



Plantarhyperhidrosis: The Efficacy Of Iontophoresis With Tap Water, Glycopyrronium Bromide And Indomethacin

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Abstract: Hyperhidrosis is an excessive production of sweat more than the physiological amount necessary to maintain thermal homeostasis. Primary focal hyperhidrosis is a disorder of unknown etiology, causing excessive, bilateral, symmetrical sweating on the soles of the foot is called plantar hyperhidrosis. The condition results not only in physical impairment, but also interferes with professional and social life. Although not life-threatening, it is very uncomfortable and cause embarrassment and psychological trauma. Iontophoresis is a helpful method, which includes the presentation of particles into the body tissue through the skin. The essential principle is to place the ion particles under an electrode with the same charge, i.e. negative ion placed under cathode and positive ion placed under anode. This complete process is also known as "technique of ion transfer" into the body tissues by using electrical current as a driving force. It is a comparative study with pre and post intervention. 30 subjects with plantar hyperhidrosis were selected based on the inclusion criteria. The study duration was for about 4 weeks 30 subjects of age group between 15 – 25 years with idiopathic plantar hyperhidrosis of both male and female subjects were included in this study. Subjects with cardiac and respiratory disorders, pregnant or lactating, any cuts, abrasions, eczema or infections on plantar aspect, metal implants like pacemakers, Hypersensitivity to the active substance were excluded. The subjects were divided into 3 group Group A treated with iontophoresis using tap water alone. Group B were treated with iontophoresis using tap water along with 3%-5% of anticholinergic drug, glycopyrronium bromide solution. Group C were treated with iontophoresis using tap water along with 1% of indomethacin (NSAID). The result of this study shows that there were significant changes in outcome measures. On comparing Mean values of Group A, Group B & Group C on Minor test (Starch - Iodine Test) tap Water along with Glycopyrronium Bromide (Group B) shows 1.60 which has the Lower Mean value is effective than Group A and Group C. On comparing Mean values of Group A, Group B & Group C on Visual Analog Scale score tap Water along with Glycopyrronium Bromide (Group B) shows 3.80 which has the Lower Mean value is effective than Group A and Group C. On comparing Mean values of Group A, Group B & Group C on Hyperhidrosis Disease Severity Scale tap Water along with Glycopyrronium Bromide (Group B) shows 1.40 which has the Lower Mean value is effective than Group A and Group C. On comparing all the three groups, Group B shows better result than Group C and Group A in outcome measure. This study concluded that Tap water along with glycopyrronium bromide reduces the excessive sweating and decrease the sweating symptoms in subjects with plantar hyperhidrosis.

Keywords: Plantar hyperhidrosis, Iontophoresis, Tap water Iontophoresis, Glycopyrronium bromide, Indomethacin

