An Exploratory Study of the Mechanism of Action of Patch-It® by Assessing Blood Circulation in Patients with Mild PAD

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Abstract- Peripheral arterial disease (PAD) is generally characterized by inadequate blood flow and usually affects lower limbs. It results in considerable discomfort with symptoms such as aching, itchiness, tiredness and swelling in the legs. In chronic state, pharmacological treatments (surgery, sclerotherapy and mechanical compression) are generally advised because they are easy to administer and well tolerated compared to less compliant compressive treatments (eg. elastic stockings). However, in the early state, conventional treatments such as lifestyle changes and use of topically applied natural or herbal phlebotonics are preferred by patients for the symptomatic relief and Patch-It® (Nutriworks Ltd, Hong Kong) is one such treatment, wherein a herbo-mineral adhesive patch consisting of mandarin wood vinegar, green tea powder and black tourmaline is applied to soles of the feet. It has been already reported to be efficacious in alleviating recurring swelling and aching in lower limbs, although its mechanism of action remains unexplored. This pilot study was planned to investigate the possible mechanism of action of Patch-It® by assessment of transcutaneous oxygen pressure ($TcPO_2$) and regional perfusion index (RPI). Twenty-five subjects were screened to achieve a population size of 10 subjects with mild grade PAD, assumed to be appropriate for this preliminary assessment. Subjects with ankle-brachial index (ABI) of $\geq 0.5 - < 1.0$ at rest in at least one leg, distal to proximal peak systolic velocity (PSV) ratio of < 2 and $< 50\%$ stenosis were screened and only eligible subjects were recruited. Enrolled subjects were instructed to apply Patch-It® for 14 days on both soles of the feet at night for at least 7 hours. Changes in limb's blood circulation were assessed by $TcPO_2$ and RPI. An increase was observed in $TcPO_2$ (3%) as well as in RPI values (33%) in subjects characterized by left limb stenosis (71% of the subjects). However, the changes were not statistically significant. A significant increase of 5% ($p = 0.044$) and 12.01% ($p < 0.001$) was observed in the ABI values in subjects with lower limb stenosis at day 1 and day 14, respectively, which is an indicator of improved blood circulation as compared to baseline. The results obtained from the study suggest that Patch-It® enhances the limb blood circulation by improvement in microcirculation, through a direct or indirect effect on capillary permeability as evident from changes in TcPO2 and RPI. Due to the limited number of subjects, no definitive conclusion can be drawn and further large-scale investigation is required to substantiate the current findings.

Index Terms- Ankle-brachial index, Peripheral arterial disease, Regional perfusion index, TcPO2, Patch-It®.

I. INTRODUCTION

Peripheral arterial disease (PAD) is an atherosclerotic process that causes stenosis and occlusion of non-cerebral and non-coronary arteries.[1] Over 10 million people in the United States were reported to suffer from PAD, caused by fatty buildups in the inner walls of arteries which blocknormal blood flow. Prime line medical therapy of PAD includes modification of cardiovascular risk factors with implementation of strict preventive measures such as surgery, sclerotherapy and mechanical compression.[2] Also, a large domain of PAD population can be treated with lifestyle changes, medicines or both. Often, conventional strategies such as use of compression stockings and leg elevation are implemented to relieve PAD associated swelling, aching and discomfort but these methods are not always the preferred choices due to inconvenience experienced by the patients. Generally, in the early state, use of topical natural or herbal phlebotonics is preferred by these patients for the symptomatic relief, though most of them lack clinically relevant evaluation.

