Medicina Sportiva (2017), vol. XIII, no 1, 2812-2819
Journal of the Romanian Sports Medicine Society

Ethanol and polysorbate-20 as permeability enhancer for iontophoretic administration of glucosamine sulphate in patients with low back pain

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Abstract Transdermal drug administration through iontophoresis may require permeation enhancer because most drugs do not achieve sufficient concentration in tissues. 95% Ethanol are usually used as surfactants while polysorbate 20 is rarely utilized for skin preparation during the procedure of iontophoresis in the management of cases of Low Back Pain (LBP). The primary aim was to compare the effects of ethanol and polysorbate 20 as glucosamine sulphate permeability enhancer in the management of symptoms of Low Back Pain. Fifty – four subjects with symptomatic low back pain were recruited. Electrical muscle stimulator (MS-Dx-07 muscle stimulator) was used to administer glucosamine sulphate using galvanic current. Ethanol, Polysorbate 20 and Tap water were used as skin cleansing agents prior to administration of glucosamine sulphate cream for participants with LBP in groups 1, 2 and 3 respectively. The Low back Pain Rating Scale Questionnaire was used to assess back and leg pain, disability index and physical impairments. Each patient was treated twice a week for a period of 6 weeks. Descriptive, Paired t-test (dependent) and Repeated Analysis of Variance (ANOVA) statistics were used to analyse the data obtained. The level of significance was set at 0.05. At onset, there was no significant difference in all the clinical and disability indices excluding physical impairment of Ethanol group that was significantly higher than that of polysorbate group ($p = 0.01$). Same trend was observed after six weeks ($p = 0.008$). The within group assessment for polysorbate-20 showed that there was significant decrease in the pain and disability indices after six weeks ($t = 13.02$, $p = 0.001$; $t = 5.14$, $p = 0.001$). Similar trends were observed for physical impairments and spinal range of motion. However, there was no significant difference between spinal flexibility at onset and six weeks post intervention. There were no significant differences in all the clinical indices, pre and post intervention after six weeks for both Ethanol and Tap water groups. It was concluded that Polysorbate-20 was a better permeation enhancer for glucosamine sulphate iontophoresis than Ethanol and Tap water in the management of symptoms of low back pain**.**
Key words: *Glucosamine sulphate iontophoresis, surfactants, polysorbate-20, Ethanol, Tap water, Low Back Pain*.

Introduction

Low back pain is a major problem worldwide and the annual prevalence and incidence is on the increase (1). The management focuses majorly on pain control, swelling, minimizing disability and improving quality of life of patients using medication and non-pharmacologic interventions (2). Pharmacological approaches include mostly use of oral Non – steroidal anti – inflammatory drugs (NSAIDS) to reduce pain and inflammation but it is associated with serious potential side effects such as nausea, vomiting, peptic ulcer disease, gastro-intestinal hemorrhage and cardiovascular episodes (3).

The transdermal route is considered alongside with oral treatment as the most viable in drug delivery, with almost 40% of the drug delivery studies related to dermal system (5). Several topical medications such as glucosamine sulphate, methyl salicylate creams have been developed to by-pass the gastrointestinal tract and therefore mitigate the adverse effects associated with oral administration (6-9). There are several means of administering medications but electromotive administration through the skin (iontophoresis and ultrasonophoresis) are gaining wider acceptance among physiotherapists. Iontophoresis of ionized drug products provides a multiple fold increase in penetration over topical application (10).

Iontophoresis (noninvasive, non-traumatic, painless and specific) is the transdermal administration of medicinal ions or bioactive agents using an electromotive force generated from the application of electric current (galvanic current) (8, 11, 12). Transdermal drug administration requires a delivery system to facilitate absorption and maximize bioavailability because drugs cannot deliver themselves (6, 13). In application of iontophoresis, the drug is delivered directly into the bloodstream without delay, although, it delivers less than a local injection, but provides much higher local concentration in the targeted tissue than oral administration (14). Iontophoresis remains one of the major mechanisms of enhancing drug flux through the skin (12). Most drugs that are suitable for iontophoretic application do not achieve sufficiently high blood levels for pharmacological activity when administered transdermal, hence, it is sometimes necessary to enhance the delivery (7). This can be achieved by chemical means through the use of absorption promoters such as dimethylsulfoxide and surfactants (15).