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I. INTRODUCTION

Hyperhidrosis, also known as polyhidrosis or sudorrhea, is a condition characterized by excessive sweating.¹ The sweating can affect just one specific area or the whole body. Hyperhidrosis could be a condition characterized by abnormally accrued sweating, in more than that needed for regulation of vital sign though primarily a physical burden, hyperhidrosis will deteriorate quality of life from a psychological, emotional, and social perspective. sweat is regulated even though the person isn't partaking tasks that need muscular effort, and it doesn't rely upon the exposure to heat. Common places to sweat will embrace underarms, face, neck, back, groin, feet, and hands. It's been referred to as 'the silent handicap'.¹ sweating is a physiological process vital for the body to maintain thermoregulation.¹ Other functions of sweat are enhancing the grip for hands or feet during physical activities, moisturizing the skin, controlling the desquamation of stratum corneum and releasing molecules that are pro- or anti-inflammatory.^{2,3} Human sweat consists of approximately 99% water and has a pH of 5.0-7.0 depending on the production.¹ Substances such as sodium, potassium, chloride, lactate, urea, ammonia, proteolytic enzymes, human epithelial growth factor and glucose can also be found in human sweat.^{1,2} Humans have three different types of sweat glands: eccrine, apocrine, and apoeccrine. Eccrine sweat glands are distributed all over the skin and they mainly secrete water and electrolytes through the surface of the skin. The thermoregulatory center in hypothalamus control the temperature of body regulating eccrine sweat output and blood flow. Sweat glands are stimulated by emotion and thermoregulatory changes. A total of 1.6-4 million eccrine sweat glands are dispersed throughout the skin.⁴ The density of the eccrine glands on the palms and soles are 600-700/cm² whereby only 64/cm² on the back. An eccrine gland is a merocrine, coiled, tubular structure consisting of a duct and a secretory portion. The secretory part is situated in the dermis and is 2-5mm long.⁵ It consists of clear cells, dark cells and myoepithelial cells. While clear cells produce the isotonic fluid that becomes sweat, the role of dark cells is unclear.⁴ Myoepithelial cells surround the secretory tubules and discharge the fluid into the tubular secretory portion.⁶ Their function is regulating sweat production by acting as valves, allowing some cells to use the surrounding metabolites for sweat production while sealing others.⁷ Eccrine glands are innervated by sympathetic cholinergic sudomotor axons.^{1,2} Nerve impulses are transmitted via synapse to the gland. This transmission is facilitated by acetylcholine vesicles docking on the presynaptic membrane and discharging their content.^{2,8} Normal sweating is a physiological mechanism for regulating body temperature while in hyperhidrosis the sweating is excessive and tormenting in affected individuals.¹³ Hyperhidrosis is a disease characterized by excessive sweating occurs mainly in the soles of the feet called plantar hyperhidrosis.¹⁴ Hyperhidrosis has an unknown etiology and is associated with intense emotional, occupational and social stress. It usually begins in childhood or adolescence and entails an important impairment in the quality of life of individuals.¹⁵ There is a distinction between primary (PH) and secondary (SH) hyperhidrosis. PH is usually restricted to certain areas while SH is mostly general and rarely focal.¹¹ Other types of hyperhidrosis such as gustatory, emotional, compensational, and thermal types are usually termed due to the provoking stimuli. Primary hyperhidrosis (PH) is idiopathic and occurs as focal or multifocal.¹³ The

