Clinical Research

Hemodynamic effects of *Sarvanga Swedana* (Ayurvedic passive heat therapy): A pilot observational study

Sanjeev Rastogi, Francesco Chiappelli¹

Department of *Panchakarma*, State Ayurvedic College and Hospital, Lucknow University, Lucknow, India, ¹Department of Oral Biology and Medicine, UCLA School of Dentistry, CHS 63-090, 10833 Le Conte Avenue, Los Angeles, CA 90095-1668, USA

Abstract



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Sarvanga Swedana is a common procedure done in Ayurvedic Panchakarma units. Passive body heat therapy, which is akin to Sarvanga Swedana is known to cause systemic hemodynamic changes. Such studies would have been required to find the possible hemodynamic changes following the Sarvanga Swedana sessions also. An observational study was planned to observe hemodynamic changes among patients routinely receiving Sarvanga Swedana in a Panchakarma setting at an Ayurvedic hospital. Significant increase in blood pressure and pulse rate (PR) was observed in all patients immediately after the completion of Sarvanga Swedana therapy. Upon continuation of Sarvanga Swedana in a subgroup; however, a significant reduction in systolic blood pressure and PR was also observed.

Key words: Blood pressure, hemodynamic changes, Panchakarma, Swedana

Introduction

Swedana (body heating) is a treatment modality common to Ayurvedic clinical practice. Practiced either as a preparatory component to *Panchakarma* (five detoxification procedures) or as an independent intervention, *Swedana* is praised for its relaxing and detoxifying effects all through the classical Ayurvedic texts. Out of two basic methods of *Swedana*, *Niragni* represents the method where the body is warmed without getting heated directly. This method is similar towhatwe understand as active heat therapy. Common examples to this variety are heavy clothing, exercise, etc. *Saagni*, the other method of *Swedana* utilizes various methods of applying dry or moist heat directly upon the body to make it warm.^[1] This method is similar to conventional methods of passive heat therapies.

Sarvanga Swedana is a common method of Swedana procedure applied in most Ayurvedic hospitals. It uses a closed steam chamber with a retractable lidwhere the patients are placed lying supine and in head out position and is warmed with the help of steam impregnated with Ayurvedic decoction flowing into the chamber. The procedure is carried out for few minutes every day preceding a minimal oil massage of the whole body.

Address for correspondence: Dr Sanjeev Rastogi, Department of *Panchakarma*, State Ayurvedic College and Hospital, Lucknow University, Lucknow - 226 003, Uttar Pradesh, India. E-mail: rastogisanjeev@rediffmail.com This procedure is recommended as a first line therapy to many musculoskeletal and neuromuscular conditions identified as *Vataja Nanatmaja* (caused by *Vata* alone) diseases in Ayurveda.

Incidentally, *Swedana* is identified as one most frequently observed procedures adopted in Ayurvedic *Panchakarma* clinics. It constitutes approximately 95% of total procedures carried out in Ayurvedic *Pancha Karma* clinics.^[2] Out of total enrolments for *Swedana*, approximately 30% come from *Sarvanga Swedana* alone.^[2] Clinical effects of *Swedana* have previously been identified through patient response surveys^[3] and clinical interventional studies.^[4,5]

Passive heat therapy is known to have its systemic effects.^[6] Ayurvedic *Swedana* therapy, being akin to passive heat therapy on account of methods employed to warm the body, utilizes principles similar to that of passive heating and thereby is hypothesized to have similar systemic hemodynamic effects.

Strikingly, despite of its vast use in Ayurvedic clinical practice, little is known about the prospective hemodynamic effects pertaining to *Sarvanga Swedana* therapy. This is important to note that *Swedana* therapy is recommended and utilized for longer periods and a substantial number of patients utilizing this therapy belong to the elderly group suffering with various musculoskeletal and neuromuscular conditions. For this specific subpopulation, a pre-existing compromise to hemodynamic functions accounting to age or co-existing illness could not be ruled out. Studying hemodynamic effects of *Sarvanga Swedana* therapy thereby may prove to be of immense help in establishing its safety in such subpopulations. This can also help proposing the mechanistic postulates of *Swedana* to understand it dynamics better. To understand hemodynamic effects of *Sarvanga Swedana* therapy, an observational study was designed to observe the hemodynamic changes in terms of systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulserate (PR) upon patients receiving *Sarvanga Swedana* as a component of their regular therapy. A significant rise in the blood pressure both in SBP and DBP was observed immediately after *Sarvanga Swedana* therapy, which was found to reach near basal levels after commissioning of 5 min rest following the therapy. Incidentally, a continued *Sarvanga Swedana* therapy was noted to cause a significant decrease in PR and SBP comparing to the basal levels observed at the beginning of the *Sarvanga Swedana* therapy.