Surfactants are compounds that lower the surface tension of a liquid, the inter facial tension between two liquids, or that between a liquid and a solid (16). They are classified by the presence of formally charged groups in its head. It can be an ionic or a non-ionic surfactant a non-ionic surfactant will likely not compete with either the positive or negative charge; hence, it prevents ionic competition during iontophoresis. Surfactants had also been used to augment physical penetration enhancement strategies for ultrasound and iontophoresis (17, 18). Polysorbate 20 (Scattics, Alkest TW 20 and Tween 20) is a polysorbate surfactant whose stability and relative non-toxicity allows it to be used as a detergent and emulsifier in a number of domestic, scientific, and pharmacological applications (19). Surfactants are speculated to facilitate or enhance the permeation of drugs through the skin but very few studies focused on non – ionic surfactants such as Polysorbate 20 especially those involving low back pain.

Glucosamine is presently in wide use because of its purported beneficial effects in patients with osteoarthritis (OA). It is a naturally occurring amino monosaccharide and is a precursor for glycosaminoglycan, a major component of joint cartilage and synovial fluid (9). Quite a number of studies in Nigeria used 95% ethanol for enhancing permeation of glucosamine sulphate iontophoresis in cases of knee OA but rarely utilize polysorbate 20 especially in the management of symptoms of Low Back Pain. The primary aim of this study was to compare the effects of ethanol and polysorbate 20 as glucosamine sulphate permeability enhancer in the management of symptoms of Low Back Pain. It was hypothesized that there would be no significant difference in pain intensity, active spinal range of motions (flexion and extension) and physical function between the groups that used polysorbate 20 and ethanol surfactants prior to glucosamine sulphate iontophoresis.

Material and Method

Fifty – four subjects with symptomatic low back pain were recruited for the study. The subjects must have had symptomatic evidence of low back pain, maintained a steady regimen of same drugs and the duration of onset must be a minimum of 3 months. Those excluded were subjects with metallic implants and skin lesions, severe cardiovascular disorders/complications, impaired skin sensation, irrational behavior, cardiac pacemaker, pregnancy, thrombophlebitis, peripheral vascular disease and seizure disorders.

The main used instruments were Electrical Muscle Stimulator (MS-Dx-07 muscle stimulator), glucosamine sulphate, a 10-point semantic pain differential scale, methylated spirit (95% Ethanol), polysorbate 20, Schober's method for assessing spinal range of motion and Low Back Pain Rating Scale Questionnaire Manniche et al (20). The Low Back Pain Rating Scale Questionnaire was divided into three sections: back and leg pain, disability index and physical impairment. The interpretation being: minimum score for sub-scores as 0, maximum pain index: 60, maximum disability index: 30, maximum physical impairment: 40 and maximum total points: 130. Higher scores mean greater disability and impairment.

Patients were purposively selected and randomly assigned using the Fish bowl technique into three groups.

The research was a pre and post experimental design.

Prior to the commencement of the study, ethical approval was sought and obtained from the Research and Ethical committee of Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile-Ife, Osun State, Nigeria. Subjects were adequately informed of the procedure, after which they consented to participate. They were randomly allocated into three groups through balloting. The first group received glucosamine sulphate iontophoresis (2 FTU, an equivalence of 1g) with polysorbate 20 as the surfactant.

The treatment skin area prior to application of glucosamine sulphate iontophoresis was rinsed and cleansed with 3ml of polysorbate-20. Also, the two electrodes were wrapped in gauze and soaked in 5ml of polysorbate-20 for 10 seconds while1g of glucosamine sulphate was applied to the positively charged electrode (Anode). The anode and cathode electrodes were fastened to the low back using a Velcro strap or bandage with inactive on L1 and active (positive) on S1. For participants in group 2 the same procedure as described for group one except that 3ml of 95% ethanol was used instead of polysorbate 20 for skin cleaning. The two electrodes were also soaked in 5ml of Ethanol for 10 seconds. The third group was the control group and the participants also received 1g of glucosamine sulphate iontophoresis but 3ml and 5ml of tap water were utilized as surfactant and soaking electrodes for 10 seconds respectively.

