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The effect of histamine iontophoresis on the heart rate and blood pressure of female subjects

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Summary

The main purpose of this study was to determine the effect of histamine iontophoresis on the Blood Pressure (BP), and heart rate (HR) of female subjects. Twenty apparently healthy female undergraduates of Obafemi Awolowo University, Ile-Ife (average age 24.2 ± 2.9) participated in the study. An automated electronic sphygmo-manometer that monitors both BP and HR was used to measure the Systolic Blood Pressure (SBP) and diastolic Blood Pressure (DBP) over the left brachial artery. The histamine gel used in this study contained 1 percent histamine dihydro-chloride. The gel was applied to the right biceps brachii and active was applied below the cubital fossa. The current intensity Interrupted Direct Current (IDC) was gradually increased and subjects were instructed to indicate immediately they experienced tingling sensation under the electrode. The same procedure was carried out the second time on the subjects with the same intensity of IDC current but without histamine for each subject. The treatments were administered on different days but within a two-week interval. The cardiovascular response was monitored five minutes before the administration, twenty minutes during the administration and five minutes after the termination of each treatment. Blood Pressure and heart rate did not change significantly from the baseline during the histamine iontophoresis and direct currents treatments ($P > 0.05$). The findings suggest that the subjects' BP and HR were not affected by histamine iontophoresis during the twenty minutes treatment. It was concluded that local administration of 1 per cent histamine dihydrochloride into the subcutaneous tissue of females' right upper arm with the aid of direct current did not appreciably affect the blood pressure and heart rate after 20 minutes of treatment.

Keywords: *Iontophoresis, histamine, heart rate, blood pressure.*

Résumé

Le but principal de cette étude était de déterminer l'effet de l'iontophoresie d'histamine sur la tension artérielle (BA) et le rythme cardiaque (RC) aux sujets femelles. Vingt femelles étudiantes apparemment saine de l'université d'Obafemi Awolowo participaient à cette étude. Un sphygmo-nanometre électronique était utilisé pour mesurer le systole et diastole de la tension artérielle (DTA) sur l'artère gauche et le rythme cardiaque. Le gel utilisé contenant 1% d'hydrochlorure était appliqué sur le biceps droit du bras et sous la fosse cubitale. L'intensité du courant interrompu du courant direct augment

ait graduellement et les sujets subissaient une sensation de la tension sous l'électrode. L'expérience était répétée sans application d'histamine pour chaque sujet. Les traitements étaient administrés des jours différents en deux semaines d'intervalle. La réponse cardiovasculaire était surveillée 5 minutes avec l'administration, 20 minutes après l'application et 5 minutes après la fin du traitement. La tension artérielle et le rythme cardiaque ne changeaient pas la normale pendant l'iontophoresie d'histamine et le traitement au courant électrique direct ($P > 0.05$). Les résultats du TA et RC n'étaient pas affectés par l'iontophoresie d'histamine pendant les 20 minutes de traitement. Il a été conclu que l'administration locale 1% d'hydrochlorure dans le tissu subcutané dans l'avant bras droit des femelles avec l'aide du courant direct n'avait pas d'effet appréciable sur la tension artérielle et le rythme cardiaque pendant les 20 premières minutes de traitement.

Introduction

Iontophoresis which involves the movement of ions across biological membranes by means of an electric current for therapeutic purpose is not entirely new in Physical therapy [1]. Iontophoresis has been shown to be effective in some area where systemic antibiotic has proved to be ineffective [2,3]. The efficacy of histamine iontophoresis for the treatment of peripheral indolent ulcers has been reported [4,5,6]. This action of histamine is based on the fact that it causes arterial vasodilation and increased capillary permeability. The untoward reactions associated with intra-muscularly administered histamine include a fall in the blood pressure, an increase in heart rate, sweating and flushing of the skin [5]. In the previous studies of histamine iontophoresis, the common side effects reported include, headache, dizziness, lightheadness, local itching and swelling [7].

These untoward reaction suggests a perturbation of the cardiovascular system which has not been fully investigated. The work of Balogun *et al* [7] showed that the overall Blood Pressure and Heart Rate did not significantly change from the base line values. This has not been confirmed by other researchers. Also, female subjects are different from males in some physical characteristics.