Materials and Methods

Setting

The study is performed at *Pancha Karma* unit of State Ayurvedic College Hospital, Lucknow, North India. *Pancha Karma* unit of this hospital gets around 60-70 procedure enrolments every day for various procedures. The study protocol was reviewed and approved by departmental review board.

Patient selection

Patients for the study were selected from the Pancha Karma unit of the chosen hospital during working hours on all working days during the study period (March-April 2011). Only those patients who had a prescription of Sarvanga Swedana were included in the study. Patient inclusion was irrespective of their disease, duration, or sex. Patients of 18 to 75 years were taken into the study. Every selected patient was explained about the procedure of hemodynamic observations upon him, its benefits and thereby was obtained with consent. All registered patients have received a recommendation for Sarvanga Swedana by their respective Ayurvedic consultants from state Ayurvedic College, Lucknow during their out-doors in reference to the clinical observation of the patient. As the recommendations were made by qualified Ayurvedic physicians after thorough clinical examination of the patients, it was presumed that the patients belong to swedya group. 160 mmHg SBP was considered as the upper limit of blood pressure for including the patients into the study.

Procedure standardization

Sarvanga Swedana apparatus constituted a wooden insulated chamber of approximately 7 feet length, 3 feet width, and 4 feetdepth. The chamber contained a retractable lid andan under lying wooden couch at approximately 2 feet depth where the patients were asked to lie. The inner chamber was connected to a steam generator where steam of Dashamula decoction was produced and circulated inside the chamber. This apparatus of Sarvanga Swedana was under use at Pancha Karma unit for over 10 years and was in concordance to the conventional apparatuses used for the same purpose throughout the country [Figure 1]. Patients recommended for Sarvanga Swedana were initially given snehana (whole body oil massage) with Saindhavadi oil. After snehana, the patients were asked to lie supine in the Sarvanga Swedana chamber (lying type) in a head out position. Dashmula decoction steam was circulated inside the chamber for approximately 5 min and then the lid of the chamber was opened allowing the patient to come out.

During the process, the patients were covered with a small wet towel at their head. The patients who had undergone *Sarvanga Swedana* therapy were then allowed to change and rest in an enclosed area (without a direct air exposure) for few minutes before they could leave.

Data collection

Every enrolled patient who had undergone Sarvanga Swedana therapy was recorded for outcome measures such as blood pressure and PR. The data were collected at 3 time points: at baseline (before Swedana), immediately after a Swedana session of 5 min, and 5 min after the completion of Swedana session. Blood pressure was observed through a mercury based sphygmomanometer and PR was observed manually. Every session of Sarvanga Swedana (to the same patient or to different patients) and thereby the variable observations at every session were considered as independent observations and were used in data analysis accordingly. Those who continued the therapy for 7 consecutive days were also subjected to "number of therapy days" related findings.

Statistical analysis

The raw data were tabulated upon Microsoft Excel and sorted between normo-tensives (NTN) (SBP 129 mm Hg and below) and hypertensives (HTN) (SBP 130 mm Hg andabove) based upon baseline observations. The data were recorded as an independent observation for every treatment session to every patient. A within group and between group analysis to observe significance of change in variables before and after the therapy was carried out using unpaired and paired *t*-test. For "therapy days" related inferences the observations of same patient on consecutive days of therapy were tabulated separately to delineate a treatment frequency related hemodynamic changes.

Out of total observations, the data were further cleaned up to consider complete observations only (where all the variables were recorded for all the time intervals) for a subsequent statistical analysis.

