CONCISE REPORT

Preliminary thermographic evaluation of new nitroglycerine tape on the peripheral circulatory disturbance in systemic sclerosis

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Objective: To evaluate the effects of newly developed nitroglycerine (NTG) tape on the peripheral circulatory disturbance in systemic sclerosis (SSc).

Methods: The finger temperature (FT) of 25 patients with SSc was monitored by thermography before the application of NTG tape to the wrist and one hour afterwards. To check the placebo effect, the change of FT with placebo tape in six patients who had shown a distinct rise in FT ($>2^{\circ}\text{C}$) with NTG tape was monitored.

Results: Twenty one patients with SSc had a low FT before the application of NTG tape (colder than mean $\pm 2\text{SD}$ of normal controls). FT was significantly raised in patients with SSc after the application of NTG tape ($p < 0.01$). Patients with low FT showed a distinct rise in FT more often than patients with a normal FT ($71\% \text{ v } 0\%$, $p < 0.01$). FT was raised with NTG tape more than with placebo tape ($4.2 \text{ (SD } 1.9)^{\circ}\text{C v } 2.2 \text{ (} 2.8)^{\circ}\text{C}$, $p < 0.05$).

Conclusion: The application of NTG tape increases peripheral circulation in patients with SSc who have distinct circulatory disturbance. The application of NTG tape may improve peripheral circulatory disturbance in SSc.

The pathogenesis of Raynaud's phenomenon and peripheral circulatory disturbances in systemic sclerosis (SSc) are multifactorial and not fully understood. Intimal proliferation of arteries after endothelial damage and platelet aggregation are considered to result in progressive vascular occlusion.^{1–3} Despite previous trials with a wide range of vasoactive drugs, treatment of Raynaud's phenomenon and circulatory disturbance in SSc still remains difficult.

Nitroglycerine (NTG) has a powerful vasodilator activity. Although topical NTG^{4–8} has been used in an attempt to alleviate primary and secondary Raynaud's phenomenon, including that in SSc, its effect is not widely recognised. In addition, we could not find any reports which examined the effect of NTG on the peripheral circulation of SSc.

Millisrol tape developed in Japan is a convenient soft film containing 5 mg of NTG per film ($5 \times 10 \text{ cm}$) and has been widely used for angina pectoris. Upon application, NTG is absorbed gradually and continuously through the skin, producing its clinical action within 30 minutes, and maintaining effective blood concentration for up to 12 hours. To evaluate the effects of this new NTG tape on peripheral circulation in SSc, we monitored the change in finger temperature (FT) before and after the application of NTG tape using thermography.

MATERIALS AND METHODS

Twenty five consecutive patients with SSc (20 women, five men; aged 54.8 (13.1) years, mean (SD)) were enrolled in this

study. Disease duration ranged from one year to 32 years (9.0 (7.6) years). All the patients met the American College of Rheumatology's preliminary criteria for SSc⁹ and were followed up in our department. The patients were divided into two groups comprising 14 patients with diffuse cutaneous SSc and 11 patients with limited cutaneous SSc.¹⁰ Raynaud's phenomenon was found in all the patients, digital ulcer in 14/25 (56%), and shortening of the finger in 8/25 (32%). Four patients were smokers (about 10 cigarettes a day). The patients had been treated with vasoactive drugs such as diltiazem hydrochloride, a calcium blocker ($n=1$); nifedipine, a calcium blocker ($n=2$); limaprost alfadex, an analogue of prostaglandin (PG) E, ($n=2$); beraprost sodium, an analogue of PGI₂ ($n=10$); ticlopidine hydrochloride, an antiplatelet aggregation inhibitor ($n=1$); cilostazol ($n=3$), sarpogrelate hydrochloride ($n=4$), a small dose of aspirin ($n=4$). These drugs were prescribed concomitantly to this study.

The FT of 19 normal volunteers (16 women, three men, 46.0 (16.0) years) was measured to establish a basal measurement. Six normal volunteers (five women, one man, 49.0 (20.5) years) were examined as normal controls to monitor the changes in FT after NTG tape application.

FT was measured by thermography (Avio Thermal Video System TVS-4300 ME, Japan) in an air conditioned room at 25°C . After 20 minutes of habituation in a seated position, we put half a sheet of NTG tape (Millisrol tape) on the wrist of each patient. We usually measured FT at the middle part of the distal phalanx, but we changed the measuring place to the most distal part of the finger if the patient's finger was shortened so that the distal phalanx was lost. After measuring the temperature of all the fingers on both hands to determine which finger was the coldest, we monitored its FT after NTG tape application. We also monitored the coldest finger of the opposite hand. For the preliminary investigation we examined three inpatients, monitoring the change in FT at 10, 30, and 60 minutes after NTG tape application. The patients were then allowed to return to the ward and the FT was measured three and 12 hours later. The FT of two patients increased within 10 minutes after NTG patching, reached the highest level in one hour, and did not decline for up to 12 hours. The third patient showed no rise in FT during the monitoring time. Therefore, we decided to measure the FT after one hour's application of NTG tape in the subsequent study. We defined a distinct rise in FT as a rise of more than 2°C after one hour's application of NTG tape.

