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Comparison of two devices for the treatment of keloid scars with the use of intralesional cryotherapy: An experimental study ☆

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ABSTRACT

Background: Intralesional (IL) cryotherapy is a new technique for the treatment of keloid scars, in which the scar is frozen from *inside*. Two cryodevices are available, which were recently evaluated. Both devices showed promising results, but differed in clinical outcome. To explain these differences, more understanding of the working mechanism of both devices is required.

Objective: This experimental study was designed to investigate and compare the thermal behavior of an *argon gas*- and a *liquid nitrogen*-based device. Thermal behavior constitutes: (1) minimum tissue temperature (°C), (2) the freezing rate (°C/min). The thermal behavior was measured inside and on the outer surface of the scar. Both devices were tested *ex vivo* and *in vivo*.

Results: Ex vivo, when determining the maximum freezing capacity, the argon gas device showed a higher end temperature compared to the liquid nitrogen device (argon gas: −120 °C, liquid nitrogen: −140 °C) and a faster freezing rate (argon gas: −1300 °C/min, liquid nitrogen: −145 °C/min).

Results: In vivo, measured inside the keloid, the argon gas device showed a lower end temperature than the liquid nitrogen device (argon gas: −36.4 °C, liquid nitrogen: −8.1 °C) and a faster freezing rate (argon gas: −14.7 °C/min, liquid nitrogen: −5 °C/min). The outer surface of the scar reached temperatures below −20 °C with both devices as measured with the thermal camera.

Conclusion: In conclusion, the argon gas device displayed a lower end temperature and a faster freezing rate *in vivo* compared to the liquid nitrogen device. Although this resulted in lower recurrence rates for the argon gas device, more hypopigmentation was seen compared to the liquid nitrogen device following treatment. Finally, the low outer surface temperatures measured with both devices, suggest that some hypopigmentation following treatment is inevitable.

Introduction

Keloid scars result from an abnormal healing response after injury of the skin. Treatment is difficult, with high recurrence rates as the main problem. Cryotherapy is one of the treatment options [15,16]. For decades, liquid nitrogen has been applied externally by using a contact probe. However, to achieve cryonecrosis in the core of the keloid, a long hold time of the cryoprobe was required. Consequently, the surface epithelium was greatly affected, resulting in side effects such as blistering, hypopigmentation and infection [15,16]. To minimize epithelial damage, the hold time of the cryoprobe was limited, which resulted in higher recurrence rates and less volume decrease [6].

To solve these problems, Weshahy introduced a new technique in 1993 called Intralesional (IL) cryotherapy [14]. With this technique, the scar is frozen from the inside; by using a hollow needle inserted in the scar, a cryogen is administered directly to the core of the keloid. In this manner, the exact location of the pathology is targeted, whilst the surface epithelium is less affected [14]. Two IL-cryotherapy devices are currently available; a liquid nitrogen-based device (Cryoshape) and an argon gas-based device (Seednet) [12,13].

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In recent clinical studies, both devices showed a similar volume decrease (argon gas 62%, liquid nitrogen 63%). However, more hypopigmentation (argon gas 38%, liquid nitrogen 31%) and less recurrence (argon gas 17%, liquid nitrogen 24%) was reported using the argon gas device [12,13]. Importantly, the argon gas device study included 9 scars, previously treated unsatisfactory with liquid nitrogen-based IL-cryotherapy. Out of these 9 scars, 3 developed a recurrence after treatment with the argon gas device. Excluding these patients would thus result in a recurrence rate of 9.5% for the argon gas device.

Two important parameters, the freezing rate and the minimum end temperature, constitute the *thermal behavior* of these cryodevices. Differences in the thermal behavior of both devices are likely to account for the dissimilar outcomes in both studies. To target fibroblasts inside the keloid low tissue temperatures (<−20 °C) are required. However, these temperatures are equally associated with surface complications such as hypopigmentation or wound dehiscence [15]. The freezing rate is of equal relevance as it determines ice-crystal formation. Fast freezing rates will cause cell necrosis, while slow freezing rates cause apoptosis, which has proven to be an irreversible process [1].

To investigate and compare the thermal behavior of a liquid nitrogen- and argon gas-based device, we designed an experimental study.