Results

Total 61 patients approached to Pancha Karma unit for Sarvanga Swedana during the study period. Among them, 42 have given



Figure I: Swedana box

consent and there by enrolled in the study. Among enrolled patients 31 were female and 11 were male. The mean age for enrolled patients was 41.9 years (maximum = 75 years, minimum = 20 years). Maximum patients were found to come under 41-60 year age group (n = 22,52.2%) [Table 1]. Among enrolled patients, as per the baseline observations, 29 were NTNs and 13 were HTN. For these patients, 123 independent therapy sessions and subsequent observations for measurable variables were made. Out of total 70 observations among NTNs, 43 observations were found complete in terms of data collection. Among 53 observations in HTN group, the number of complete observations was 31. The complete observations were subsequently taken further to statistical analysis. 49 incomplete observations were dropped from the analysis owing to the missing of either of before therapy (BT), immediately after the therapy (IAT) and 5 min after the therapy (FMAT) observations.

Out of total 42 patients initially enrolled for the study, a subset of those who continued the therapy for 7 days was identified. Six patients were identified in this subset who continued the therapy for seven consecutive sessions. A subset analysis was carried out for these patients to find any difference between "day 1" and "day 7" variables. Among total 42 enrolled patients, 19 found to receive single treatment session whereas 23 received multiple treatment sessions ranging between 2 and 7 therapies.

Table 1: Demography of the enrolled patients						
Age group	Male	Female	Total	%		
1-20 years	0	1	1	2.6		
21-40 years	6	11	17	40.5		
41-60 years	4	18	22	52.2		
61 years and above	1	1	2	4.7		
Total	11	31	42			

For NTN group

An increase in all the measured variables (SBP, DBP, and PR) comparing to the basal values was observed in NTN group IAT and FMAT. This increase was found significant comparing to the basal data in IAT groupfor all the variables except for DBP. This increase of variables was found transient as it reached similar to the basal values in FMAT group. No significant difference was observed between basal observations and FMAT in any of the variables. For NTN group following were the matched *t*-test observations [Tables 1 and 2]:

- Within group comparison of pulse (IAT to BT) (matched *t*-test) → Statistically significant (*P* = 0.010)
- Within group comparison of DBP (IAT to BT) (matched t-test) \rightarrow NOT statistically significant (P = 0.07)
- Within group comparison of SBP (IAT to BT) (matched t-test) \rightarrow Statistically significant (P = 0.006).

For HTN group

Among HTN, mean changes from baseline to IAT observations were 5.42 for pulse, 6.58 for SBP, and 3.81 for DBP. In this group, the changes among all the variables were found statistically significant comparing to the basal data with that of IAT data. For pulse, this was (matched *t*-test) statistically significant (P = 0.012). For DBP, this was (matched *t*-test) statistically significant (P = 0.0007) and for SBP this was (matched *t*-test) statistically significant (P = 0.0007) and for SBP this was (matched *t*-test) statistically significant (P = 0.0007) and for SBP this was (matched *t*-test) statistically significant (P = 0.049). The IAT increase among the variables retuned to near basal values after 5 min of therapy [Tables 2 and 3].

Changes in variables after seven sessions of Sarvanga Swedana therapy

For patients who continued the Sarvanga Swedana therapy for seven consecutive sessions, all variables were compared for their

Table 2: Hemodynamic changes among NTN and HTN after Sarvanga Swedana therapy Veriables

Variables	NTN (<i>n</i> =43) mean±SD			HTN (<i>n</i> =31) mean±SD		
	BT	IAT	FMAT	BT	IAT	FMAT
Pulse	82.14±7.94	86.60±9.46	82.09±7.75	81.74±8.89	87.16±9.52	82.06±8.32
SBP	119.77±10.05	125.49±10.36	119.91±10.79	141.87±6.65	148.45±8.64	140.45±8.50
DBP	80.56±7.50	83.02±8.17	79.67±7.10	92.52±8.93	96.32±8.84	90.45±7.60

NTN: Normotensives, HTN: Hypertensives, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BT: Before therapy, IAT: Immediately after therapy, FMAT: 5 min after the therapy, SD: Standard deviation

