

Is Patch It[®] better than placebo in alleviating swelling and ache in the lower legs and feet? A randomized, placebo-controlled, double blind, crossover, sequential trial

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Background: Existing therapeutic measures for swelling, aching and discomfort in the lower limbs, which include compression stockings and leg elevation, are difficult to use and inconvenient. Patch It[®], a proprietary herbomineral patch is an easy-to-use alternative therapy. This trial was conducted to compare its efficacy against that of a placebo in swollen and aching lower legs and feet.

Methods: This randomized, placebo-controlled, double blind, crossover, sequential trial was conducted in the private clinics of physicians. A total of 100 patients (24 men and 76 women), aged 25 to 60 years, with recurring swelling in the feet and (optionally) up to two more related complaints, having an average visual analog score (VAS) of at least 60 (scale 0–100) for each complaint were recruited into the study. Patches (active or placebo) were applied to both soles overnight for 8 weeks: 4 consecutive weeks each with active or placebo in randomized sequence. Outcome measures included the average VAS score (baseline to week 4, and week 5 to week 8), preference for either patch (difference of >5 mm in average VAS score reduction), ankle figure-of-eight measures, investigator's global assessment (good, fair, poor), patient's willingness to continue using the patch after the trial (yes, no), and adverse events.

Results: Out of 100 patients, 86 completed the trial, while ten were excluded for noncompliance, three withdrew, and one was lost to follow-up. The active placebo boundary of the sequential chart was crossed when 82 patients completed the trial. Active patch was also superior to placebo patch by mean reductions in average VAS scores (13.14 versus 9.6, $P = 0.02$), mean reduction in figure-of-eight ankle measurements (1.21 cm versus 0.79 cm, $P = 0.003$), investigator's global assessment ($P < 0.01$), and by proportion of patients willing to continue using the patch after the trial ($P < 0.01$). Ten percent of patients experienced localized itching with each patch, but this did not require interruption of treatment.

Conclusion: Patch It had greater efficacy than the placebo in alleviating recurring swelling and aching in the legs and feet, and is well tolerated.

Keywords: ankle swelling, leg ache, dermal patch, reflexology, sequential analysis, figure-of-eight

Background

Swelling and discomfort in the lower legs and feet verbalized by patients as aching, tightness, heaviness, and fullness affecting both legs, is not uncommon. When no systemic or local condition is found to explain these complaints, sluggishness of local circulation is often suspected as a possible cause, although this is difficult to prove or demonstrate. The partial or temporary relief offered by raising the lower extremities, or by wearing compression stockings, is sometimes the only available treatment

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for this condition. However, leg elevation is uncomfortable for prolonged periods of time, as well as while sleeping. Besides, in some geriatric patients, edema can remain despite leg elevation.^{1,2} Similarly, compression stockings can be uncomfortable due to the heat generated, and the difficulty in keeping them up. Besides this, changes in leg girth can change the amount of pressure exerted by the stockings, resulting in a significant reduction in local blood flow, leading to increased risk of ischemia and ulceration.^{3,4}

Although these measures provide some relief, they are not convenient to all patients at all times; hence, therapeutic alternatives are needed.

One such alternative is Patch It® (NutriWorks Ltd, Hong Kong), a herbomineral patch applied to the soles of the feet overnight. It is thought to stimulate reflexogenic zones in the feet while having a beneficial effect on blood circulation. While its mechanism remains to be studied, there is a need to document its effect in comparison to a placebo patch. This was the objective in undertaking the present trial. This article evaluates the efficacy of Patch It in alleviating recurring swelling and aching of the legs and feet versus placebo as documented by subjective as well as objective measures.

Methods

The study followed the Declaration of Helsinki. Its plan was reviewed and approved by the Inter-System Biomedica Ethics Committee (Medical Research Centre, Kasturba Health Society, Mumbai, India); good clinical research practice (GCP) was followed during its conduct, and written informed consent was obtained from all patients. The trial was carried out in the private clinics of six physicians comprising family physicians as well as specialists.