Patch-It® (Nutriworks Ltd, Hong Kong) is one of such treatments and a proprietary herbo-mineral adhesive patch considered as easy-to-use alternative therapy. It is recommended for patients with mild to moderate pedal edema and also claims a good safety profile through consumer feedback and utility in sleep disturbances and low back pain. It consists of 98.5% mandarin wood vinegar (vinegar / dextrin) which is pyroligneous acid powder from wood cuttings of the mandarin orange *(Citrus reticulate Blanco)* tree, 0.5% green tea powder (*Camellia sinensis)* and 1% nano-sized black tourmaline (Brazilian type) particles. Mandarin wood vinegar has been widely used for supporting blood circulation, detoxification and healing of minor wounds in traditional Chinese medicine.[3] Green tea was found to be more active than black tea for an anti-inflammatory effect, plausibly due to the higher flavonoid contents of green tea[4,5]although green tea in Patch-It® is included to provide skin protection by its antioxidant effect.[6,7] Tourmaline has pyroelectric and piezoelectric properties and radiates far-infrared rays.[8] It was examined for effects on human leukocyte activity and on lipid peroxidation of unsaturated fatty acids and found to be safe and capable of potentiating leukocyte functions without

promoting oxidative injury.[9] Also, it has been reported that exposure to far-infrared rays eventually induces an increase in temperature of the body tissues, thus leading to an elevated motility of body fluids to the exposed region due to decrease in size of water clusters.[10]

Patch-It® demonstrated favorable results in relieving inflammation in the lower limbs.[11] Though, the product has been evaluated clinically, its mechanism of action still remains unexplored. An unpublished preliminary study conducted to explore the mechanism of action using thermo-graphic imaging showed an improvement in circulation four hours after patch application, but was not sufficient enough to indicate the exact mode. Hence, the current exploratory study was designed to evaluate the mode of action of Patch-It® in subjects with mild to moderate peripheral arterial disease (PAD) by assessment of transcutaneous oxygen pressure ($TcPO_2$) and regional perfusion index (RPI). Subjects with mild to moderate PAD were chosen to assess the product's effect in lower limbs with and without stenosis.

II. MATERIALS AND METHODS

Study Design and Procedure:An open-label design was chosen for this exploratory study. The study was reviewed and ethically approved by Medanta Institutional Ethics Committee (MIEC), Gurgaon, India and conducted according to the principles of Good Clinical Research Practice and the Declaration of Helsinki. Voluntary, written and signed informed consent was obtained from all subjects prior to initiation of any study related procedure. Twenty five potential subjects were screened from the patient pool attending the Division of Peripheral Vascular & Endovascular Sciences, Medanta Hospital, Gurgaon, India. Male and female subjects aged 35 – 75 years with mild to moderate peripheral arterial disease as confirmed by ankle-brachial index (ABI) of ≥ 0.50 but < 1.0 at rest in at least one leg, distal / proximal peak systolic velocities (PSV) ratio < 2 and $< 50\%$ stenosis were recruited in the study.[12, 13]The participant flow diagram has been depicted in **Figure 1**.Subjects with a history of severe claudication, clinical evidence of varicose veins, diminished arterial pulsations, ulcerative lesions and ABI < 0.5 (suggestive of severe arterial occlusive disease) were excluded from the study.[14] Also, the subjects with a history of cardiac, hepatic, renal, hemopoietic, endocrinal diseases, (predisposition to) deep vein thrombosis or other systemic condition, subjects on vasodilators or diuretics, pregnant or lactating women and those who had a history of hypersensitivity to any of the ingredients in the patch were excluded which according to the investigator were unsuitable for this analysis. In addition to clinical assessments, laboratory tests comprising complete blood count (CBC), erythrocyte sedimentation rate (ESR), serum glutamic pyruvic transaminase (SGPT), serum creatinine, urine routine and microscopy, electrocardiogram (ECG) and pregnancy test (UPT) were performed to screen subject's eligibility for participation.Seven enrolled subjects were invited to the site for the baseline visit on day 0 (8:00 am in the morning). After day 0, assessments including TcPO2 were conducted; subjects were called in the evening for the application of Patch-It® on the soles of both feet and were retained overnight at the site. The outcome measures were recorded the following day (day 1), followed by dispensing of Patch-It® for the next 12 days. Subjects were called again on the evening of day 13 for application of Patch-It® with an overnight stay, followed by day 14 assessments. During the study span, subjects were not allowed to consume any medications for the symptoms studied. Medicines such as vasodilators, nifedipine, calcium channel blockers, nitrates, nitroglycerin patch, pentoxifylline, complamina retard (xanthinolnicotinate), etc. were prohibited during the study. Medications for other complaints, which the subject had been using prior to his/her participation in the study, were permitted without any alteration in prescribed dosage as per investigator's approval. Regular monitoring at the investigational site was conducted to ensure validity of data quality and compliance to study protocol and good clinical research practice. Compliance was verified at day 14, by counting the number of used or unused patches. AEs were recorded if and when they occurred. Pulse rate, respiratory rate and blood pressure were measured at each visit. No biochemical tests were performed as ingredients of Patch-It® have a long history of usage without any serious side effect.