disease affects women and men in equal proportions.¹⁶ Primary hyperhidrosis affects 0.6% - 1% of the population.¹⁷ The reported prevalence of primary hyperhidrosis ranges from 1% to 2.8%. Most commonly 41.1% (feet) people are affected with plantar hyperhidrosis. It is estimated that roughly 3% of world's population i.e. around 200 million people have this medical condition.^{18,19} In tropical countries, the prevalence rates range from 1.5% to 9%.^{20,21,22} Almost 3% of the general population largely people aged between 25-64 years experiences hyperhidrosis.²³ Self-reported family history for PH is described in 30-50%.²⁴ A genetic background with an autosomal dominant transmission and a variable penetrance has been suggested as a possible cause.^{25,26} Some authors have not found any pathological changes in the sweat glands,^{27,28} while others have described an increased number of cells and a larger myelin sheath in the sympathetic ganglion in those with PH.⁸ An overstimulation of the sympathetic nerve fibers innervating the sweat glands has been suggested as a mechanism for the excessive sweat production.²⁹ Hyperhidrosis occurs as a primary process of autonomic neural dysfunction. This dysfunction tends to occur in areas where there is a higher concentration of eccrine glands such as palms, soles and axillae, which are sweat producing glands.³⁰ The nerves innervate sweat glands are sympathetic, postganglionic and acetylcholine as their neurotransmitter.³¹ Norepinephrine and vasoactive intestinal peptide (VIP) may play a role, but neither of these amplifies cholinergic sweat secretion.³² Sweat glands on the palms and soles alone are activated mostly by emotional stimuli. Frontal and premotor projections to hypothalamus probably promote sweating during enhanced emotions.³³ Sympathetic cholinergic nerves activate both thermoregulatory and emotional sweating and are controlled by different central nervous system neurons.³⁴ Exacerbating factors in PH have been described as stress, anxiety, heat, humidity and exercise.³⁵ Food such as spices, coffee and alcohol can also worsen the problems. While some patients report an amelioration of symptoms with hard exercise others report the opposite.³⁶ Primary hyperhidrosis has negative impacts on the psychosocial health of the individuals. The disease reduces the overall quality of life and interferes with the daily activities of those affected.^{37,38} Individuals express stress and anxiety in conjunction with their sweating but also prior to private or social interactions.³⁹ The impact of hyperhidrosis on patient's life is broad and affects all areas of life such as daily life, psychological well-being, social life, professional life, dealing with the condition, unmet health care needs and physical impact.⁹ The impact of PH can be different depending on the site of the body affected. Individuals may experience discomfort in relation to having wet feet that cause cracked skin. Plantar hyperhidrosis can cause the foot to slip off the brake when driving a car, a slip in a sandal to cause a twisted ankle, or fill a shoe with sweat. Fear of leaving sweating marks. Performing daily activities such as walking usually requires more time. Decisions such as choosing career path or occupation can be difficult and coping hyperhidrosis is often stressful. In the society excessive sweating is associated with being nervous or unhygienic.³⁹ Iontophoresis is defined as the introduction of an ionized substance through application of a direct current on intact skin.⁴⁰ Though the exact mechanism of action is unknown, this technique facilitates transdermal movement of solute ions by generation of an electrical potential gradient. Penetration of neutral compounds is also facilitated. Tap water, anticholinergic agents (glycopyrrolate) are used in iontophoresis, resulting in a more efficient reduction of sweat production.⁴¹ Duration of

effect is only a few days with tap water and anticholinergic iontophoresis.⁴² Indomethacin (NSAID) can block the synthesis of prostaglandins, at least in the kidney, can increase sodium and water excretion, a relationship between indomethacin, eccrine gland prostaglandins and hyperhidrosis may very well exist.⁴³ Indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues. Iontophoresis was found to increase the permeation of indomethacin.⁴⁴ The general population, especially in developing countries like India is seldom aware of this condition and sparsely seeks medical attention. The tropical climate and the environment also influence and aggravate this condition to a greater extent. Most patients try to modify their lifestyle and get adapted to this problem. This can be a hindrance to their normal professional and social life. Many relevant studies had been conducted, yet only a very few published data are available from India.⁴⁵ This study is an attempt to compare and analyse the effects of iontophoresis with tap water, glycopyrronium bromide and indomethacin. Assessment tools include starch-iodine test, VAS scale and hyperhidrosis disease severity scale using which pre and post assessment taken.

2. METHODOLOGY

The procedures were followed according to the recommendations of Helsinki Declaration of 1964 (as revised in 2008). This study was registered under Faculty of Physiotherapy, Dr.MGR educational and Research institute

with A-29/PHYSIO/IRB/2018-2019. This study was an experimental study with duration of 4 weeks. 30 subjects with plantar hyperhidrosis based on the inclusion and exclusion criteria between the age group of 15 – 25 years were randomly selected from A.C.S Medical College and Hospital, Chennai. 30 Subjects with plantar hyperhidrosis were randomly selected and divided into Group A, Group B and Group C equally. Both male and female subjects, who had focal, visible, excessive sweating without apparent cause, Impairment of daily activities Positive family history and the lower age limit for iontophoresis is 5 years were included in this study. Subjects with cardiac and respiratory disorders, who are pregnant or lactating any cuts, abrasions, eczema or infections on plantar aspect, with metal implants like pacemakers and hypersensitivity to the active substance were excluded from this study. Minor test (Starch iodine test), Hyperhidrosis Detecting Questionnaire, Hyperhidrosis Specific Questionnaire (HSQ) (pre and post treatment questionnaire), HSQ includes visual analogue scale (VAS). Hyperhidrosis disease severity scale (HDSS) are used as outcome measure.