Patients

Male and female patients aged 25 to 60 years with bilateral swelling in the lower legs or feet, which decreased upon lying down or after elevation of the legs, and with up to two other related complaints – voiced as and not limited to aching, tightness, heaviness, fullness, weariness, burning sensation, and cramps – were enrolled in the trial if physical examination and laboratory investigations did not reveal any systemic or local pathological cause of symptoms, thereby indicating a possibility of subclinical venous incompetence. Other requirements were: duration of at least 3 weeks, visual analog score (VAS) intensity of at least 60 for each complaint, and willingness to give written informed consent.

In addition to clinical assessments, laboratory tests including complete blood count (CBC), erythrocyte

sedimentation rate (ESR), serum glutamic pyruvic transaminase (SGPT), serum creatinine, serum proteins, urine routine and microscopy, bleeding time (BT), clotting time (CT), prothrombin time (PT), electrocardiogram (ECG), and urine for pregnancy test (UPT) were performed to screen patients' eligibility for participation in this study.

As the test treatment is only palliative, patients excluded were those who had a history of intermittent claudication, unilateral swelling in the leg, or an absence in swelling decrease in the feet even after leg elevation, and those with lower limb pathologies including varicose veins, diminished arterial pulsations, skin eruptions, and ulcerations. Patients with cardiac, hepatic, renal, hemopoietic, endocrinal or any other major systemic disorders, jugular venous pressure above 4 cm, coagulation disorders and history of (or predisposition to) deep vein thrombosis (score of >3 by Wells' criteria)⁵ were also excluded; as were patients on diuretics, pregnant or lactating women, those who had recently participated in another clinical trial, and those who had a history of hypersensitivity to any of the ingredients in the patch.

Study design

A randomized, placebo-controlled, double-blind, crossover, sequential design was selected with a 4-week period of active patch, followed by a 4-week period of placebo patch, or vice versa. No washout was provided in between treatment sequences, primarily as transdermal absorption and subsequent carry-over effects were not expected to occur, given the design of the patch. Accordingly, outcome measures were recorded on day 1 (at baseline visit), day 28, and day 56 (but not on day 29), as it was expected that by day 56, the effect of the first patch would have worn off and the effect of the second patch would plateau.

Randomization and blinding

Trial supplies were labeled and packaged by patient ID and visit week in active-placebo or placebo-active sequences, with each identical packet containing patches sufficient for 14 days based on the master randomization chart generated by random drawing of chits by a research coordinator not involved in the trial. Patients, investigators, and study coordinators were blinded to the investigational product allocations for each period of the trial. The labeling ensured that if unblinding became necessary for any patient, the investigator would only find out what patch the patient was on in that particular period, while other patients' blinding was maintained.

The active and the placebo patches were physically indistinguishable. Patch It is hygroscopic, and turns brownish in

color after use. Hence, the pouch containing the powdered ingredients in both the active and placebo patches was manufactured from non-woven fabric dyed black to mask colour changes, and ensure continued blinding after patch removal.

Concomitant medications

While involved in the trial, patients were not allowed to consume any medications for the symptoms studied. Medications for other complaints which the patient had been using prior to their participation in the study were permitted. No alteration in the dosage of such medications was to occur without the approval of the investigator.

Interventions

The intervention – Patch It – used in this trial contains three ingredients. The primary ingredient is pyroligneous acid powder from wood cuttings of the mandarin orange (*Citrus reticulata* Blanco) tree. The two other ingredients are Tourmaline (black Brazilian type) and green tea (*Camellia sinensis* [L.] Kuntze) powder.

Both the active and the placebo patches were 4" × 3" in size, with the adhesive surface protected by a detachable film. One patch was applied to the sole of each foot at bedtime by pressing it firmly against the arches, which was left on for at least 7 hours, and removed in the morning. This regimen was determined with reference to traditional Chinese medicine (TCM) (and is based on the TCM concept of a body clock where liver detoxification function occurs best between 1am and 3am),⁶ anecdotal feedback from consumers and a previously unpublished clinical trial testing the effect of the product on lower back pain. The duration of 7 hours is prescribed as most people sleep between 6–8 hours.