To check the placebo effect, we monitored the change of FT with OpSite, a semipermeable polyurethane film, in six consecutive patients who had shown a distinct rise in FT with

Abbreviations: BP, blood pressure; FT, finger temperature; NTG, nitroglycerine; PG, prostaglandin; SSc, systemic sclerosis

Figure 1 Change in finger temperature (FT) in patients with systemic sclerosis (SSc) and normal controls after the application of NTG tapes. (A) NTG tape to normal controls (n=6). No obvious rise in FT was noted. (B): NTG tape to patients with SSc (n=25). FT was raised significantly after the application of NTG tape ($28.7 (3.0)^{\circ}\text{C}$ v $30.8 (2.6)^{\circ}\text{C}$, $p < 0.01$). The dotted lines represent 32.4°C (mean - 2SD of 19 normal controls).

NTG tape. None of the six patients was aware of whether the tape was NTG tape or OpSite.

Adverse effects of NTG tape, such as headaches, palpitation, and blood pressure, were checked during the NTG application.

The data were analysed using paired *t* test, unpaired *t* test, or χ^2 analysis.

RESULTS

In 19 normal controls, the lowest FT was $34.4 (1.0)^{\circ}\text{C}$ (mean (SD)), and we defined low FT before the application of NTG tape as below 32.4°C (mean - 2SD of the lowest FT in 19 normal controls) (dotted lines in fig 1). Twenty one of 25 (84%) patients with SSc had low FT.

In six normal controls no distinct rise in FT was found after the application of NTG tape (fig 1A). In contrast, 15/25 (60%) patients with SSc showed a distinct rise in FT after the application of NTG tape (fig 2). As a whole, FT was significantly raised in patients with SSc after the application of NTG tape ($28.7 (3.0)^{\circ}\text{C}$ v $30.8 (2.6)^{\circ}\text{C}$, $p < 0.01$, fig 1B). The raised temperatures with NTG tape were significantly higher than with placebo tape ($4.2 (1.9)^{\circ}\text{C}$ v $2.2 (2.8)^{\circ}\text{C}$, $p < 0.05$, fig 3). The

Figure 3 Change of finger temperature (FT) after one hour's application of NTG tape or placebo tape. Six patients who showed a distinct rise in FT ($> 2^{\circ}\text{C}$) with NTG tape were monitored using placebo tape. The degree of raised temperature with NTG tape was significantly higher than with placebo tape ($4.2 (1.9)^{\circ}\text{C}$ v $2.2 (2.8)^{\circ}\text{C}$, $p < 0.05$).

FT was raised equally after the application of NTG tape both on the side to which tape had been applied and the side to which it had not (NTG tape side: $2.1 (2.1)^{\circ}\text{C}$; non-applied side: $1.8 (2.0)^{\circ}\text{C}$).

All the 15 patients with a distinct rise in FT had a low FT before the application of NTG tape, whereas six further patients with low FT failed to show any obvious rise (fig 1B). Thus NTG tape raised the FT of patients with low FT before the application of NTG more commonly than those with normal FT (71% v 0%, $p < 0.01$). No correlation was found between the rise in FT with NTG tape and the subset of SSc, Raynaud's phenomenon, digital ulceration, or the shortening of a finger (data not shown).

Figure 2 Representative thermographic images of hands in a patient with systemic sclerosis (SSc) and a normal control before and after the application of NTG tape. An obvious rise in finger temperature was seen in a patient with SSc after the application of NTG tape (A, before; B, after) but not in a normal control (C, before; D, after).

We also compared the response to NTG tape with the patients' drug history and smoking. Patients taking oral prostaglandin (PGI₂) had a raised finger temperature more often than patients without PGI₂ drug treatment (100% v 57%, $p < 0.05$). There was no significant correlation between the rise in FT and other drugs or smoking.

Systolic blood pressure (BP; $n = 21$) fell significantly after one hour's application of NTG tape (126.9 (27.4) mm Hg v 119.9 (26.0) mm Hg, $p < 0.05$). We noted a distinct fall of systolic BP ($\Delta BP < -30$ mm Hg) in one patient (5%), a slight fall (-30 mm Hg $< \Delta BP < 0$) in 15 (71%), no change in one (5%), and a slight increase in four (19%). During the measurement of FT ($n = 25$), headaches or flush occurred in six patients (24%).

DISCUSSION

In this study we found that application of NTG tape raised the FT in patients with SSc who had a low FT, which suggests that application of NTG tape improves peripheral circulation in patients with SSc who have distinctive circulatory disturbance.

Six patients with low FT did not respond to NTG tape. Although we could find no peculiar clinical features that correlated with the unresponsiveness to NTG, four of the six patients had severe digital ulcers. Severe obstruction of the digital artery was confirmed by angiography in one patient. In these patients, irreversible organic changes of peripheral arteries may have been responsible for the lack of response.

A correlation between PGI₂ drug treatment and responsiveness to NTG was found. Franks suggested adjunctive effects of NTG ointment to sympatholytic treatment such as methyl-dopa and guanethidine.¹¹ Radomski *et al* reported the cooperative effect of nitric oxide (NO) and PGI₂.¹² Similarly, we suggest in this study a cooperative effect of NTG and PGI₂.

Teh *et al* reported that headaches were the most common adverse effect of NTG patching.¹³ In our study six patients (24%) reported headaches, and a slight drop in blood pressure developed in 16/21 (76%) patients. These adverse effects must be carefully checked when NTG tape treatment is given.

This preliminary study suggests that NTG tape improves the peripheral circulatory disturbance in SSc. To determine the clinical efficacy of NTG tape, including its use for digital ulceration, a double blind, cross over study is needed.

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