The study of this nature is therefore necessary, because patients with peripheral vascular diseases, rheumatoid arthritis or recalcitrant ulcers who may benefit from histamine iontophoresis may also have an underlying cardiovascular disease. The purpose of this study was to determine the blood pressure and heart rate responses

during histamine iontophoresis treatment in apparently healthy female undergraduates. We hypothesized that, the overall Blood Pressure and heart rate will not change significantly from the baseline and after the treatment.

Materials and methods

Before the commencement of the study, the experimental protocol was approved by the Human Ethics Committee of Obafemi Awolowo University Teaching Hospital Complex, Ile-Ife, Nigeria.

Subjects

Sample of convenience was adopted in this study. Twenty apparently healthy female undergraduates of the Obafemi Awolowo University, Ile-Ife, volunteered to participate in the study. The average age of the subjects was 24.2 ± 2.9 years. Average height was 1.6 ± 0.1 M and the average weight was 54.0 ± 6.0 kg. None of the subjects had previous history of cardiorespiratory problems.

Their cardiovascular responses, that is HR, SBP and DBP were monitored during histamine iontophoresis and direct current treatments.

Experimental design

A quasi-experimental (time series) design was adopted in this study[8]. Each subject acted as her own control, and cardiovascular responses were monitored periodically under two treatment conditions i.e. histamine iontophoresis and direct current stimulation conditions. The treatments were administered on different days but within a two-week interval for each subject. The order of presentation of the experimental condition was randomized.

The Blood Pressure and heart rate were monitored on the left upper limb by a digital blood pressure and heart rate monitoring device (A & D Medical 1555 Mc Candelas Drive, CA 95035). This instrument measured BP and HR rate and simultaneously displays them on its screen. Prior to the main study, the validity of the automated sphygmo-manometer was established among twenty healthy subjects. The blood pressure was measured using automated sphygmomanometer and the conventional mercury type(Accoson, England). Correlation ($r = 0.98$; $p < 0.01$) was obtained between the readings for SBP and ($r = 0.96$; $P < 0.01$) for DBP.

The histamine gel (1:100 concentration) was prepared by a pharmacist. Recommended dosage of histamine gel was used for the experiment [9]. The gel contained 1 percent histamine dihydrochloride, 45 percent bentonite, 15 percent glycerine and 39 percent water. Direct current of Endomed 581 (Enraf-Nonius equipment Box 810, 2600 AV DELFT, Netherlands) was used to introduce the histamine ion into the subjects' subcutaneous tissue. The current output ranges from 0-80mA.

Procedure

Prior to data collection, the procedure of the study was explained to all the subjects and their ages were recorded. Subsequently, their weights and heights were measure. The treatment protocol described by Balogun *et al* [7] was adopted in

this study. Subjects were instructed to lie supine on a wooden plinth and a pillow was placed under both knees to aid relaxation. Each subject was in supine resting position for 10 minutes of either histamine iontophoresis or direct current stimulation treatment. For each subject, histamine gel was evenly applied over the middle of biceps brachii muscles of the right upper limb (measuring 3cm x 3cm) using a wooden spatula. The electrodes of the stimulator were padded with 8 layers of lint moistened in water. The active (anode) electrode was placed over the gel and the dispersive (cathode) electrode was placed below the cubital fossa. Both electrodes were held in place with a Velcro strap covering the entire electrode area to ensure even distribution of pressure. The active and dispersive electrodes were connected to the positive and negative poles of the stimulator respectively. The same protocol was followed during the direct current stimulation condition except that the histamine gel was not applied to the biceps brachii muscles.

With the electrode in place, the current intensity of IDC was gradually increased and the subjects were instructed to indicate immediately they started to experience a tingling sensation under the electrodes. For each subject, the current intensity (mA) was maintained at the sensory threshold i.e. when the patient experience tingling sensation during treatment.

During the treatment phase, the BP and HR was monitored in every fifth minute of the 20 minutes treatment period. Blood pressure and heart rate were also measured at the end of the first minute and at the end of the fifth minute of recovery. Immediately and 24 hours post treatment, subjects were asked if they had experienced any unusual local and general side effects as a result of the treatments.