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 the ingredients. This mechanical barrier is of sufficient density to prevent leakage, but is air permeable. Given this layer, transdermal absorption, if any, of the ingredients of the patch, is negligible.

The placebo patches used in this trial were identically manufactured patches filled with organic rye flour which has a texture similar to that of the powder mix in the active patch.

Treatment compliance was verified at each fortnightly visit by counting the number of patches returned unused. Patients were expected to have a minimum usage of 85% of total patches supplied; failing this, patients were withdrawn from the study.

Outcome measures

Outcome measures included average VAS score, preference for either of the patches, reduction in ankle figure-of-eight (Fo8) measures, the investigator's global assessment, the patient's willingness to continue patch use after the trial, and adverse events.

Average VAS score

VAS scores for each complaint, and their average, on day 1 (baseline), day 28 (last day of first treatment), and day 56 (last day of second treatment) were recorded as reflective scores for the preceding 1 week at each time point. Reductions in average VAS scores were calculated as (day 28 – day 1) for first treatment, and (day 56 – day 1) for second treatment.

VAS scores were averaged for patients with more than one symptom, to ensure that changes in scores posttreatment were comparable in the two groups, given that the total number and nature of complaints for each patient were different. A similar approach was adopted by Mönnikes and colleagues in their study for assessing gastrointestinal symptom scores.⁷ The averaged VAS scores thus provided a global summing up of the performance of the patches.

Patch preference

A change of 5 mm on a VAS for leg symptoms was defined as a minimal clinically important difference (MCID) between the two patches, akin to Haselen and Fisher in their study.⁸ If the reduction in average VAS score(s) on one treatment was five or more units greater than that for the other treatment, a preference was recorded for the former; otherwise the responses were considered not materially different (tied pair). Hence, in this study, patient preference was determined by comparing the averaged VAS score reductions on the two treatments, and was defined as a reduction of greater than 5 mm by one treatment over the other. The preferences were plotted on the sequential chart. As the data from six sites were pooled, the order of patients was predefined by sorting them first by date of enrollment, and then by initials within the date, in ascending order.

Fo8 measurement

Esterson's technique was used as modified by Petersen and colleagues to measure the extent of ankle swelling in this study.^{9,10} The Fo8 method was selected for the measurement of ankle edema instead of water volumetry as the latter (though more accurate) is inconvenient and might not be readily available with most practising physicians. The Fo8 method is easy to perform, does not require special

apparatus for measuring water displacement, and has been determined as a reliable and valid indirect method of measuring ankle edema because it most closely resembles water volumetry.^{11–13} This measurement was made on days 1, 28, and 56. A single study coordinator took three readings of each patient at each visit, and documented the average of these readings in order to circumvent intra-rater variability.

Investigator's global assessment

The investigator assessed each patient's response to the respective treatment on days 28 and 56 as: good, if both VAS score and Fo8 measures were reduced; fair, if either of these were reduced; poor, if neither of these were reduced.

Patient's willingness to continue treatment after trial

This was recorded as "yes" or "no" on days 28 and 56 for respective treatments.

Adverse events

Clinical adverse events were recorded if and when they occurred, with nature, intensity, and possible relation to treatment. Local itching, redness, and burning were specially looked for. Pulse rate, respiratory rate, and blood pressure were measured at each visit. No biochemical tests were performed, as the ingredients of the active patch have a long history of usage, and were not expected to be absorbed or produce any systemic effects.

Data analysis

Primary analysis

Wald's sequential analysis (True Epistat, v5.3, Epistat Services, Richardson, TX), was used to analyze the VAS scores of the complaints, which requires paired responses (eg, from crossover of treatments) to classify the result of each pair as: active > placebo, placebo > active, or active = placebo (a tie). The criterion to determine this was the reduction in the average VAS score of a patient's complaints at the end of each of the treatment periods (baseline, week 4 versus baseline, week 8). A difference of <5 mm was taken as a "tie"; a difference of 5 mm or more indicated a preference for the patch that caused the greater reduction. The program plotted the results sequentially, as they accumulated, on a chart (Figure 3) with boundaries for active > placebo, placebo > active, and no difference. To generate these boundaries, the placebo patch response rate was taken as 40%,^{14–16} the active patch response rate of 60% or more as a clinically worthwhile improvement, a significance level of 5%, and a power of 90%.