Galvanic current mode of the Electrical Muscle Stimulator (MS-Dx-07 muscle stimulator) was used for the procedure of glucosamine sulphate iontophoresis. The intensity was gradually increased and maintained at the patient's threshold for 15 minutes (7, 21). The electrical stimulator current intensity was modulated to 3mA. The surface area of the electrode was 10.89cm^2 and the current density was 0.46mA/cm^2 (8). All procedures were done with patient lying prone. All the participants in the groups had baseline treatment program in the form of 1g of glucosamine sulphate iontophoresis, infra - red radiation for 15 minutes and exercise therapy (Back extension and flexion exercises) 10 reps each (22). The spinal ROMs were measured using standard procedure as described by Schober's. Back flexion and extension were assessed in standing position with the use of a tape rule. C7 and S1 spinous processes were taken as reference points. For flexion, a baseline measurement with the patient standing upright was taken, second measurement with the subject in the forward bending position was taken. The difference was noted and documented. For extension, a baseline measurement with the patient standing upright was taken, then a second measurement with the subject in the backward bending position was taken. The difference was also recorded.

Each patient was treated twice a week for a period of 6 weeks. Flexibility test (modified sit and reach test) was used to assess the flexibility of the participants in all the groups as described by (8). The subjects sat on a mat with the hip at 90^0 and the two arms outstretched, a flexibility box was placed at the feet of the lower limbs (with the shoes removed) touching the sole of the feet with an adjustable (100cm) meter ruler fixed at the center of the box and in between the 2 big toes with the zero meters at the tip of the right middle finger. The subjects flexed the spine and traced the ruler with fingers as far as possible to a new position. The point of the tip of the middle finger on the ruler was recorded and was taken as the flexibility. The pain intensities, spinal range of motions (ROM), flexibility, disability and physical impairment were assessed before and after every treatment session.

For the Low back Pain Rating Scale Questionnaire, the 3 indices form a rank scale (back and leg pain, disability index and physical impairment), an asymptomatic person scores 0 and a person with extreme disability scores 130 points. However, Smeets et al (23) recommended that the total sum score should not be used, as sub-scores provide valuable information and are not subject to weighting bias. Thus, this study took the 3 clinical indices individually without making use of the total score in data analyses.

Data analysis. Mean, standard deviation and range were computed for all variables. Analysis of Variance (ANOVA) was used to compare Pain intensities, spinal ROMs, disability and physical impairment. Repeated ANOVA was be used to compare within and across group effects. Paired t-test (dependent) was used to compare the pre and post treatment values for spinal ROM, pain intensity and physical function within treatment sessions. The level of significance will be set at 0.05.

Results

Comparison of age, height and weight of participants in the three groups. The result of Analysis of Variance (ANOVA) showed that there was no significant difference in the age and weight but there was significant difference in the heights of participants in the 3 groups. The result of the Post Hoc (LSD) show that the height of participants in the ethanol group (group 2) was significantly higher than that of polysorbate – 20 group ($p = 0.04$) and tap water group ($p = 0.03$) (Table I).

Table I. Age and selected anthropometric parameters of the three groups

	Polysorbate-20		Ethanol		Tap water	
	Mean	SD	Mean	SD	Mean	SD
Age	56.47	11.13	57.75	7.59	57.27	5.00
Height	1.67	0.08	1.72	2.07	1.67	0.08
Weight	81.73	12.43	85.00	11.09	88.93	8.57

Among group 1, there are 7 male (46.7%) and 8 female (53.3%) participants. The mean age, height and weight were 56.47±11.13 years, 1.67±0.08 meters and 81.73±12.44 kilogram. Pain index was 30.53±12.50 points at onset out of 60 points. The disability index at onset was 6.20±4.26 points out of 30 points while the physical impairment was 16.20±3.69 points at onset out of 40 points.
The spinal range of motion and flexibility are presented in table II. In Group 2, there are 9 male (56.3%) and 7 female (43.8%) participants. The mean age, height and weight were 57.75±7.59 years, 1.72±0.07 meters and 85.00±11.09 kilogram. Pain index was 28.56±9.60 points at onset. The disability index at onset was 8.44±3.27 while the physical impairment was 19.81±3.78 points at onset. The spinal range of motion and flexibility are presented in table II. The mean age, height, weight, spinal range of motion, flexibility, pain index, disability index and physical impairment are presented in table 2 for group 3 participants.

