresis on the flexor surface of dominant forearm with soft cotton pad (3.5 x 3.5 cm) soaked in 2 ml of 2% (pH 5.28), 4% (pH 5.12), 8% (pH 4.98), 16% (pH 4.72), 32% (pH 4.52) procaine hydrochloride solution at 4 mA for 10 minutes (total current 40 mA · min) using anodal direct current. The study was performed in a randomized, double-blind design. After procaine iontophoresis, the duration of anesthesia were evaluated at five minute intervals on five random locations in the iontophoretically area using a 21-gauge sterile hypodermic needle pressed with 1 mm invagination until sharp pin-pricking pain sensation returned. The data were analyzed with one-way ANOVA to determine significant differences between groups. Duncan post hoc was performed at level .01. The relationship between anesthetic duration and procaine concentration was assessed with Pearson Product-Moment Correlation Coefficients. ANOVA tests showed significant differences in the anesthetic duration between the concentration of procaine solution ($p<.001$). Procaine iontophoresis with 4% concentration produced cutaneous local anesthesia of significantly longer duration(15.56 min) than iontophoresis with 2%, 8%, 16%, and 32% of procaine HCl($p<.01$). Whereas the anesthetic duration had no correlation with concentration of procaine solution ($r=-0.41$, NS). These results support the 4 % procaine solution was an effective concentration of iontophoresis for induced cutaneous local anesthesia.

key words : Procaine, Iontophoresis, Local Anesthesia, Electrotherapy

[§]This article was presented at the Hong Kong Physiotherapy Association International Congress 1997, Hong Kong International Trade & Exhibition Centre, Kowloon, Hong Kong. 1st-2nd November 1997.

This work was supported in part by a grant from Wonkwang Health Science College Academic Research Fund.

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INTRODUCTION

Iontophoresis has been defined as the introduction by means of the electric current, of ions of soluble salts into the tissues of the body, often for therapeutic purposes; a form of electro-osmosis (Friel, 1981). This definition, however, was no longer appopriated because not only ionic molecules but also many nonionic substances such as polypeptides can be delivered into the tissues by iontophoresis (Behl et al., 1989; Costello and Jeske, 1995). Now a day, iontophoresis can be defined as an delivery of ionized and nonionized drugs into the tissues across biological membranes by electric current.

Over the past 90 years, since LeDuc's scientific work, the use of iontophoresis have been fluctuated in clinical practice. Recently, there has been increased interest in the use of iontophoresis for local transdermal delivery of various drugs in physical therapy (Costello and Jeske, 1995) and other clinical fields such as pain clinic (Demirtas and Oner, 1998), dermatology (Odia et al, 1996), plastic surgery (Greminger et al, 1980), ENT (Laffree et al, 1989), ophthalmology (Sarraf and Lee, 1994), dentistry (Lutins et al, 1984), and pharmacology (Phipps et al, 1989).

The iontophoresis is less discomfort, anxiety and risks (Russo et al, 1980; Zeltzer et al, 1991). It bypasses gastrointestinal and hepatic absorption and metabolism, and can controlled the amount of drug delivered to tissues (Chien et al, 1989; Costello and Jeske, 1995). Therefore, the iontophoresis seems an effective method for drug delivery into the target tissues without any systemic side effects.

The iontophoresis with local anesthetics is widely used in pain relief on inflammatory and myofascial disorders of musculoskeletal problems (Lark and Gangarosa Sr, 1990; Parham and Pasieka, 1996; Schiffman et al, 1996) and local anesthesia for minor surgeries (Sisler, 1978; Meyer et al, 1990; Sirimanna et al, 1990) and tooth extract (Tharian and Tandon, 1994).