Secondary analyses

These included comparison of the mean VAS score and mean Fo8 reductions by paired and two sample *t*-test, and comparison of the investigator's global assessments, and the patient's global responses by McNemar's paired Chi-square test.

Results

Patient disposition

Of a total of 100 patients who enrolled, 86 completed the study while ten were withdrawn because of inadequate (<85%) compliance to the treatment, three were unwilling to continue and one was lost to follow-up (Figure 1). By the time the sequential plot crossed the active > placebo boundary, 82 patients had either completed the trial or were discontinued; the remaining 18 were already enrolled, and therefore allowed to complete the study.

Baseline status

All patients in the study were Indian (Asian) with more female patients compared to males, at a ratio of 3:1. The baseline demographic and clinical characteristics of both the groups – those on active patch in the first period and those on placebo patch in the first period – are shown in Table 1. Figure 2 displays the frequency of different complaints of the trial patients.

Primary efficacy analysis

Of the 86 paired results, 49 were not tied and, as shown in Figure 3, the program plotted these as a stroke upwards and to the right for active > placebo and as a stroke to the right for placebo > active. The upper decision boundary was crossed at the 39th result, indicating that the active patch was superior to placebo patch.

As a washout period between the two treatment periods was not provided, the average VAS scores of the 49 patients on days 1, 28, and 56 were analyzed by ANOVA to examine any sequence effect, which was absent ($F_{1,47} = 0.01$, $P = 0.93$). However, the difference among days was significant ($F_{2,96} = 54.64$, $P = 0.00$), indicating that the preferences recorded for patients were based on the differences in scores on days 1, 28, and 56.

Secondary efficacy analysis

VAS score reduction

For all patients completing the trial ($N = 86$), the mean (SEM) reduction in VAS score was: 13.13 (1.54) mm with Patch It, and 9.6 (1.12) mm with placebo, the difference being 3.53 (1.5) mm and significant ($P = 0.02$).

