Journal of Tissue Viability xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Tissue Viability

journal homepage: www.elsevier.com/locate/jtv

Topical treatment of tissue damage due to extravasation of iodinated contrast using thermal compresses

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ARTICLE INFO

Keywords:
Tissue damage
Extravasation of contrast media
Vascular system injuries
Patient safety
Inflammation

Objective: To study the effectiveness of the topical application of dry cold or dry hot compresses in the treatment of non-ionic iodinated contrast extravasation injury.
Methods: A multicenter, consecutive, non-probabilistic experimental clinical trial was carried out between June 2017 and September 2020. The study included patients with extravasation of non-ionic iodinated contrast, administered through an injector pump during a computed tomography procedure. In the experimental group, a dry heat pack was applied in the first hour of treatment followed by a dry cold pack; the control group received only the cold pack. The size of the extravasation, pain, details of contrast administration, anthropomorphic data and the patient's clinical history were recorded. Follow-up was carried out at 24h.
Results: 65 patients were included, of which 32 were treated with cold pack only and 33 with heat and cold. In those receiving heat treatment, 30 (90.9%) patients had complete resolution, while those with cold treatment only had complete resolution in 13 (40.6%); $p<0.001$ and odds ratio 14.6 (95% CI 3.7-58.1). With the initial application of dry heat, local inflammation improved by 1.2% more than in those with dry cold treatment only.
Conclusions: The application of dry heat during the first hour of treatment was more effective, by more than 50 percentage points, at diffusing contrast and modulating the inflammatory process.

1. Introduction

Tissue damage due to infiltration or extravasation of drugs constitutes an adverse event that represents between 10% and 30% of the complications of peripheral intravenous lines, both in adult and pediatric patients [1–3].

In the field of diagnostic radiology, this injury may occur in association with certain tests that are performed routinely in health centers, such as computerized tomography angiography (CTA). This procedure requires the intravenous injection of iodinated contrast, which is not without potential complications. The most common adverse events are anaphylaxis and hemostasis reaction [4], although complications caused by extravasation such as compartment syndrome [5] or tissue necrosis [6] have also been described. Despite extravasation being an uncommon adverse event, with a mean incidence of 0.43% [7], there is a lack of consensus for its immediate management to minimize tissue injury and complications [8].

The severity of the injury is largely affected by the type of contrast. Ionic iodinated contrast agents can produce greater tissue damage than non-ionic agents due to their electrical charge and hyperosmolarity [9]. The scientific literature recommends the same interventions for both types of contrast, based only on studies on the extravasation of other

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https://doi.org/10.1016/j.jtv.2021.12.006
Received 6 February 2021; Received in revised form 30 November 2021; Accepted 21 December 2021
Available online 24 December 2021

drugs, rather than the current non-ionic contrast media used in CTA, which has low osmolarity and low toxicity [3,8].

Computed tomography angiography requires the administration of contrast through a high pressure injection pump with speeds ranging between 3 and 6 ml/s. Extravasation can cause the movement to the interstitial space of up to 150 ml of contrast in a few seconds, resulting in a compressive effect on the adjacent tissues, which represents the main problem of non-ionic contrast.

The density and temperature of the administered contrast also affect the extent and outcome of tissue injury by extravasation. High-density contrast causes greater pressure on the vascular wall, which also leads to greater stress on the surrounding tissues. Preheating the iodinated contrast reduces its viscosity and may help mitigate complications in the event of extravasation [10].

Regarding the management of tissue injury, in most cases, topical care is sufficient without the need for surgical consultation [11]. The Royal Australian and New Zealand College of Radiologists [12] and the most recent guidelines on contrast management from the American College of Radiology [13] recommend the application of hot or cold compresses. The European Society of Urogenital Radiology [14] recommends only the application of cold compresses. However, Reynolds et al. [15] propose the application of heat in cases of contrast extravasation to facilitate its elimination, promoting venous return and modifying its viscosity. Applying wet heat is not recommended as it can lead to tissue maceration [16].