Most of the reports on iontophoresis using local anesthetics are based on lidocaine hydrochloride, amide-type local anesthetics, therefore the ideal parameters of lidocaine iontophoresis is well known (Gangarosa et al, 1978; Russo et al, 1980; Costello and Jeske, 1995). The reason of widely use of lidocaine is that the lidocaine is more rapid, potent of anesthetic effect in the tissues. Procaine is an ester-type chemical compound that is less toxicity and side effects than other local anesthetics. However, to date insufficient research exists as to the procaine hydrochloride and their optimal concentration required to iontophoresis.

The purpose of this study was to determine the effective concentration of procaine hydrochloride solution iontophoresis for cutaneous local anesthesis.

METHODS

Subjects

Forty-five healthy students (13 male, 32 female) volunteered to participate in this study and gave their informed consent. The subjects ranges in age from 19 to 34 years (21±2.7) and had no history of neuromuscular problems associated with pain and allergic disease. We asked all subjects to refrain from intake of analgesic drugs and alcohol for 24 hours before participating in this study. The study was performed in a randomized, double-blind design.

Procedure

The subjects were randomly assigned into 5 groups using a table of random digits, with 9 subjects in each group. The subjects of each group was iontophoresed with procaine hydrochloride solution of 2%, 4%, 8%, 16%, and 32%, respectively. Procaine HCl (Kookjeon Chemical Co., 269 Hyojae-Dong, Chongro-Ku, Seoul 100-480, Corea) solutions were prepared in salt-free 2% (pH 5.28), 4% (pH 5.12), 8% (pH 4.98), 16% (pH 4.72), and 32% (pH 4.52), respectively.

Each subject sat on a chair with the right forearm comfortably placed on a treatment table. The electrode placement sites on the flexor surface of right forearm were cleaned before iontophoresis with 70% etyhl al-

cohol and cotton to degreasing, disinfection and reduce skin resistance. The dispersive electrode with sterile saline soaked soft cotton pad (3.5 x 3.5 cm) was held on the distal 1/3 of flexor surface of the right forearm, and attached to the negative terminal of the direct current generator. The active electrode with soft cotton pad (3.5 x 3.5 cm) soaked with 2 ml of procaine HCl solution placed on the proximal 1/3 of flexor surface of right forearm. The active electrode was attached to the positive outlet of the direct current generator (Iontophor-PM; Life-Tech, Inc., PO Box 36221, Houston, Texas 77326-6221, USA).

The direct current was increased slowly from 0 to 4 mA over the first minute, and maintained at 4 mA for the remaining 9 minutes of iontophoresis. During this time, the subject was observed and questioned about any adversed effect such as tingling, burning sensation. If any adversed effects were noted, iontophoresis was ceased. At the termination of iontophoresis, the current was slowly decreased to 0 mA before removal of the electrodes. Total duration of iontophoresis was 10 minutes. After iontophoresis, the electrode placed areas of subject was inspected about skin irritation, blister and burn.

Measurement

Before iontophoresis was begun, each subject was tested the pain sensation. A sterile 21-gauge hypodermic needle gently pressed with 1 mm invagination on 2 random points of forearm to ensure that the subject could feel and properly interpret the sharp pin-pricking pain sensation. Immediately after procaine iontophoresis, the duration of local cutaneous anesthesia were evaluated with the needle pressed on five random locations in the iontophoretically area. Each site was evaluated at five minute intervals until pin-pricking pain sensation returned at least one of the five sites. Duration of local anesthesia was determined by the time immediately before the presence of sharp pin-pricking pain as described by the subject.

Data Analysis

The values obtained after iontophoresis from measurement of duration of local anesthesia for each concentration of procaine HCl solution were analyzed using an one-way analysis of variance (ANOVA). Statistically significant was followed up with post hoc test for Duncan's multiple range test at level .01. The relationship between the duration of anesthesia and concentration of procaine hydrochloride solution were assessed by Pearson Product-Moment Correlation Coefficients. The data were analyzed by SPSS/PC.