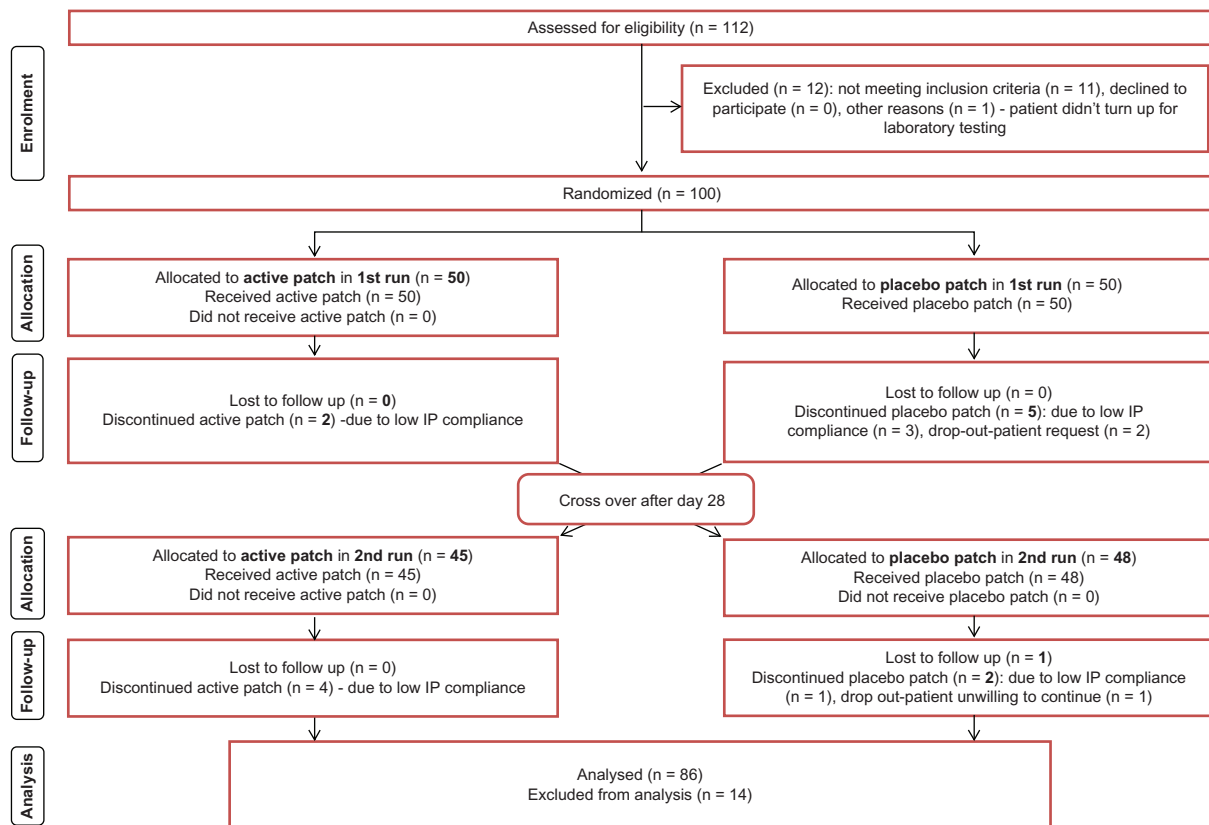


Figure 1 Patient Disposition.

Note: Of the 100 patients who were recruited, 45 patients from the active-placebo sequence and 41 patients from the placebo-active sequence completed the study.

Abbreviation: IP, investigational product.

Fo8 measure reduction

Likewise, the mean (SEM) reduction in Fo8 measure was: 1.21 (0.18) cm for Patch It, and 0.79 (0.15) cm for placebo, the difference of 0.42 (0.13) cm being significant ($P = 0.003$).

Investigator's global assessment

The results are shown in Table 2. Out of 86 patients, 25 showed no difference in their response to the two patches; 46 showed a better response to the active patch than to the placebo patch; and 15 had a better response to the placebo patch than to the active patch ($\chi^2 = 20.1$,

$P = 0.000016$). A good or fair response was seen in 74 (86%) patients on the active patch, and in 45 (52%) patients on placebo patch.

Patient's willingness to continue treatment

Out of 86 patients who completed the trial, four were unwilling to continue either treatment, and 47 were willing to continue both treatments, but 35 agreed to continue only one of the two treatments (Table 3). Of these 35 patients, four opted for placebo and 31 for the active patch, the difference being highly significant ($\chi^2 = 19.3$, $P = 0.00001$). Thus, across both study runs, 78 patients (91%) were willing to continue the active patch, and 51 (59%) were willing to continue the placebo patch.

Safety analysis

For safety, data of all patients who had used at least one patch, and who had at least one follow-up visit were analyzed. No serious adverse events (SAE) occurred. A total of 30 adverse events were recorded in 25 patients (Table 4). All were mild in nature and did not lead to any withdrawals or dropouts from the study. Vital functions also did not reveal any unfavorable changes during treatment.

Table 1 Baseline comparison of the sequence groups

Variable	Sequence active-placebo N = 50	Sequence placebo-active N = 50
Sex		
M	13 (26)	11 (22)
F	37 (74)	39 (78)
Age (yrs)	47.24 (1.22)	46.84 (1.36)
Weight (kg)	71.2 (2.25)	69.94 (1.76)
Avg VAS	67.84 (0.80)	67.95 (0.69)
Fo8 (cm)	52.57 (0.96)	51.49 (0.74)

Note: Values are n (%) or mean (SEM).

Abbreviations: SEM, standard error of the mean; VAS, visual analog score.