Methods and patients

The thermal behavior of a liquid nitrogen-based (CryoShape®, Etgar Group International Ltd, Kfar Saba, Israel) and an argon gas-based cryoneedle (IseSeed®, Galil Medical, Yokneam, Israel) was measured. Both devices were investigated *ex vivo* to determine the maximum freezing capacity of the devices in an isolated test setting. Then, the devices were tested *in vivo* to evaluate the thermal behavior in clinical practice.

Ex vivo test setting

A thermocouple (thermo measuring device) was attached by means of a strong wrapped narrow band of adhesive tape (3 M Scotch Magic Tape) (clamp contact) to the distal end of the cryoneedle of the liquid nitrogen and the argon gas device. The temperature was recorded with a 4 Channel Pt100 Input Temperature Data Logger (Omega Engineering Ltd. Toronto) and a data acquisition card (National Instruments NI PCI-6221). Data was processed using Labview and was summarized in the following outcome parameters: (1) minimum tip temperature of the needle (°C), (2) the freezing rate (°C/min). Prior to the measurements, the thermocouple was calibrated at three temperatures, melting ice (0 °C), boiling water (100 °C) and boiling liquid nitrogen (−195.8 °C). The thermocouple was mounted at the tip of the isolated needle, which was exposed to open air in a laboratory environment (20 °C). After the start of data acquisition, the needle was exposed to a cooling medium. The experiment was continued until the temperature of the tip of the needle reached a plateau. The freezing rate was calculated in the linear part of the graph, at the beginning of the test until the plateau phase.

In vivo test setting

Patients

Eight patients with 10 keloid scars [10] were treated with IL-cryotherapy at the plastic surgery department of the VU University Medical Centre (Amsterdam, the Netherlands). Patients were randomly assigned to treatment with the *liquid nitrogen* or the *argon gas* device.

Five patients with 6 keloid scars were treated with the liquid nitrogen device and 3 patients with 4 keloid scars with the argon gas device.

Procedure

The cryoneedle (liquid nitrogen device or argon gas device) was introduced longitudinally at mid-height and mid-width of the scar in a forward rotary movement, as described in clinical studies [12,13]. Following the introduction of the cryoneedle, two thermocouples (thermo measuring device) were introduced to measure the internal temperature of the keloid scar (Fig. 1). One thermocouple was placed superficially (80% from the cryoneedle towards the surface) and one thermocouple deeper in the scar, at 20% distance from the cryoneedle (with a minimum of 4 mm). To measure the outer surface temperature, a thermal camera (Xenis Gobi 384) was positioned. The thermal camera did not record temperatures below −20 °C (253 K). See Fig. 3. The following outcome parameters were recorded with Labview: (1) minimum tissue temperature (°C). (2) freezing rate (temperature decrease per minute; °C/min) (3) scar surface temperature (°C) (see Table 1). The medical ethical council of VU University in the Netherlands approved the study.

Results

Ex vivo

When determining the optimal freezing capacity, the thermal behavior of both devices differed substantially. The argon gas device showed a higher end temperature compared to the liquid nitrogen device (argon gas: −120 °C, liquid nitrogen: −140 °C) and a faster freezing rate (argon gas: −1300 °C/min, liquid nitrogen: −145 °C/min). See Fig. 2.

In vivo

In clinical practice, the thermal behavior measured *in vivo* differed from the *ex vivo* results. See Table 2.

Internal temperature

The superficial thermocouple measured, on average, lower temperatures with the argon gas device compared to the liquid nitrogen device (argon gas: −36.4 °C, range: −50 °C to −23 °C. Liquid nitrogen:−12.4 °C, range: −26 °C to −1 °C).

The deep thermocouple displayed the same trend as the superficial thermocouple, although less cold temperatures were reached (argon gas: −27.5 °C, range: −18 to −32 °C. Liquid nitrogen: −8.1 °C, range: −2 to −25.7 °C). Notably, the liquid nitrogen device showed no consistency in the reached temperature since a large range was measured, both superficially and deeply.

Internal freezing rate

The superficial thermocouple measured higher freezing rates with the argon gas device compared to the liquid nitrogen device (argon gas: −14.7 °C/min, liquid nitrogen: −7.3 °C/min).

The deep thermocouple measured the same trend as the superficial thermocouple (argon gas: −13.4 °C/min, liquid nitrogen: −5.0 °C/min).

Outer surface temperature

The thermal camera measured the outer surface of the keloid scars during treatment.

Fig. 3 shows a thermal camera image during treatment with the liquid nitrogen device (a) and with the argon gas device (b). During treatment with the argon gas device, temperatures below −20 °C

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