Table 3: Within group	comparison of	variables
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Variables	Within the group comparison (paired <i>t</i> test)						
	N	ITN (<i>n</i> =43) mean±S	D	F	ITN (<i>n</i> =31) mean±S	D	
	BT versus IAT	IAT versus FMAT	BT versus FMAT	BT versus IAT	IAT versus FMAT	BT versus FMAT	
Pulse	<i>t</i> =3.73	<i>t</i> =6.81	<i>t</i> =0.05	<i>t</i> =5.14	<i>t</i> =5.50	<i>t</i> =0.43	
	<i>P</i> <0.01	<i>P</i> <0.001	<i>P</i> >0.05	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> >0.05	
SBP	<i>t</i> =5.72	<i>t</i> =6.88	<i>t</i> =0.16	<i>t</i> =5.26	<i>t</i> =7.78	<i>t</i> =1.37	
	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> >0.05	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> >0.05	
DBP	<i>t</i> =3.28	<i>t</i> =4.29	<i>t</i> =1.22	<i>t</i> =2.52	<i>t</i> =5.66	<i>t</i> =1.87	
	<i>P</i> <0.01	<i>P</i> <0.001	<i>P</i> >0.05	<i>P</i> <0.02	<i>P</i> <0.001	<i>P</i> >0.05	

P>0.05 not statistically significant, P<0.05 statistically significant, P<0.02 statistically significant, P<0.01 statistically highly significant, P<0.001 statistically highly significant: NTN: Normotensives, HTN: Hypertensives, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BT: Before therapy, IAT: Immediately after therapy, FMAT: 5 min after the therapy, SD: Standard deviation day 1 and day 7 value. For six patients who continued *Sarvanga Swedana* therapy for 7 days, a significant decrease in base line SBP was observed (P = 0.0483) [Tables 4 and 5].

Discussion

Sarvanga Swedana is a commonly utilized intervention in *Panchakarma* units of Ayurvedic hospitals. As per one observation, *Snehana* and *Swedana* constitute approximately 95% of the total input in any *Panchakarma* setting.^[1] Among those who receive *Swedana*, *Sarvanga Swedana* alone constitutes around 30% of all inputs.^[1]

Panchakarma procedures by and large are considered safe and effective. This connotation have also been reported in a recent patient based survey aiming at identification of patient centered rating of safety, effectiveness, and quality of services offered at *Panchakarma* units of Ayurvedic hospitals.^[2]

Despite the general perception of safety pertaining to common *Panchakarma* procedures, it is not clear whether *Panchakarma* treatments, especially, *Sarvanga Swedana* is safe for HTN and cardiac patients. Such safety information is more critical given that these treatments are seen received by elderly with possible co-morbidities affecting the hemodynamic function. Current literature on the hemodynamic effects of *Panchakarma* is either limited or absent. In such a situation, a study of this nature is proposed to add value to the credentials of *Sarvanga Swedana* by defining about the hemodynamic changes that might be associated with it. Furthermore, this study is also expected to guide researchers in this field to design and execute clinical research studies more effectively.

Whole body heating is known to cause significant cardiovascular stress in healthy individuals. An increase of body temperature due to passive heating substantially increases the cutaneous vascular conductance followed by a corresponding increase in systemic conductance. A barometric homeostasis; however, is maintained in such cases by corresponding decrease of conductance at non-cutaneous beds^[7] and also by corresponding increase of the cardiac output.^[8]

A reduction in central venous pressure (CVP) occurs almost immediately with the onset of passive heating.^[8-13] This reduction is presumed to be the cause of increased cardiac output and also a redistribution of blood from central to peripheral circulation.^[9] In a non-randomized time control study to evaluate effects of passive body heating on parameters such as alteration of central blood volume and systemic blood volume distribution noted an increased cutaneous conductance and heart rate. In this study, heat stress was also found to raise left ventricular ejection fraction significantly (P = 0.02).^[6] Our study indicates, the congruent observations in reference to studies on the hemodynamic responses in case of heat stress. In both NTN and HTN groups, we have seen a significant rise in PR, SBP, and DBP indicative of an increased cardiac output and ejection fraction. The increase however was transient as it reached to near basal levels just after 5 min of completion of the therapy.