2.1 Minor Test (Starch-Iodine Test)

Tincture of iodine is applied to the feet and allowed to air-dry (fig 1). After drying, the area is dusted with cornstarch. When sweat reaches the surface of skin, the starch and iodine combine, causing a dramatic colour change (yellow turns into dark blue) (fig 2), allowing sweat production to be easily visualized.



Fig.1 Feet Coated with Iodine



Fig.2 Areas of Hyperhidrosis Turn Blue-Black After Dusting with Starch Powder

Group A: Includes 10 subjects with plantar hyperhidrosis, who were treated with iontophoresis using tap water alone. Sometimes, tap water in certain geographic locations may be

too “soft” for iontophoresis to work; it does not contain many minerals or electrolytes.

Group B: Includes 10 subjects with plantar hyperhidrosis, were treated with iontophoresis using tap water along with

3%-5% of anticholinergic drug, glycopyrronium bromide solution.⁴²

Group C: Includes 10 subjects with plantar hyperhidrosis, were treated with iontophoresis using tap water along with 1% of indomethacin (NSAID). Indomethacin is not a water solvent hence it is mixed with 40% ethanol or the solution was prepared using absolute ethanol: propylene glycol: dimethylacetamide 19: 19: 2. All the three groups were treated by faradic foot bath, with muscle stimulator, treatment is given for 3 times a week for 4 weeks. After checking for any general and local contraindications. Make certain, the subject removes all jewelry and any small cuts or abrasions were covered with Vaseline or some other water-resistant material. The subject was made to sit over the wooden stool. Foot is placed in a treatment tray kept over the spread mackintosh. Hip and knee are flexed to about 90°. The subject is asked to hold the hip knee firmly to maintain contact by using body weight. The tray as to be filled with tap water at room temperature to the top of the electrodes. Both the feet as to be placed in a bath containing enough water to cover the toes. Electrodes (anode and cathode) must be placed under the heel or the metatarsal heads of the right and left foot based on the area of severity of sweating symptoms assessed by starch-iodine test. The apparatus as to be checked unit turned on and "intensity"

knob at zero gradually increase the amperage using the intensity knob to the therapeutic range of 15-18mA. Normally, the intensity may range from 5mA to 20mA, varied according to the subject's tolerance and treatment for 10mins. At the end of the 10 mins, the current flows gradually decreased to zero and the polarity being reversed (change the direction of current flow at the unit) i.e. the negative ion placed under the cathode electrode gets interchanged and treated for 10 mins. Repeat the same procedure. Each session lasts for about 20 minutes. Remind the subject to keep foot in the water for complete duration. Removing the foot or touching the electrodes during the treatment may result in a slight shock. Because the intensity of the current flow is greatest at that part of the foot that is closest to the electrodes. Instructions were given to the subject to inform if there is any burning sensation, tingling sensation or if it becomes uncomfortable. After the treatment gets over the area/part treated has to be checked and end of the session. Patients should be asked to record their response to the treatment by rating each sole each day following treatment as 'dry', 'slightly wet', 'moderately wet', or 'very wet'. At the end of 4 weeks of treatment session post-test analysis to be done using outcome measurements and followed up at 8 weeks.



Fig.4.A Starch Iodine Test: Pre Treatment



Fig.4.B Post Treatment

3. STATISTICAL ANALYSIS

The collected data were tabulated and analyzed using both descriptive and inferential statistics. All the parameters were assessed using statistical package for social science (SPSS) version 24. One Way ANOVA includes of following tests (Test of Homogeneity of Variance, ANOVA, Post Hoc test Tukey HSD) (multiple comparison) was adopted to find statistical difference between three groups.