RESULTS

Results of the duration of local anesthesia by various concentrations of procaine hydrochloride solution iontophoresis with 4 mA for 10 minutes are presented in Table 1. One-way ANOVA showed significant differences in the duration of anesthesia between the concentrations of procaine hydrochloride solution ($F=5.83$; $df=4, 40$; $p<.001$, Table 2). Iontophoresis with concentration of 4% procaine hydrochloride solution produced an average duration of local anesthesia of 15.6 minutes, which was significantly longer duration than iontophoresis with concentrations of 2%, 8%, 16%, and 32% procaine hydrochloride solution($p<.01$, Fig. 1). The duration of local anesthesia of iontophoresis with 4% procaine concentration was longer 2 fold than 2% procaine concentration, and approximately 3 fold than concentrations of 8%, 16% and 32% procaine. The local analgesic potency of procaine iontophoresis was most effective at 4% concentration of procaine hydrochloride solution. The Pearson correlation analysis showed that the duration of anesthesia had no correlation with concentrations of procaine HCl solution ($r=-0.41$, NS).

Table 1. Mean and standard deviation of duration of local anesthesia(minutes) induced by iontophoresis using various concentrations of procaine hydrochloride solution

Group	n	Mean±SD
2%	9	5.00±2.50
4%	9	15.56±6.35
8%	9	8.33±6.61
16%	9	8.89±3.33
32%	9	7.22±4.41

The most frequent complaint was a tingling or prickly sensation reported in some cases. No side effects other than erythema were observed after iontophorsis using procaine hydrochloride during the study.

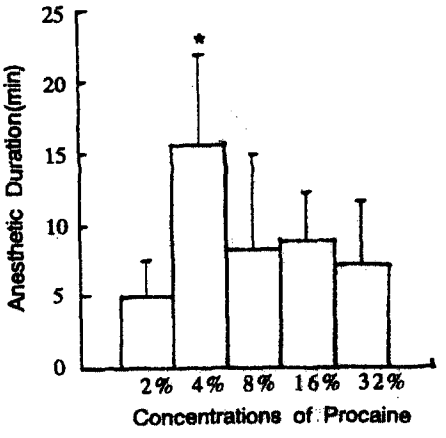

Fig 1. Duration of cutaneous local anesthesia induced by iontophoresis using various concentrations of procaine HCl. Each value represents the mean for 9 subjects per group. Error bars are standard deviations. The iontophoretic administration of 4% procaine HCl solution with 4 mA for 10 minutes. Asterisk indicates statistically significant increase the anesthetic duration when compared with 2%, 8%, 16% and 32% of value($p<.01$).

DISCUSSION

In this study, we have found that the procaine hydrochloride iontophoresis of various concentrations produced cutaneous local anesthesia in healthy subjects. It suggest that the procaine ions delivered transdermally by anodic direct current with 4 mA for 10 minutes. The iontophoresis of 4% concentration of procaine hydrochloride produces a significantly greater duration of local anesthesia than iontophoresis of 2, 8, 16 and 32% concentrations of procaine hydrochloride. The duration of anesthesia did not correlates with concentration of procaine hydrochloride solution. These results demonstrate that a concentration of 4% procaine hydrochloride solution is the most effective concentration on iontophoresis, whereas, increasing the concentrations of procaine hydrochloride solution did not increase the duration of local anesthesia.

The efficiency of iontophoretic transdermal drug delivery of local anesthetics influenced by physicochemical factors, such as concentration and pH of solution, as well as electrical factors, such as current density, duration of electric current application. Also differences between subjects in regional blood flow, skin thickness and impedence, quantity of pores per unit surface area may contribute to a variable the duration of anesthesia (Russo et al, 1980; Costello and Jeske, 1995; Turner and Guy, 1977). This study focused on the concentration as an physicochemical factor of procaine hydrochloride solution for anesthetic duration.