For all the subjects, the means of DBP and SBP, HR at rest during treatment and recovery were calculated. Analysis of Variance (ANOVA) was employed to compare the responses during the histamine iontophoresis at different treatment time frames. AP-value of less than 0.05 was considered statistically significant.

Results

Presented in Table 1 are the results of histamine iontophoresis treatment on systolic blood pressure (SBP). There was no significant difference ($P > 0.05$) when H.R. and B.P. of treatment conditions were compared with the means resting value and also with that of 5 minutes recovery. The SBP retained the pretreatment levels at the end of the fifth minute of recovery. Table 1 also results showed no significant difference in DBP at different time frames. There was no significant difference in HR at different time frames of iontophoresis treatment.

The control experiment, i.e. direct current (DC) treatment on SBP, DBP and HR, showed no significant difference during the different phases of the experimental conditions and fifth minute recovery compared with mean resting measures (Table 2).

Table 3 shows the result of the ANOVA used to compare SBP values during the different phases of the histamine iontophoresis and DC treatment (resting, treatment and recovery). There was no significant differences in SBP ($P >$

0.05) between histamine iontophoresis and DC in all the different experimental phases.

Discussion

The primary objective of this study was to determine the effect of histamine iontophoresis on the parameters of cardio-

Table 1: Changes in blood pressure and heart rate during histamine Iontophoresis (n = 20)

Variables	Resting		Treatment (minutes)					Recovery	
	Mean	± SD	1min	5min	10min	15min	20min	Mean	± SD
SBP (mmHg)	105.3±	6.4	105± 5.1	103.9± 5.5	104.8± 6.1	103.1± 5.8	103.1± 4.7	103.7± 6.4	0.49NS
DBP (mmHg)	60.7±	0.6	62.4± 5.7	64.4± 6.3	64.4± 6.3	62.5± 6.2	62± 5.7	63 ± 5.6	1.400NS
HR (beat mm-H)	65.5±	10.6	67.7± 10.2	67 ± 8.8	63.8± 8.7	67.3± 8.8	67.3± 8.8	62.1± 9.7	0.379NS

NS = No significant difference at ($P > 0.05$)

Table 2: Changes in blood pressure and heart rate during current treatment (n = 20)

Variables	Resting		Treatment (minutes)				Recovery		
	Mean	± SD	1min	5min	10min	15min	20min	Mean	± SD
SBP (mmHg)	105.5±	5.5	104± 5.3	103.7± 5.7	106.8± 5.1	105.1± 6.9	104± 5.1	105.1± 6.9	1.04NS
DBP (mmHg)	63.2±	6.2	64.4± 5.7	62.6± 5.2	63.7± 5.7	65.4± 5.5	62± 5.7	64.0± 6.6	0.676NS
HR (beat mm-H)	65±	10.4	66.7± 8.6	67.1 ± 8.5	65.1±10.5	65.6± 8.2	65.6± 10.1	65± 8.9	0.25NS

NS = No significant difference at ($P > 0.05$)

Table 3: Changes in blood pressure following histamine Iontophoresis and direct current (n = 20)

Variables	Histamine Iontophoresis			Direct Current			F ratio	F critical	
	Resting	Treatment	Recovery	Resting	Treatment	Treatment			Recovery
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD			Mean ± SD
		1min	5min	10min	15min	20min			
SBP (mmHg)	104.4±5.4	102± 5.6	101.9± 5.5	106± 5.5	105± 5.6	104.4± 8.4	105.1± 6.6	0.504NS	1.35
DBP (mmHg)	63.4±6.1	63.4± 6.2	63.2± 6.3	63.2± 6.0	64.1± 5.7	64.7± 4.6	62.1 ± 6.8	0.600NS	1.35
HR (beat mm-H)	60.7±0.6	62.4± 5.7	64.4 ± 5.0	62.5± 5.0	62.9± 4.6	65.0± 6.6	64.0± 6.6	0.504NS	1.35

NS = No significant difference at ($P>0.05$)

Table 4: Untoward reactions during histamine iontophoresis treatment (n = 20)

Complaint	Frequency	% of subject
Burning sensation	18	90
Itching	9	45
Wealing	6	30
Dizziness	2	10
Burn	1	5
Heaviness of the limbs	-	-

No subject had any complaint or untoward reaction during and following direct current stimulation treatment for at least 24 hours after the treatment. However, subjects complained of discomfort like itching, burning sensation, wealing, dizziness, scalding, during histamine iontophoresis. One of the subjects sustained minor burn (Table 4).

vascular system such as (SBP; DBP and HR) of female subjects. Studies of this nature are needed as physiotherapists desire to be sensitive to potential physiological stresses imposed by physiotherapeutic modalities on either the healthy or the compromised cardiovascular system.