4. RESULT

Table I On comparing Mean values of Group A, Group B &

Group C on Minor test (Starch - Iodine Test) shows significant decrease in the Post test Mean values, but Tap Water along with Glycopyrronium Bromide (Group B) shows 1.60 which has the Lower Mean value is effective than Tap Water along with Indomethacin (Group C) 2.30 and followed by Tap Water Iontophoresis (Group A) 2.50 at $P \leq 0.05$. Hence Null Hypothesis is rejected. Table 2 On comparing Mean values of Group A, Group B & Group C on Visual Analog Scale score shows significant decrease in the Post test Mean values, but Tap Water along with Glycopyrronium Bromide (Group B) shows 3.80 which has

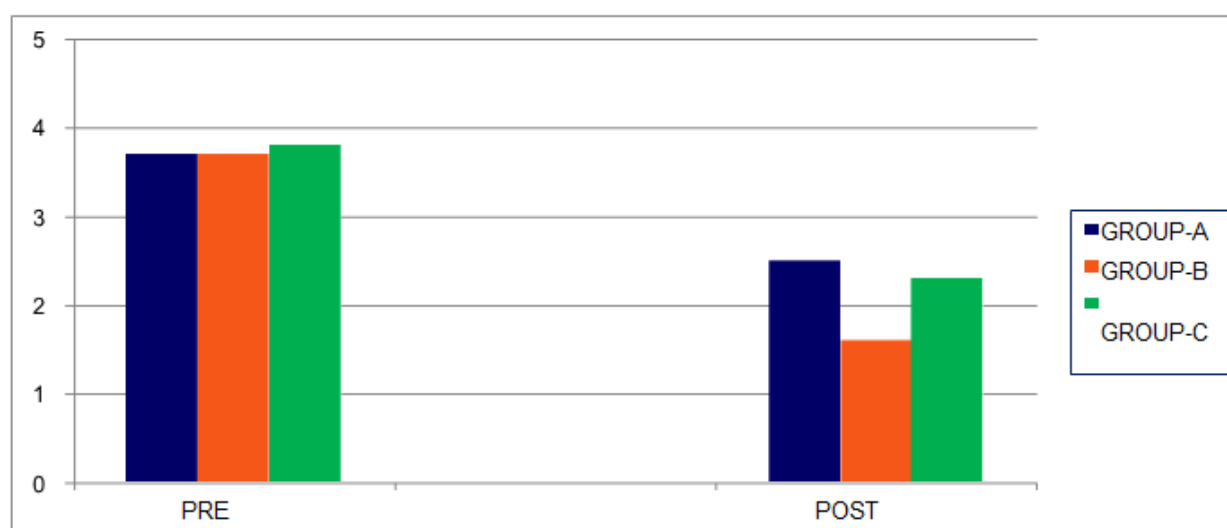
the Lower Mean value is effective than Tap Water along with Indomethacin (Group C) 5.70 and followed by Tap Water Iontophoresis (Group A) 6.00 at $P \leq 0.05$. Hence Null Hypothesis is rejected. Table 3 On comparing Mean values of Group A, Group B & Group C on Hyperhidrosis Disease Severity Scale score shows significant decrease in the Post

test Mean values, but Tap Water along with Glycopyrronium Bromide (Group B) shows 1.40 which has the Lower Mean value is effective than Tap Water along with Indomethacin (Group C) 2.10 and followed by Tap Water Iontophoresis (Group A) 2.50 at $P \leq 0.05$. Hence Null Hypothesis is Rejected.

Table-I. Comparison Of Pre-& Post Minor Test (Starch - Iodine Test) Using Test Of Homogeneity Of Variance & One Anova Test Between Group A, Group B And Group C

Test	Group A		Group B		Group C		Df		F Value	Sig
	Mean	S. D	Mean	S. D	Mean	S. D	Df1	Df2		
Pre	3.70	1.15	3.70	.948	3.80	1.03	2	27	.030	.970*
Post	2.50	1.08	1.60	.516	2.30	.674	2	27	3.54	.003**

The above table reveals the Mean, Standard Deviation (S.D), Homogeneity variance, ANOVA test, degree of freedom(df), F-value & P value between (Group A), (Group B) & (Group C) and shows that there is a significant difference in post-test values between (Group A), (Group B) & (Group C) (**- $P \leq 0.05$).