Intervention: Patch-It® is a herbo-mineral patch and intended for overnight application to soles of the feet to improve blood circulation and reduce swelling in lower limbs. The patches are 4 x 3 inches in dimension with an adhesive surface protected by a detachable liner paper. One patch was applied to the sole of each foot at bedtime by pressing it firmly against the arches (as shown in **Figure 2**), which was left on for at least 7 hours and removed in the morning. Unlike transdermal patches, which are designed for drug delivery across the skin, Patch-It® has a barrier in the form of a non-woven fabric that prevents direct contact between the skin and ingredients.

Outcome measures:All outcome measures were selected based on the expected information to be acquired from the respective assessments to allow justified correlation of results with plausible mechanisms of action. These measures ($TcPO_2$, RPI and ABI) were assessed on day 0, day 1 and day 14.

Transcutaneous oxygen pressure ($TcPO_2$) is used as a diagnostic tool in a number of clinical applications such as diagnosis of PAD, ischemia, diabetic foot syndrome, prediction of wound healing, predicting amputation, suggesting amputation level and amputation level healing prognosis. It is a direct indication of the microvascular function and a useful tool for non-invasive monitoring of the oxygen tension in the skin, which reflects the amount of oxygen that diffuses from the capillaries through the epidermis. Technically, a Clark-type electrode is placed on the skin and heated. The heat from the electrode dilates the underlying capillaries increases the local perfusion and opens the pores of the skin. O_2 diffuses through the skin to the electrode where pO_2 generates a current which is measured in terms of $TcPO_2$.[15,16]In the current study, $TcPO_2$ levels were assessed with the help of PeriFlux scan 5000 (using thermostatic probe 457) combined with a probe holder (PF 450) (Perimed AB, Sweden. Electrode was placed at the dorsum of right and left foot, dorsum of the left hand (wrist), chest (subclavicular region) and medial distal thigh (lower limb with low ABI readings),

ensuring that the electrode was not directly over any major veins. All assessments were done at an ambient temperature (21-23°C) with the subject resting in supine position and in stabilized state. The instrument was switched on and allowed to warm up for 15 minutes. Body hair was removed and area was cleaned before application of probes. Smoking and consumption of caffeine or other stimulants were strictly prohibited before $TcPO_2$ assessments.

The Regional Perfusion Index (RPI) is used to eliminate the cardio-respiratory influence and simplify the $TcPO_2$ interpretation. Limb $TcPO_2$ is normalized to chest values to get the RPI value as a ratio of $TcPO_2$ (limb) to $TcPO_2$ (chest). Normal RPI is around 0.41. RPI < 0.4 indicates poor blood circulation whereas RPI > 0.6 predicts excellent blood flow and better wound healing.[17] This test is easy to perform, reproducible, non-invasive, highly specific and directly reflective of the underlying vascular pathophysiology.[18] In this study, RPI was calculated by taking the ratio between the TcPO2 at the following specified locations: Dorsum of right foot v/s chest; Dorsum of left foot v/s chest; Medial distal thigh v/s chest.

The ankle-brachial index (ABI) is the ratio of the systolic blood pressure (SBP) measured at the ankle to that measured at the brachial artery. This index is used for the noninvasive diagnosis of lower-extremity peripheral artery disease (PAD). The most commonly used ABI threshold for the detection of PAD is ≥ 0.9.[19,20]A decrease in ABI is a prominent marker of lower extremity PAD. ABI was measured by Doppler method in the current study.