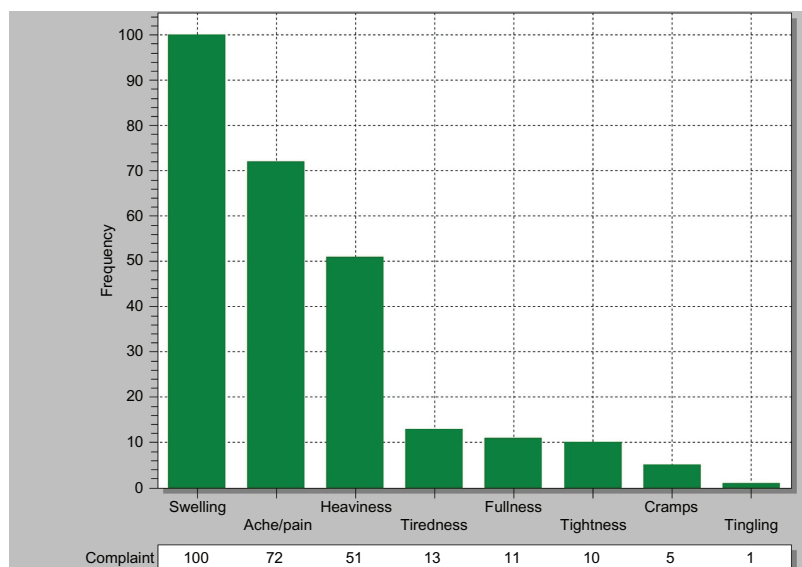


Figure 2 Chart showing frequency of complaints in the study sample.

Note: Swelling was reported by 100%, ache by 72%, and heaviness by 51%.

Discussion

Sequential analysis, a method developed by Wald during the Second World War,¹⁷ is based on a continual analysis of preferences by sequential probability ratios. The preferences may be generated by comparing two treatments either within patients (using a crossover design) or between patients (using matched pairs). Variations within patients are bound to be fewer than those between patients. Hence, a crossover study

design was selected, which used each patient as his/her own control. Further, Wald's sequential method for primary analysis of the results was chosen for two reasons: (1) it would allow the trial to be closed as soon as a decision point was reached, or when it was concluded that reaching a decision point was unlikely;¹⁸ and (2) based on the average VAS scores reductions of the two patches, it required categorization of each patient's response as active > placebo, placebo > active

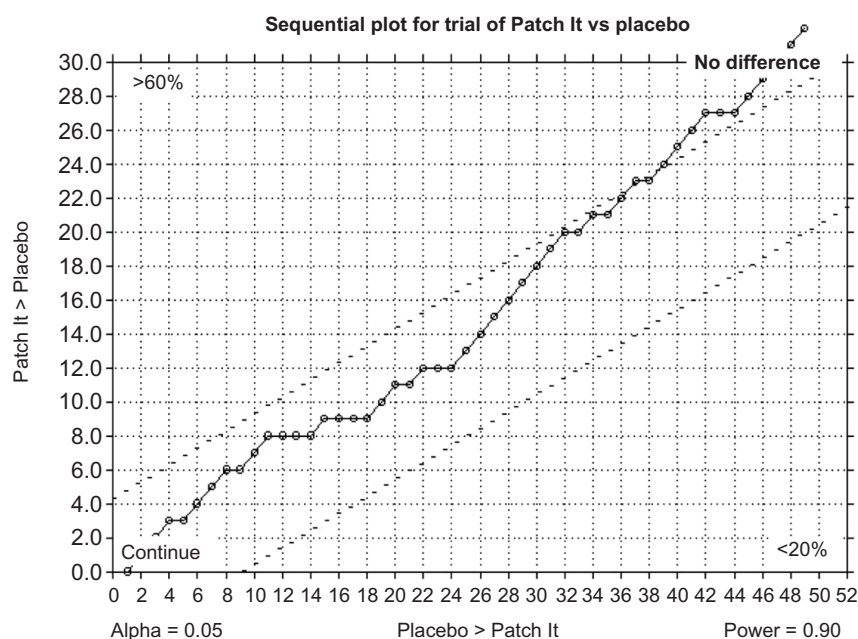


Figure 3 Sequential analysis chart showing preference for active over placebo patch.

Note: Chart shows the various preferences plotted during the study. The line representing the preference for active patch was crossed when the 39th observation was plotted, signaling the superiority of the active patch (Patch It®) over the placebo patch.