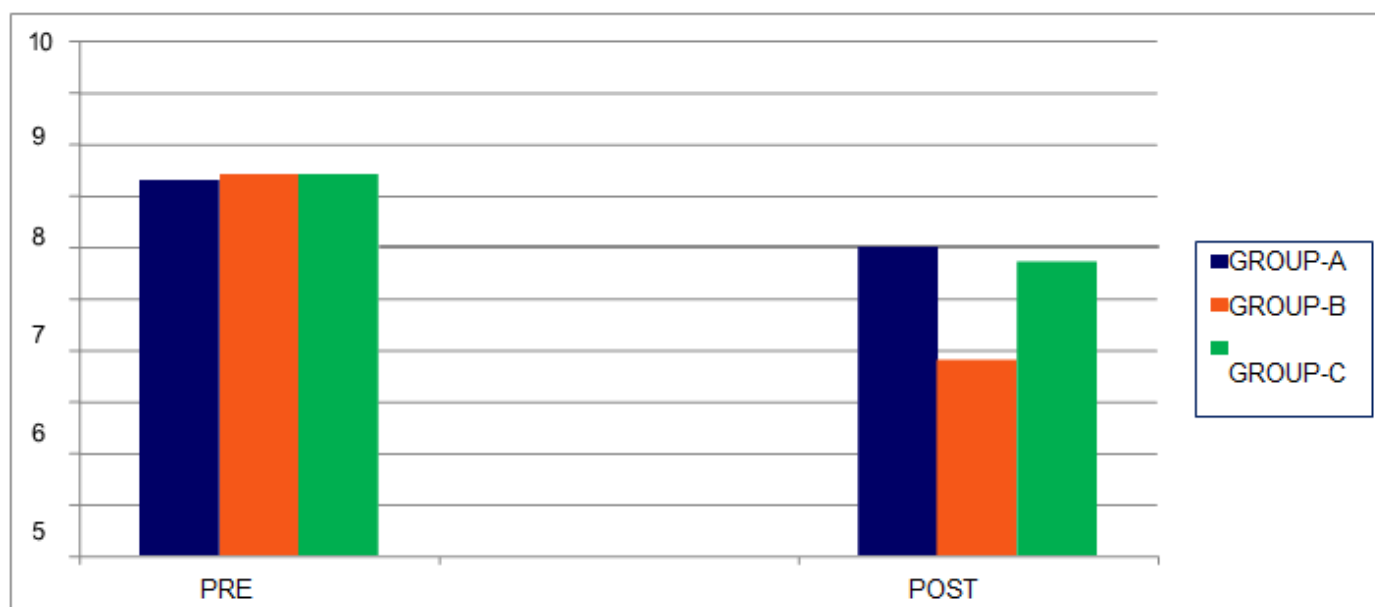


GRAPH – I Comparison Of Pre-& Post Minor Test (Starch - Iodine Test) Using Test Of Homogeneity Of Variance & One Anova Test Between Group A, Group B And Group C

Table- 2. Comparison Of Pre-& Post Visual Analog Scale Score Using Test Of Homogeneity Of Variance & One Anova Test Between Group A, Group B And Group C

Test	Group A		Group B		Group C		Df		F Value	Sig
	Mean	S. D	Mean	S. D	Mean	S. D	Df1	Df2		
PRE	7.30	1.33	7.40	1.17	7.40	1.17	2	27	.022	.948*
POST	6.00	1.49	3.80	1.31	5.70	.948	2	27	8.79	.003**