Statistical analysis:Values obtained for all outcome parameters were summarized as mean ± standard deviation and mean changes in $TcPO_2$, RPI and ABI from day 0 to day 1 and day 14 were analyzed using student's paired t-test. All statistical tests were performed at 95% confidence interval and the level of significance was set as ≤ 0.05.

III. RUSULTS

The details of the subjects screened, recruited and those completing the study are represented in **Table 1**. Subjects were assigned to Patch-It® [N=7] for a period of 14 days. Out of seven recruited subjects, one subject was lost to follow up at day 14 visit and six subjects completed the study. Last observation for this subject was carried forward during analysis.

Baseline characteristics: The total number of subjects (N=7) comprised of 4 males and 3 females. The lower extremity with stenosis was right for 2 (29%) subjects and left for 5 (71%) subjects. The other demographic parameters are listed in Table 1. Mean arterial stenosis for the subjects included in the study was 21.43% ± 6.27% and PSV ratio of 0.55 ± 0.12. None of the recruited subjects had abnormalities in the pathological screening parameters. None of the subjects had any wound, ulcer or skin discoloration.

Transcutaneous pressure of oxygen: The $TcPO_2$ values for all the measurement sites (Chest, Thigh, Right foot and Left foot) are presented in **Table 2** and **Figure 3**. Compared to day 0, thigh $TcPO_2$ increased by 14% and 22% on day 1 and day 14, respectively and left foot $TcPO_2$ was decreased by 8% on day 1 and found to be insignificantly increased by 3% on day 14. A reduction was observed in the $TcPO_2$ values for chest.

Regional perfusion index: The RPI values were derived from the $TcPO_2$ data and are presented in **Table 3**. An increase of 27% and 51% was observed in thigh RPI at day 1 and day 14, respectively. However, there was a reduction in the right foot RPI (10% on day 1 and 9% on day 14). In case of left foot RPI, a decrease of 4% (day 1) and increase of 33% (day 14) was observed. All these changes were statistically insignificant.

Ankle Brachial Index: ABI values were analyzed for the lower limb, with and without atherosclerotic changes in the femoral artery. Based on the ABI values, limbs were divided into two groups: the lower extremity with stenosis (ABI ≤ 0.9) and without stenosis (ABI > 0.9). For one subject, the ABI values for both lower extremities were 0.9; hence both were evaluated as limbs with stenosis. Thus, the number of limbs with stenosis was 8 and without stenosis were 6. There was an increase of 5% and 12% ($p < 0.001$) in the ABI values for lower extremity with stenosis and 6% each ($p = 0.033, 0.002$) for the lower extremity without stenosis at day 1 and day 14, respectively. (**Table 3**)

Safety: No adverse events or serious adverse events were reported in the study. Vital function measures did not reveal any unfavorable changes during the course of the study.

IV. DISCUSSION

This study was undertaken to explore the mechanism of action of Patch-It®. $TcPO_2$ is a gold standard to define the oxygenation and blood supply to the limb and has been widely used in therapeutics to assess the limb capacity to predict wound healing and to decide the level of amputation, if needed. In contrast to pressure and volume assessments, $TcPO_2$ maps the actual oxygen supply available for the skin tissue cells and has been advocated as a measurement of tissue perfusion in PAD. In other words, $TcPO_2$ is an important outcome measure to analyze extent of microcirculation in PAD. The changes seen in $TcPO_2$ measurements at all the measurement

sites (chest, thigh and feet) were highly variable, due to the fact that the range for $TcPO_2$ values is wide.[21] However, an increase was seen in thigh $TcPO_2$ and RPI. Similarly, an increase was seen in the $TcPO_2$ as well as RPI values for left foot at day 14, which was the limb with stenosis for 71% of the subjects in the study. RPI is a standard measure of tissue oxygenation and an improvement in RPI in the left foot (limb with stenosis) indicates that there is some improvement in tissue perfusion and hence in limb's microcirculation.[22] Although statistical significance was not achieved, this indicates that the oxygenation improved in the limb with stenosis and statistical insignificance could be attributed to the factors such as small sample size, wide range of values and short duration of study.