Table 2 Investigator's grading of patients' global response to treatment

Response to Patch It	Response to placebo			Total
	Good	Fair	Poor	
Good	18	10	26	54
Fair	8	2	10	20
Poor	6	1	5	12
Total	32	13	41	86

Notes: Using True Epistat 5.3, McNemar's paired chi-square = 20.06 ($P = 0.000016$). In the table above, the grey-shaded diagonal cells represent patients with equal grade for both patches ($N = 25$); the cells above and to the right represent better grades for active patch than for placebo ($N = 46$); and the cells below and to the left represent better grades for placebo than for active patch ($N = 15$). Upon analysis of this data by McNemar's paired chi-square test, efficacy ranking for the active patch was found to be better for significantly more ($P = 0.000016$) patients than it was for the placebo patch.

or a tie, thus providing a realistic and global summing up of the relative performance of the patches.

The study needed only 39 preferences (82 patients) to cross the decision boundary. As 18 additional patients were already in the trial, they were permitted to complete it for secondary analyses. Of the 39 patients in whom a decisive result occurred for sequential plotting, 24 (62%) showed active > placebo whereas 15 (38%) showed placebo > active. These figures are very close to the assumptions of placebo patch response rate of 40% and active patch response rate of 60%, which were used in drawing the sequential analysis plan.

For VAS scores, the patient's top three complaints were used rather than a fixed list of symptoms. The reason was that perception of symptoms is likely to vary from patient to patient, depending on their lifestyles and activities. The average VAS scores of these complaints represented a summary measure of the patient's discomfort. Focusing on the three most disturbing complaints rather than using an instrument containing a fixed list of items, some of which might not be relevant to the patient, was a patient-centric approach consistent with day-to-day clinical practice.

It was thought this would be practical for routine use by clinicians for extending the observations of this study for their

Table 3 Patient's opinion on treatment continuation

	Patient opinion-placebo		Total
	No	Yes	
Patient opinion-active			
No	4	4	8
Yes	31	47	78
Total	35	51	86

Notes: Using True Epistat 5.3, McNemar's paired chi-square = 19.31 ($P = 0.00001$). Patient opinion was yes-to-t-and no-to-p in many more patients than yes-to-p-and no-to-t. The odds ratio favoring t over p was 7.75 (95% CI, 2.74 to 21.95). As the CI does not include 1, the odds favor t.

Abbreviations: p, placebo; t, active patch; CI, confidence interval.

Table 4 Incidence of adverse events: N (%)

Description	Patch It N = 100	Placebo N = 100
Itching with or without burning at the site of patch application	10 (10.5)	10 (10.2)
Redness at the site of patch application	0 (0.0)	3 (3.1)
Mild abrasion at the site of patch application	1 (1.0)	2 (2.0)
Others (eg, pain in thigh, fever, cough, cold etc)	2 (2.1)	2 (2.0)

Notes: A total of 30 adverse events were recorded in 25 patients. Out of the 30 AEs, 13 AEs were recorded for the active patch while 17 AEs were documented against use of placebo patch. An equal incidence in itching (10) and other unrelated complaints (2) were recorded for both the active as well as placebo patches. There were no incidents of redness at the site of application of the active patch while 3 patients experienced this AE while on placebo. Two patients on the placebo patch and one patient on the active patch experienced mild abrasions at the site of patch application.

Abbreviation: AE, adverse event.

patients who present with similar complaints. All patients in this study had swelling of the feet (not attributable to any detectable local or systemic disorder and that subsided or decreased upon leg elevation, warranting a possible clinical diagnosis of venous incompetence of a subclinical intensity) as a common complaint when they entered this study, while 72% also had aching legs and/or feet, and 51% complained of heaviness in the legs and/or feet. Hence, Patch It may be more useful to patients with these specific complaints.

Reductions in VAS scores and Fo8 measures by the active patch for all 86 patients were significant as compared to those by the placebo patch at the end of the study.