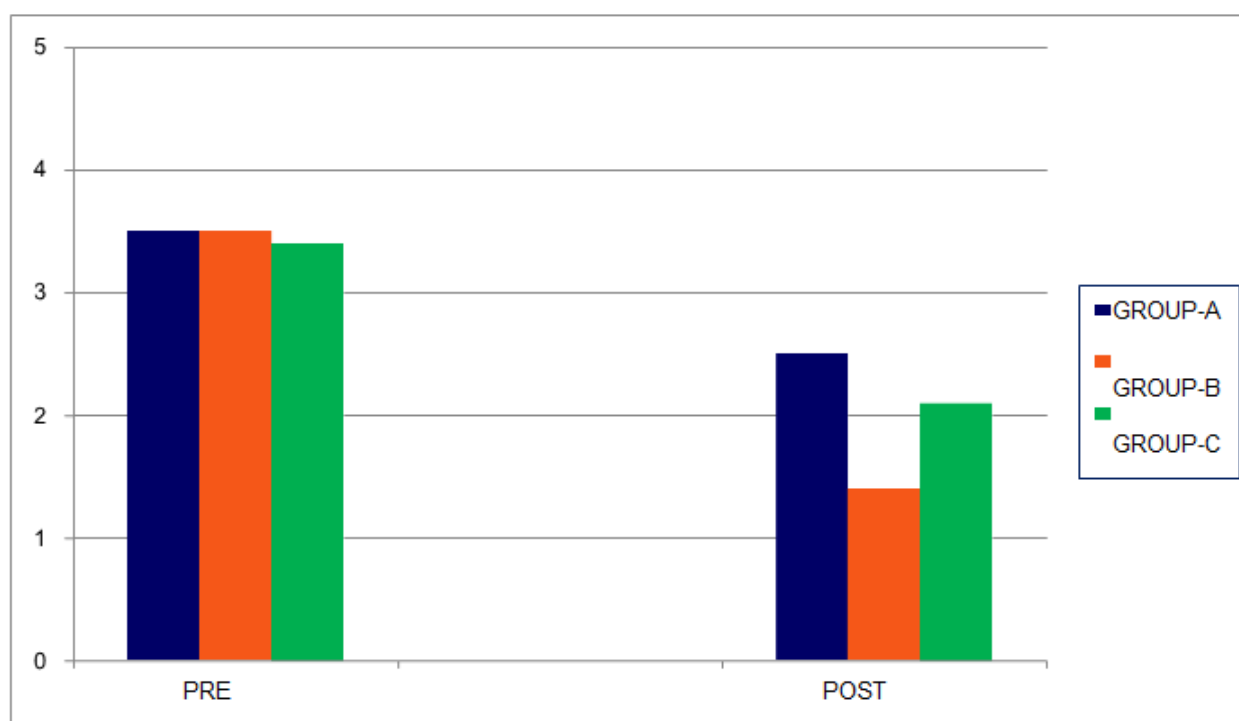
The above table reveals the Mean, Standard Deviation (S.D), Homogeneity variance, ANOVA test, degree of freedom(df), F-value & P value between (Group A), (Group B) & (Group C). This table shows that there is a significant difference in post-test values between (Group A), (Group B) & (Group C) (**- $P \leq 0.05$).



Graph – II Comparison Of Pre- & Post Visual Analog Scale Score Using Test Of Homogeneity Of Variance & One Anova Test Between Group A, Group B And Group C

Test	Group A		Group B		Group C		Df		F Value	Sig
	Mean	S. D	Mean	S. D	Mean	S. D	Df1	Df2		
Pre	3.50	.971	3.50	.527	3.40	.843	2	27	.052	.950*
Post	2.50	.971	1.40	.516	2.10	.567	2	27	6.06	.004**

The above table reveals the Mean, Standard Deviation (S.D), Homogeneity variance, ANOVA test, degree of freedom(df), F -value & P value between (Group A), (Group B) & (Group C). This table shows that there is a significant difference in post-test values between (Group A), (Group B) & (Group C) (**- $P \leq 0.05$).