The direct current stimulation was included in the study design to delineate the additive influence of electrical stimulation required during histamine ionic transfer. In line with our hypothesis, no significant difference was recorded in the overall blood pressure values and heart rate value from the resting period during the histamine iontophoresis and direct current stimulation of the 20 healthy female subjects. The finding supports the work of Balogun *et al* [7] which found out that the overall blood pressure of 15 healthy male undergraduates did not change significantly from the baseline during the experimental procedure. However, in the fifth minute histamine iontophoresis was significantly lower when compared with the

responses during direct current stimulation. The difference was attributed to chance because of lack of concordance with the findings in other time frames during treatment and for the other variables measured. Apart from this cited work, no previous work has scientifically evaluated the effect of histamine iontophoresis on cardiovascular system.

Fall in the level of blood pressure may be attributed to vasodilatory effect of histamine. Apart from the vasodilatory effect of histamine, there may be an increase in heart rate, especially in the individuals who are hypersensitive to histamine [10]. The effects of histamine on cardiovascular system are very complex and vary greatly among the species studied. He attributed the major cardiovascular effects of histamine in human to vasodilation of the capillaries and venules. As a direct consequence of widening of these vessels, the permeability of the capillary membranes is increased, permitting the movement of plasma proteins and fluids into the extracellular spaces. This fluid accumulation results in edema. The reduction in blood pressure reflexly activated a compensatory stimulation in heart rate in an attempt to restore the circulation of an adequate amount of blood around the body [11].

Why there was no significant difference in this present study was due to the following reasons. Firstly, the amount of histamine ions that entered the system of the subjects may be very small. It is possible that a higher concentration of the ions applied for longer duration may significantly affect the blood pressure and heart rate. The number of ions that cross the skin barrier is dependent on the current density of the electrode, duration of the treatment and the concentration of the ions in the solution [12]. Secondly, the majority of subjects who participated in this study may not be hypersensitive to histamine. Harris [5] affirmed that cardiovascular effect of histamine may be pronounced in individuals who are hypersensitive to histamine.

The use of direct current stimulation at sensory threshold did not significantly alter the blood pressure and heart rate in this study. Many authors have reported the use of direct current in the treatment of recalcitrant ulcers but none has evaluated its effect on cardiovascular system [13,14,15].

It is conceivable that the amount of histamine ions absorbed into the systemic circulation during the histamine iontophoresis was not enough to raise or lower the blood pressure and heart rate significantly, but could be enough to cause the untoward reactions experienced by the subjects. The untoward reactions caused do not therefore correlate with the cardiovascular parameters considered. Majority of the subjects complained of burning sensation during the treatment, while only one subject experienced burn after the treatment.

Evidence exists that conductive gels, liquids and pester undergo electrolysis in the presence of direct current causing burns. During electrolysis, chlorine gas, or oxygen may be released at the anode and sodium hydroxide and hydrogen are released at the cathode. When the solution becomes strongly alkaline, the insulating epidermis is gradually destroyed causing decreased skin resistance. The intensity of the current in that area increased and the electrolytic production of sodium hydroxide is accelerated causing further skin burn [16].

Almost forty-five percent of the subjects in this study experienced itching during the histamine iontophoresis treat-

ment. Other untoward reactions include, headache, swelling, wealing and dizziness. Other authors have reported similar reaction [3,7]. Boone [12] reported that the skin should be thoroughly cleansed with soap and water and rinsed with alcohol before the electrode is applied to prevent burns. None of the subjects experienced burning sensation during the direct current treatment nor other untoward reactions.

Conclusion

The purpose of this study was to evaluate the effect of histamine iontophoresis treatment on the blood pressure and heart rate of healthy female subjects. The result revealed that histamine iontophoresis did not significantly affect the blood pressure and heart rate during the application of 1 per cent histamine diphosphate for twenty minutes treatment.

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