This observation draws few important inferences pertaining to the safety aspects of *Sarvanga Swedana*. Although CVP was not directly observed in this study, its subsequent reduction may be presumed following *Sarvanga Swedana* akin to heat stress. As heat stress is supposed to cause reduction in CVP and a shift in blood volume from splanchnic to cutaneous area, supine lying style *Sarvanga Swedana* is apt to be safer comparing to sitting style *Sarvanga Swedana*. In lying style even, a proposition of keeping head out of box, a mildly downward position and a wet towel cover proposes additional safety to avoid any discomfort due to a reduced CVP. Incidentally, during the process of *Swedana*, Ayurvedic texts repeatedly stress keeping these provisions to keep the vitals safe.

As after 5 min, the hemodynamic changes return to almost normal, this may be considered the minimal period for which the patients should be retained in lying position preferably at the same place and may further be allowed to cool and normalized in terms of regular hemodynamic functions.

Because of its steep effects on cardiac output, a Sarvanga Swedana should preferably be avoided in cases where hemodynamic functions are altered owing to some pre-existing pathologies. The best examples are people with hypothyroidism, cardiomyopathy, congestive heart disease, bundle branch block, and anemia. Anyone who might have suffered from myocardial infarcts or suffers with ischemic heart disease should also be avoided for being recommended with Sarvanga Swedana.

Table 5: Significance test for difference between the first day and seventh day values of the variables

Variables	Between t	Between the days comparison: Day1 versus day7				
	BT	IAT	FMAT			
Pulse	<i>t</i> =1.66,	<i>t</i> =0.46,	<i>t</i> =0.00,			
	<i>P</i> =0.0786	<i>P</i> =0.3328	<i>P</i> =0.5000			
SBP	<i>t</i> =2.04,	<i>t</i> =2.49,	<i>t</i> =1.90,			
	<i>P</i> =0.0483	<i>P</i> =0.0273	<i>P</i> =0.0582			
DBP	<i>t</i> =0.41,	<i>t</i> =0.16,	<i>t</i> =0.18,			
	<i>P</i> =0.3508	<i>P</i> =0.4416	<i>P</i> =0.4329			

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BT: Before therapy, IAT: Immediately after therapy, FMAT: 5 min after the therapy

Table 4: Comparing the first day and seventh day values of variables among patients who received Sarvanga Swedana for seven consecutive sessions (N=6)

Variables		Day 1 mean±SD			Day 7 mean±SD		
	BT	IAT	FMAT	BT	IAT	FMAT	
Pulse	83.00±12.38	83.33±12.24	82.00±10.58	76.67±8.82	84.67±7.66	82.00±6.45	
SBP	139.00±14.79	141.33±11.43	136.00±12.71	128.00±5.37	130.33±5.28	127.67±5.99	
DBP	89.67±9.42	84.67±7.34	83.33±7.97	87.67±6.86	85.33±6.28	82.67±5.01	

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BT: Before therapy, IAT: Immediately after therapy, FMAT: 5 min after the therapy, SD: Standard deviation

A comparison of first day experience of *Sarvanga Swedana* with that of seventh day upon continuation of therapy was also noteworthy. A significant decrease in the baseline levels of SBP was observed on seventh day among such patients who continued *Sarvanga Swedana*. This is important to note here that these patients were not advised for any change into their prescribed medications, which they might be taking earlier for any of their pre-existing illnesses. A mean reduction of 6.33 inpulse and a mean reduction of 11 mm of Hg in SBP was observed in those who continued *Sarvanga Swedana* for seven days.

This observation temptsus to hypothesize that Sarvanga Swedana may have two different mechanisms of action responsible for a difference of effects upon its instantand subsequent usage. Acute effects of Sarvanga Swedana seem to be more local acting upon cutaneous vascular bed and resulting compensatory mechanisms leading to a transient increase in blood pressure and pulse. Prolonged use of the same seems to have more systemic effects through altering mechanisms operating behind setting of the blood pressure to a lower point. Sustainable decrease in peripheral resistance, increased vascular flexibility, readjustment of mineralocorticoid system due to recurrent losses of salt and water through repeated sweating, improved autonomic functions due to intermittent heat stress are few such propositions, which may in part be responsible for such blood pressure reductions.

Such reductions however may also be because of improved well-being in reference to the primary disease for which the *Sarvanga Swedana* was initially recommended.

Without putting a final note upon the mechanisms through which hemodynamic alterations may occur after *Sarvanga Swedana*, this study gives us important information about the possible hemodynamic changes upon a patient who is receiving *Sarvanga Swedana* for first time or is continuing it for a prolonged period.