Graph – III Comparison Of Pre- & Post HDSS Score Using Test Of Homogeneity Of Variance & One Anova Test Between Group A, Group B And Group C

5. DISCUSSION

Primary hyperhidrosis is a condition characterized by excessive sweating. The estimated prevalence is between 0.6

and 4.4%, and it can have economic, psychological, and social consequences for affected individuals.^{9,10} The study was conducted on 30 subjects with plantar hyperhidrosis to compare and find out the effectiveness of iontophoresis.

Group A was treated with tap water, Group B was treated with glycopyrronium bromide and Group C was treated with indomethacin. Outcome measures included were starch-iodine test (fig 4A, fig 4B), VAS scale and hyperhidrosis disease severity scale which was done prior to the treatment and at the end of 4 weeks of treatment. Previous studies have shown that iontophoresis using tap water alone is effective in treating hyperhidrosis. It is a safe procedure, without any serious side-effects. Tap water is an effective and well tolerated treatment for hyperhidrosis. It is simple, inexpensive and affordable for patients. In 1936, Ichihashi demonstrated that sweating of palms could be reduced by iontophoresis. Levit published two reports in 1968 and 1980 exalting the efficacy and simplicity of tap water iontophoresis for the treatment of hyperhidrosis. Holzle et al., (1986) suggested that iontophoresis works by blocking neuroglandular transmission or inhibiting the secretory mechanism at the cellular level.⁴⁷ Abell et al., (1974) showed that the glycopyrronium bromide iontophoresis has been shown to be a simple safe and effective treatment particularly for the hands.⁴⁸ Chia Hy et al., (2012) concluded that iontophoresis using glycopyrronium bromide is an effective and well tolerated treatment for primary palmar hyperhidrosis. No serious side-effects were encountered.⁴⁹ Grice et al., (1972) suggested that iontophoresis can also exert a pharmacological effect on sweat glands by the delivery of anticholinergic drugs.⁵⁰ The duration of the effect is greater when iontophoresis is used with an anticholinergic agent. NSAIDS used in iontophoresis are applied, omitting oral administration and thus save the gastrointestinal tract. Group A pre-test & post-test mean value for Minor test (2.50) and Group B, pre-test & post-test mean value for Minor test (1.60) and Group C, pre-test & post-test mean value for minor test (2.30) (Table 1 & Graph 1) showed a significant difference. Group A pre-test & post-test mean value for VAS (6.00) and Group B, pre-test & post-test mean value for VAS (3.80) and Group C, pre-test & post-test mean value for VAS (5.70) (Table 2 & Graph 2) showed a significant difference. Group A pre-test & post-test mean value for HDSS (2.50) and Group B, pre-test & post-test mean value

for HDSS (1.40) and Group C, pre-test & post-test mean value for HDSS (2.10) (Table 3 & Graph 3) showed a significant difference. Based on this background, it has been observed that the Group B (Tap water iontophoresis along with glycopyrronium bromide) is better than Group C (Tap water iontophoresis along with indomethacin) and Group A (Tap water alone) for plantar hyperhidrosis.⁴⁶

6. CONCLUSION

This study clearly demonstrated the Efficacy of Iontophoresis with Tap water, Glycopyrronium Bromide and Indomethacin. Based on the outcome measures tap water iontophoresis along with glycopyrronium bromide is better than that of tap water iontophoresis along with indomethacin and Tap water alone for treatment of plantar hyperhidrosis. This treatment method was well tolerated without serious side effect. In future large sample size can be analyzed, and the treatment timing also can be increased, other chemicals like aluminium chloride and be used to find the comparative efficacy.

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8. AUTHORS CONTRIBUTION STATEMENT

Prof .Dr.C.V.Senthilnathan the principal investigator conceptualized the idea guided this study, G.Vaishnavi, G.Keerthana carried out the research study and drafted the manuscript, S.Nandha Kumar discussed the methodology and result Prof.Dr.Kotteeswara contributed in analyzing data.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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