Costello and Jeske (1995) have proposed that the ideal variables for lidocaine hydrochloride iontophoresis were a current of 4 mA for 10 minutes, with a 4% solution. Gangarosa et al (1978) reported the conductivity of lidocaine was best at a pH of approximately 5. Increasing the pH decreases the number of ionized molecules and may decrease the conductivity of lidocaine. The concentration of drug is an important factor of iontophoretical drug delivery to the skin via the pores. Most investigators recommend the 4% concentration of

Table 2. Oneway ANOVA for duration of cutaneous local anesthesia induced by iontophoresis using various concentrations of procaine HCl solution

Source	D.F.	SS	MS	F	p
Between Groups	4	563.3333	140.8333	5.8276	.0009
Within Groups	40	966.6667	24.1667		
Total	44	1530.0000			

lidocaine for iontophoresis (Echols et al, 1975; Gangarosa et al, 1978; Bezzant et al, 1988; Meyer et al. 1990; Maloney et al, 1992). So that, current 4 mA, duration 10 min, pH 5.1 and concentration 4% was used in the present study for procaine hydrochloride iontophoresis.

Behl et al (1989) reported that some drugs such as butyric acid, the flux increased directly proportional to the drug concentration. However, the flux of local anesthetics such as procaine was not direct proportional to the concentrations of solution. We considers that the use of a higher concentrations of ions in a solution would caused bottleneck effect which increased accumulation of ions around the available skin pores.

Procaine, an ester-type local anesthetics, is hydrolyzed for only a few part in liver, the most part in serum by plasma cholinesterase. It is broken into para-aminobenzoic acid, 80% of which is excreted in the urine, and diethylaminoethanol, 30% of which is excreted in the urine, rapidly (Harkins et al, 1996). Procaine is extremely safe, less toxicity, less local and systemic side effects than other local anesthetics such as lidocaine and cocaine etc. In this study, the effect of the 4% procaine iontophoresis was same as these of 4% lidocaine iontophoresis. Therefore, we hope that the procaine iontophoresis could be used in various painful conditions.

CONCLUSIONS

In this study, the duration of local cutaneous anesthesia was greater long in concentration of 4% procaine HCl solution. However, increasing the concentrations of procaine HCl solution did not increase the duration of local anesthesia. These results demonstrate that a concentration of 4% procaine HCl solution is the most effective concentration on iontophoresis, whereas the duration of local cutaneous anesthesia is not direct proportional to the concentrations of procaine HCl solution.

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Effective Concentration of Procaine Solution for Iontophoresis

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효율적으로 국소마취를 유발시키는 procaine 이온도입의 효과적인 농도를 조사하였다. 19세에서 34까지의 자원자 45명을 9명씩 무작위로 5군으로 나누어 배치하고, 각군 대상자의 오른쪽 전완 전면에 각각 2% (pH 5.28), 4% (pH 5.12), 8% (pH 4.98), 16% (pH 4.72), 32% (pH 4.52)의 염산 procaine용액 2 ml를 적신 3.5 x 3.5 cm의 면패드를 대고 4 mA로 10 분간 양극 직류전류를 통전시켰다. 이온도입 직후부터 5분 간격으로 21 G 주사침으로 이온도입부위를 1 mm함몰되게 눌러 바늘로 찌르는 통증을 느낄때까지 감각검사를 시행하여 국소마취지속시간을 측정하였다. Procaine의 농도에 따른 국소마취지속시간을 일원분산분석한 결과 유의한 차이를 보였으며 ($F=5.83$; $df=4, 40$; $p<.001$), 이를 사후검정한 결과 농도 4%의 국소마취지속시간이 농도 2%, 8%, 16%, 32%보다 유의하게 길었다 ($p<.01$). 또한 상관분석 결과 약물의 농도는 국소마취지속시간과 상관관계가 없었다 ($r=-0.41$, NS). 본 연구 결과 4% 농도의 염산 procaine 용액의 이온도입이 국소마취지속시간을 가장 길게 유지하여 4% 염산 procaine 용액이 이온도입에 가장 효과적인 농도였음을 알 수 있었다.