Table II. Clinical indices of participants in the groups

	Polysorbate-20		Ethanol		Tap water	
	Mean	SD	Mean	SD	Mean	SD
At onset						
Pain index	30.53	12.50	28.56	9.60	27.53	8.49
Disability index	6.20	4.26	8.44	3.27	6.80	4.65
Physical impairment	16.20	3.69	19.81	3.78	17.00	4.00
Spinal flexion	57.33	7.91	58.00	7.24	57.73	5.37
Spinal extension	4.40	1.99	3.50	2.22	3.67	2.09
Spinal flexibility	6.65	8.56	3.74	1.46	3.73	1.69
After six weeks						
Pain index	19.73	12.50	26.31	10.23	22.27	7.47
Disability index	4.80	3.73	7.81	3.41	6.13	4.42
Physical impairment	13.67	3.71	17.69	4.57	15.40	3.78
Spinal flexion	58.87	7.29	60.13	7.59	58.27	5.35
Spinal extension	3.47	2.07	3.25	1.84	3.26	2.15
Spinal flexibility	4.23	1.89	4.00	1.62	3.68	1.69

Comparison of Clinical indices at Onset and Six Weeks (Post intervention) among participants in Polysorbate – 20 group (Group 1). The result of the paired t – test showed that when polysorbate-20 was used to enhance permeation of glucosamine sulphate there was significant difference between the pain index at onset and after six weeks ($t = 13.02$, $p = 0.001$). There was also significant difference between disability index at onset and after six weeks post intervention ($t=5.14$, $p=0.001$). Similar trend was observed for disability index, physical impairment and spinal range of motion. However, there was no significant difference between spinal flexibility at onset and six weeks post intervention (table III). In groups 2 and 3, there was no significant difference in all the clinical indices pre and post intervention after six weeks when Ethanol and tap water were used to enhance permeation of glucosamine sulphate through iontophoresis (table III).
Comparison of clinical indices across the groups. At onset, the result of Analysis of Variance (ANOVA) showed that there was no significant difference in all the indices excluding physical impairment across the groups. After six weeks, there was only significant difference in the physical impairment across the groups ($F = 3.85$, $p = 0.03$), (Table IV). The Post Hoc analysis (LSD) showed that at onset physical impairment of participants in the ethanol group (group 2) was significantly higher than that of the polysorbate-20 ($p = 0.01$) and tap water group ($p = 0.05$). Similarly, the result of the Post Hoc analysis (LSD) showed that post intervention (after six weeks), the physical impairment of group 2 participants was significantly higher than that of group 1 ($p = 0.008$)

Table III. Comparison of values of pre and post intervention after six weeks within the groups

	Mean change	SD	T	p
Polysorbate 20				
Pain index	10.08	3.21	13.02	0.001
Disability index	1.40	1.06	5.14	0.001
Physical impairment	2.53	1.06	9.26	0.001
Spinal flexion	-1.53	1.06	-.60	0.001
Spinal extension	-0.93	-0.59	-6.09	0.001
Spinal flexibility	2.27	8.83	0.99	0.37
Ethanol				
Pain index	2.25	9.39	0.96	0.35
Disability index	0.63	4.10	0.61	0.55
Physical impairment	2.13	4.37	1.95	0.07
Spinal flexion	-2.13	6.07	-1.40	0.18
Spinal extension	-1.53	1.92	-0.52	0.60
Spinal flexibility	-0.25	1.68	-1.27	0.23
Tap water				
Pain index	5.27	10.29	1.98	0.07
Disability index	0.67	4.66	0.55	0.59
Physical impairment	1.60	3.93	1.58	0.14
Spinal flexion	-0.53	4.91	-0.42	-0.68
Spinal extension	-0.40	1.68	-0.92	-0.37
Spinal flexibility	0.11	2.04	0.20	0.85

Table IV. Comparison of physical impairment at onset and post intervention between the two groups

Physical Impairments	Groups		Mean	P	Between the groups F	p
At onset	1	2	-3.16	0.012		
		3	-0.80	0.570		
	2	3	2.81	0.047	3.85	0.03
	1	2	-4.02	0.008		
After intervention		3	-1.73	0.248		
	2	3	2.29	0.124	3.50	0.03

Discussion and Conclusion

Topical medication remains a widely acknowledged means but there is need to enhance permeability of topical medications being adopted in pharmacophysiotherapy management of clinical pathologies. The route of administration permits the avoidance of first pass metabolism by the liver and it also by-passes the gastric system providing higher levels and quicker tissue saturation (8, 21). It is widely accepted that transdermal delivery improves patient compliance APBN (2007).