Commonly used threshold of ABI for the diagnosis of PAD is ≤ 0.9. There was a statistically significant increase seen in ABI for the lower extremity without stenosis at day 1 ($p=0.03$) and day 14 ($p = 0.002$). For the lower extremity with stenosis, the increase acquired statistical significance on day 1 ($p = 0.044$) as well as day 14 ($p <0.001$) as compared to baseline. Also, the ABI values remain > 0.9 which indicate relief offered by Patch-It® to alleviate PAD symptoms, probably due to improvement in the blood circulation.

As mentioned in introduction, the core ingredients of this intervention individually contribute towards cumulative beneficial effect. Mandarin wood vinegar and Tourmaline improve the microcirculation plausibly by increasing motility of body fluids in exposed area, thus affecting the capillary permeability and green tea offers skin protective effect and probably helps to alleviate the inflammatory and aching symptoms in mild PAD patients as evident from the derived data.

V. CONCLUSION

The current study was an attempt to analyze possible mechanisms by which Patch-It® affects the blood circulation and helps in alleviating swelling and ache in lower limbs. From the results, a trend can be observed suggesting that Patch-It® enhances the blood circulation by improvement in limb microcirculation, through a direct or indirect effect on capillary permeability. Due to the limitation of small number of subjects, there is a need for further extensive study with greater attention paid to methodological quality and thorough evaluation of our findings from this study.

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Tables and Figures attached at the end of the document.

Table 1. Baseline Characteristics

Variables	N=7 (Mean ± SD)
Age (Years)	46.00 ± 6.51
Weight (Kg)	73.97 ± 14.83
BMI (Kg/m^2)	26.40 ± 3.99
% Stenosis	21.43 ± 6.27
PSV ratio	0.55 ± 0.12
Male, n (%)	4 (57.14)
Female, n (%)	3 (42.86)
Right Foot with stenosis [n (%)]	2 (28.57)
Left Foot with stenosis [n (%)]	5 (71.43)

Abbreviations:SD: Standard deviation; **BMI**: Body mass index; **PSV**: Peak systolic velocity.

Table 2. Effect of Patch-It® on $TcPO_2$

Variables (n = 7)	Day 0 (mm Hg)	Day 1 (mm Hg)	Day 14 (mm Hg)	*$D_1\_D_0$ (%)	*$D_{14}\_D_0$ (%)
$TcPO_2$–C	54.00 ± 12.57	53.86 ± 20.92	45.00 ± 19.05	-0.25(*p=0.98*)	-9.00(*p=0.05*)
$TcPO_2$ – T	49.14 ± 17.62	55.86 ± 17.43	59.71 ± 27.84	13.65(*p=0.34*)	21.50(*p=0.44*)
$TcPO_2$ – RF	60.29 ± 16.90	49.71 ± 07.13	40.57 ± 13.75	-17.53(*p=0.12*)	-32.69(*p=0.01*)
$TcPO_2$ – LF	48.00 ± 15.07	44.29 ± 13.30	49.57 ± 43.39	-7.72(*p=0.54*)	3.27(*p=0.92*)

Abbreviations: $TcPO_2$–C: Transcutaneous oxygen pressure of Chest; $TcPO_2$–T: Transcutaneous oxygen pressure of Thigh (index limb); $TcPO_2$–RF: Transcutaneous oxygen pressure of Right Foot; $TcPO_2$–LF: Transcutaneous oxygen pressure of Left Foot. $D_1\_D_0$: Change from day zero to day one; $D_{14}\_D_0$: Change from day zero to day 14. **p* value indicates significance of the results obtained compared to baseline.