Although interesting, the study suffers with many limitations in terms of its designing and conduction.

Being an observational study, the study observed all the patients enrolled in Pancha Karma department for *Sarvanga Swedana* for any reason. It is noted that a huge sum of observations (49) were rendered incomplete in the study. As there were multiple observations (SBP, DBP and Pulse before, during and after treatment time) any data missed for any of these observations rendered the observation incomplete. The most important reason for missing data was rush of patients and less number of volunteers to handle each patient carefully as per the time schedule fixed for individual observation.

As the patients observed under the study were not instructed for any specific protocol for their blood pressure management, in case if theywere HTNs, any corresponding change to the blood pressure levels between first day and seventh day could also be reflective of changes in the dose or schedule of antihypertensive drugs at patient's end. As the sample number for this subset analysis pertaining to analysis of differences between first day and seventh day variables was very small (n = 6), any such change under the influence of the drugmay give misleading information about net outcomes. A controlled study with large sample numbers therefore would be required to confirm the inferences observed in present study. We are aware that a change of blood pressure is also reflective of many patients, intervention and setting related confounding factors. The observations made in present study do not offer any adjustment in reference to these confounding factors, which might have a role to play in determining the final outcome.

The intervention protocol of the study was standardized empirically on the basis of conventional practices of *Sarvanga Swedana* in Ayurvedic hospitals. In lack of clear standard protocols, errors related to observation (blood pressure recording, pulse recording), to intervention protocol (duration of therapy), to status of patient (anxious before therapy) or to the anomalies of observation timings (BT, IAT, and FMAT) cannot be overruled. The data of patients receiving the *Sarvanga Swedana* for the first time and those who are receiving it subsequently is clubbed together to make the analysis. It is therefore difficult to interpret clearly if any hemodynamic differences are existing between these two groups.

The *Swedana* temperature was also not monitored. There may be a possibility of variable temperature during independent sittings and this could also have affected the results.

This is however important to see that despite of these limitations, this study gives us valuable information about possible hemodynamic changes in patients receiving lying style Sarvanga Swedana. On account of observed changes, further verified by other studies to confirm the possible blood volume shifts and increased cardiac activities, further studies to confirm the safety of such procedures among disease and age specific populations are highly warranted. In addition, this study also proposes Sarvanga Swedana as an additive non-pharmacological measure to intervene for the management of hypertension among elderly. As the study was primarily intended to observe any prospective hemodynamic changes during the process of Sarvanga Swedana, any observation in reference to Prakriti, obesity, level of blood glucose or lipids was not done. Seeing the pilot observations for such changes, a more extensive study to see the differential effects of Sarvanga Swedana in reference to various influencing factors such as Prakriti and obesity may be taken up further.

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हिन्दी सारांश

सर्वांग स्वेदन (आयुर्वेदिक निष्क्रिय ऊष्मा चिकित्सा) के रक्तसंचरण संबंधी प्रभावों का अध्ययन

संजीव रस्तोगी, फ्रान्सीस्को चेपेली

आयुर्वेदिक पंचकर्म विधियों में सर्वांग स्वेदन प्रमुखता से प्रयोग में आने वाला कर्म है । यह विधि निष्क्रिय ऊष्मा चिकित्सा के समान ही है जिसमें अनेक रक्तसंचार सम्बन्धी प्रभाव उत्पन्न होते हैं। सर्वांग स्वेदन की उपरोक्त निष्क्रिय ऊष्मा चिकित्सा से समानता होने के कारण इसमे भी समान प्रभाव उत्पन्न हो सकते हैं । प्रस्तुत शोध पत्र मे इसी सम्भावना का विचार किया गया है । इस नैरेक्षणिक अध्ययन में सर्वांग स्वेदन के समय रोगियों का रक्त चाप अधिक पाया गया जोकि स्वेदनोपरान्त पुनः सामान्य हो गया । कुछ रोगियों में जिनमें सर्वांग स्वेदन को निरन्तर कई दिनो तक दिया गया, स्वेदनोपरान्त रक्त चाप उनके प्रारम्भिक स्तर से कम पाया गया ।

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- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to
 possible articles in PubMed will be given.