The use of iontophoresis as local anesthesia, and for corticosteroid therapy for non-specific inflammatory lesions has been documented (25). Maximizing the penetration through the skin remains a huge challenge for increasing the bioavailability of drugs for effective responses coupled with lesser side effects (7). The use of electromotive force such as iontophoresis of ionized drug provides multiple folds increase in penetration over topical application; however, there is still need to use permeation enhancer to further increase the depth of effects. Chemical penetration enhancers are one means for reversibly lowering the skin barrier mainly by lipid disruption, increasing corneocyte permeability, and promoting partitioning of the drug into the tissue (26). Lavon et al (17) reported that surfactants have been used to augment physical penetration enhancement strategies, such as ultrasound and iontophoresis.

The selected anthropometric parameters of patients in the 3 groups were comparable excluding the height of patients in group 2 that was significantly higher than groups 1 and group 3. Most factors such as sex, weight and Body Mass Index had been established to affect pharmacokinetic parameters of drugs. Obesity influences pharmacokinetics and pharmacodynamics of drugs and most drugs are based on normal weights;

therefore, mistakes in the determination of the appropriate dose are often made (27). Generally, pathophysiological changes in obese patients are likely to affect drug distribution and elimination. Miya et al (28) reported that the influence of relative weight, sex and age on pharmacokinetics/pharmacodynamics should be ignored in pharmacological approaches. Pharmacokinetic reports provide differing data on renal function in obese patients. It was observed that height was the only parameter that deferred across the groups but most previous did not emphasize its effect on drug bioavailability and volume of distribution (27-29). The factors that are usually reported to affect the tissue distribution of drugs are body composition, regional blood flow and the affinity of the drug for plasma proteins and/or tissue components (29). In view of these, the differences observed in this study could not be attributed to variation in heights of the participants. However, there was no significant difference in the proportion of male and female patients with low back pain in this study. This might affect the interpretation of this study as later highlighted.

Glucosamine supplement have been sufficiently proven to be beneficial and it is still a fundamental component in the management of low back pain and osteoarthritis because it aids synthesis of joint cartilage (6-8). Onigbinde et al (1) in a study involving the use of low metal glucosamine sulphate iontophoresis in managing lumbar spondylosis concluded that iontophoretic application of the drugs had significant acute effect in reducing pain intensity. In this current report, after 6 weeks, the within group assessment for using polysorbate-20 as a permeation enhancer for glucosamine sulphate iontophoresis, showed that there was a significant reduction in the pain index, disability index and physical impairment; and increase in spinal range of motions. However, there was no significant difference in spinal flexibility. Contrarily, in the ethanol and tap water groups showed no significant difference in the clinical indices from the period of onset to six weeks post intervention.

At 6 weeks post interventions, there was no significant difference in clinical indices (pain index, disability index, spinal range of motion and spinal flexibility) across the groups excluding physical impairment which was found to be significantly higher in the ethanol group compared to polysorbate-20 group both at onset and after the periods of administration. However, there was more significant increase in level of significance increment in physical impairment for ethanol group relatively compared to others, meaning that polysorbate was a better permeation enhancer for a procedure of glucosamine sulphate iontophoresis in the management of symptoms of low back pain. It is also noteworthy that polysorbate-20 had better effects on clinical indices within the group. Onigbinde et al (8) also reported that there was no difference in the cumulative effects of 1%, 0.5%w/v sorbitan monooleate concentrations and ethanol as surfactants at the end of 4 weeks administration when pain intensity and range of motion were monitored, although, application was at the knee joint of patients with knee osteoarthritis. The non-superiority of the surfactants for most clinical indices over one another in this current study might be attributed to the mixture of both sexes in this study. Sex-based differences had been reported to affect pharmacokinetics and or pharmacodynamics and this can manifest as differences in efficacy of drugs (30). It is pertinent in all studies to separate men and women as responses have been noted to vary as a result of gender difference (30-35). This might be a limitation to the interpretation of these findings. Also, only age, weight, height and BMI were the parameters compared, whereas, factors such as regional blood flow and glucosamine binding affinity for plasma proteins were not monitored.

This study concluded that at 6 weeks there were significant changes in the pain intensities, spinal range of motions (ROM), disability and physical impairment in only the polysorbate-20 group. Polysorbate-20 significantly reduced level of physical impairments compared to the use of ethanol and tap water as permeation enhancer for glucosamine sulphate iontophoresis in the management of symptoms of low back pain**.**

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Received: January 28, 2017
Accepted: May 10, 2017