Table 3. Effect of Patch-It® on Secondary Efficacy Variables

Variables	Day 0	Day 1	Day 14	*$D_1\_D_0$ (%)	*$D_{14}\_D_0$ (%)
RPI – T: C (n = 7)	0.92 ± 0.30	1.16 ± 0.49	1.39 ± 0.53	27.17 (*p=0.31*)	51.08 (*p=0.14*)
RPI – RF: C (n = 7)	1.17 ± 0.42	1.04 ± 0.44	1.04 ± 0.51	-10.25 (*p=0.34*)	-9.49 (*p=0.44*)
RPI – LF: C (n = 7)	0.89 ± 0.23	0.86 ± 0.19	1.18 ± 0.99	-3.78 (*p=0.75*)	32.58 (*p=0.43*)
ABI – Stenosis (n = 8)	0.94 ± 0.08	0.97 ± 0.08	1.05 ± 0.10	4.72 (*p=0.044*)	11.95 (*p<0.001*)
ABI – Normal (n = 6)	0.98 ± 0.10	1.04 ± 0.08	1.05 ± 0.09	5.88 (*p=0.033*)	5.88 (*p=0.002*)

Abbreviations: RPI–T:C: Regional perfusion index of Thigh vs Chest; RPI–RF:C: Regional perfusion index of Right Foot vs Chest; RPI–LF: C: Regional perfusion index of Left Foot vs Chest; ABI–Stenosis: Ankle brachial index of limb with stenosis; ABI–Normal: Ankle brachial index of limb without stenosis. $D_1\_D_0$: Change from day zero to day one; $D_{14}\_D_0$: Change from day zero to day 14. *****p* value indicates significance of the results obtained compared to baseline.

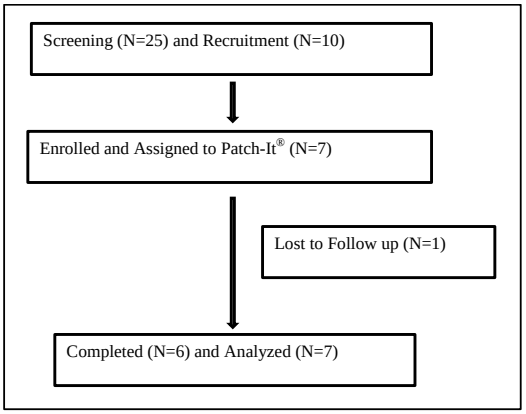

Figure 1.Disposition of Subjects.

Figure 2. Patch-It® before application (a), applied on feet soles (b) and Patch-It® after application (c).

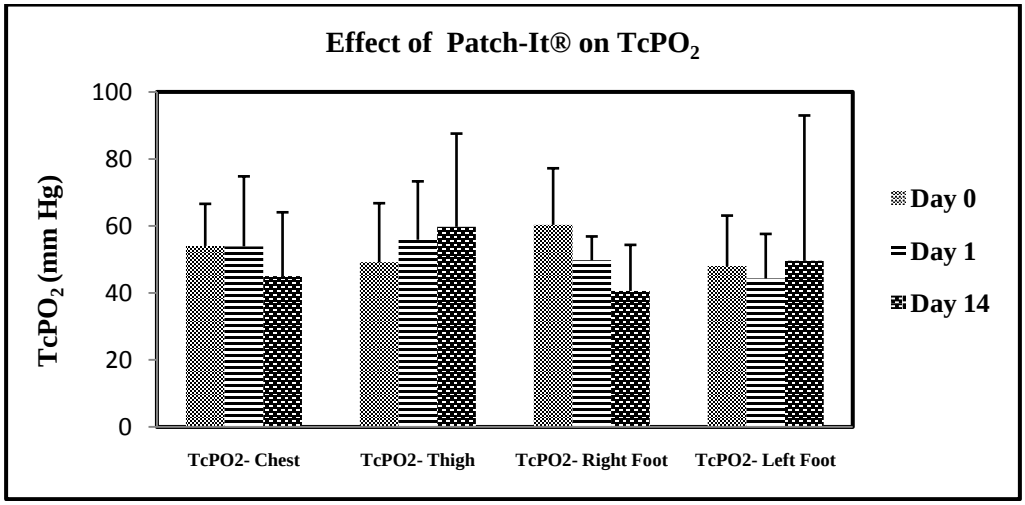

Figure 3. Effect of Patch-It® on $TcPO_2$