The investigator's global assessment found a good response in 32 (37.2%) patients after using the placebo patch. Although in 18 (more than half) of these patients, a good response was found after using the active patch, a strong placebo effect, overriding that of the active patch, was seen in the remaining 14 patients. Similarly, the proportion of patients who were willing to continue using the placebo patch after the trial (59%) versus 91% of patients willing to continue with the active patch, underscores the scope of the placebo effect and its contribution to the efficacy of various modalities of treatment, especially for relieving subjective complaints. This corroborates information found in literature on the subject, including Beecher's 1955 paper which showed a placebo response ranging from 15% to 58% in various conditions, and averaging at 35%.¹⁹⁻²¹

The secondary analyses based on mean VAS reductions of the two treatments, Fo8 measurements of the ankle, global assessment by physicians, and patients' willingness to continue the treatment after trial, yielded results that were concordant with those of primary analysis: that the active

patch was significantly more effective than the placebo patch. Such consistency across the different assessment methods is reassuring for the overall tenability of the conclusion about efficacy.

So far as local tolerability of the patches is concerned, approximately 10% of the patients experienced itchy soles on either treatment, but in no case was its severity sufficient to cause noncompliance or discontinuation of treatment. The comparable incidence of this adverse event across both treatments suggests that it was probably due to some ingredient of the adhesive material rather than any of the active ingredients themselves.²²

This study shows that Patch It alleviates swelling and other associated symptoms in the legs and feet. Patch It is believed to act partly via reflexology, a science that currently lacks clear evidence for its claimed effects, but which has nevertheless demonstrated reduction in symptoms of pain and oedema in at least two studies.^{23,24} However, the sample sizes of these studies were small, and so the blinding of participants and clinicians was not possible. How Patch It brings about its effects is yet to be established, and the scope of this trial did not include a study of its mechanism of action.

A possible limitation of this study is the lack of a washout period. The design of the patch, based on reflexology, eliminated the possibility of transdermal absorption, thereby precluding the need for washout between the study runs. Besides, lack of data on the pharmacodynamics, pharmacokinetics, the duration of action and the persistence of effects of the active ingredients (given the mode of administration), also diminished the possibility of making any realistic assumptions about an appropriate washout period. In the event, the absence of a washout period minimized the possibility of dropouts in the study.

Another limitation in the study design was the lack of the determination of interrater reliability for the Fo8 measurement of the ankle joint. However, Mawdsley and colleagues have shown that measurements of the ankle joint by a single rater performing the Fo8 method were highly correlated to measurements taken by another tester, using a foot volumeter.¹² This study was also limited in its ability to demonstrate the actual reduction in individual complaints (other than swelling) and focused instead on one or more complaints that were important to each patient who participated in the trial.

Although patients with major underlying health disorders were excluded from this study, those included represented a majority of patients who seek medical care for such

complaints. Thus the findings of this study can be generalized to patients seen in daily practice.

Future studies with larger sample sizes, and which include patients with predefined comorbidities, will improve the extent to which these results could be extrapolated to the general population.

Conclusion

Our study provides definitive assurance to both patients and physicians that Patch It is superior to placebo in alleviating recurring swelling and aching in the legs and feet, in the absence of any detectable systemic or local pathology, and is well tolerated.

Acknowledgments

HKH and AS were involved with the conception and design of the study, the analyses and interpretation of data; CSP, MVC, YDK, SVP, SGE and RMK collected patient data. AS drafted the manuscript, which was revised and approved by the other authors. Dr AS Nanivadekar provided guidance in designing the study and in statistical analysis. He works as a consultant to the CRO that conducted this study. This study was carried out by Vedic Lifesciences Pvt Ltd, a CRO based in Mumbai, India, and was funded by Nutriworks Limited.

Disclosure

HKH sponsored the study; Patch It[®] is a product of Nutriworks limited which is owned and managed by HKH. AS works as a medical writer with the CRO that conducted this study. CSP, MVC, YDK, SVP, SGE, and RMK were financially compensated by this CRO for participating in the study as investigators. HKH has paid any fees required for this paper to proceed to publication.

The authors declare that they have no other conflicts of interest in this work.

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