Faced with a lack of evidence on the best treatment, the present study was designed to evaluate the effectiveness of the topical application of dry hot and cold compresses for the treatment of non-ionic iodinated contrast extravasation injury. It was hypothesized that the immediate application of dry heat would be more effective than the application of a dry cold compress alone in reducing the area of extravasation and modulating the inflammatory effect, within a period of 24 h.

2. Material and methods

2.1. Study design

This was a multicenter, consecutive, non-probabilistic experimental clinical trial, conducted from June 2017 to September 2020. A total of 12 health centers from Barcelona, its metropolitan area and surroundings participated. Adapting the treatment proposal of the authors Shaqdan et al. [17], it was decided as an experimental study to apply dry heat in the first hour of the treatment to favor the absorption of the extravasated contrast.

The protocol was approved by the Ethics Committees of each of the participating centers and the Bioethics Commission of the University of Barcelona. The study subscribes to the principles of the Declaration of Helsinki and legal data protection regulations, and was registered at ClinicalTrials.org (NCT 03426735).

2.2. Participants

All patients with low- or iso-osmolar non-ionic iodinated contrast extravasation during CTA who consented to participate in the study were included. Contrast administration was performed using an injector pump up to a maximum speed of 6 ml/s; access was a peripheral venous line placed in an upper extremity.

The study excluded patients under the age of 18 years, those allergic to iodinated contrast, those with kidney failure, patients in whom a central line or peripheral metallic catheter was used, and those who required debridement or an urgent consultation during the first intervention. When it was not possible to follow up, it was also a cause for exclusion.

The recruitment of study participants was carried out during the first hour of application of the intervention protocol against extravasations of each hospital center. All patients who participated provided signed informed consent upon recruitment.

The assignment to the control or experimental group was done alternately. Therefore, if an experimental treatment was performed, the

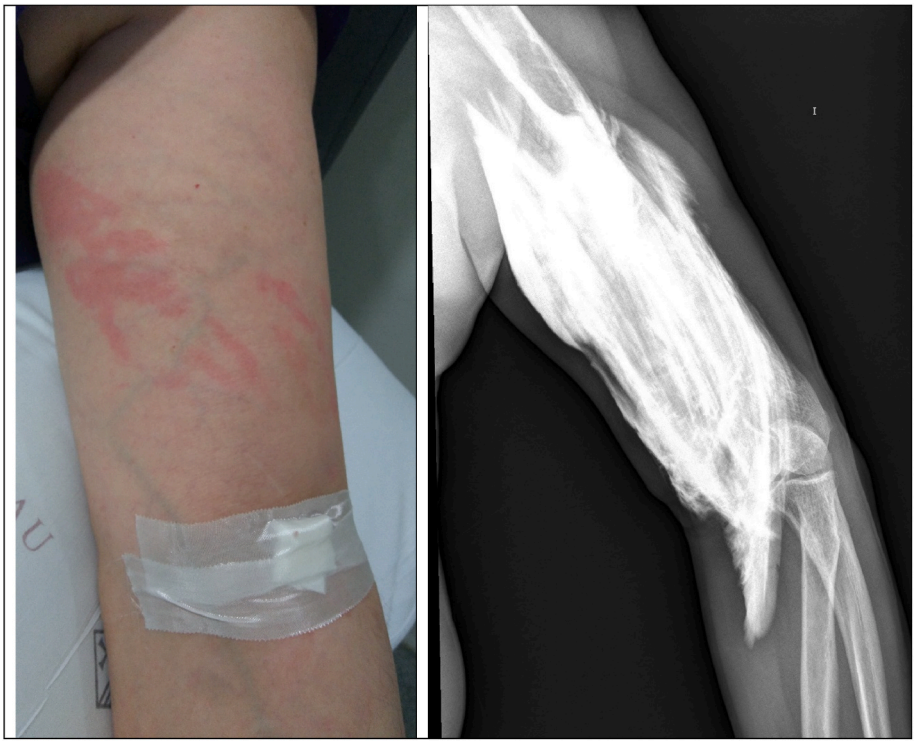

Fig. 1. Example of a photograph and x-ray of a case of tissue injury due to non-ionic iodinated contrast extravasation.

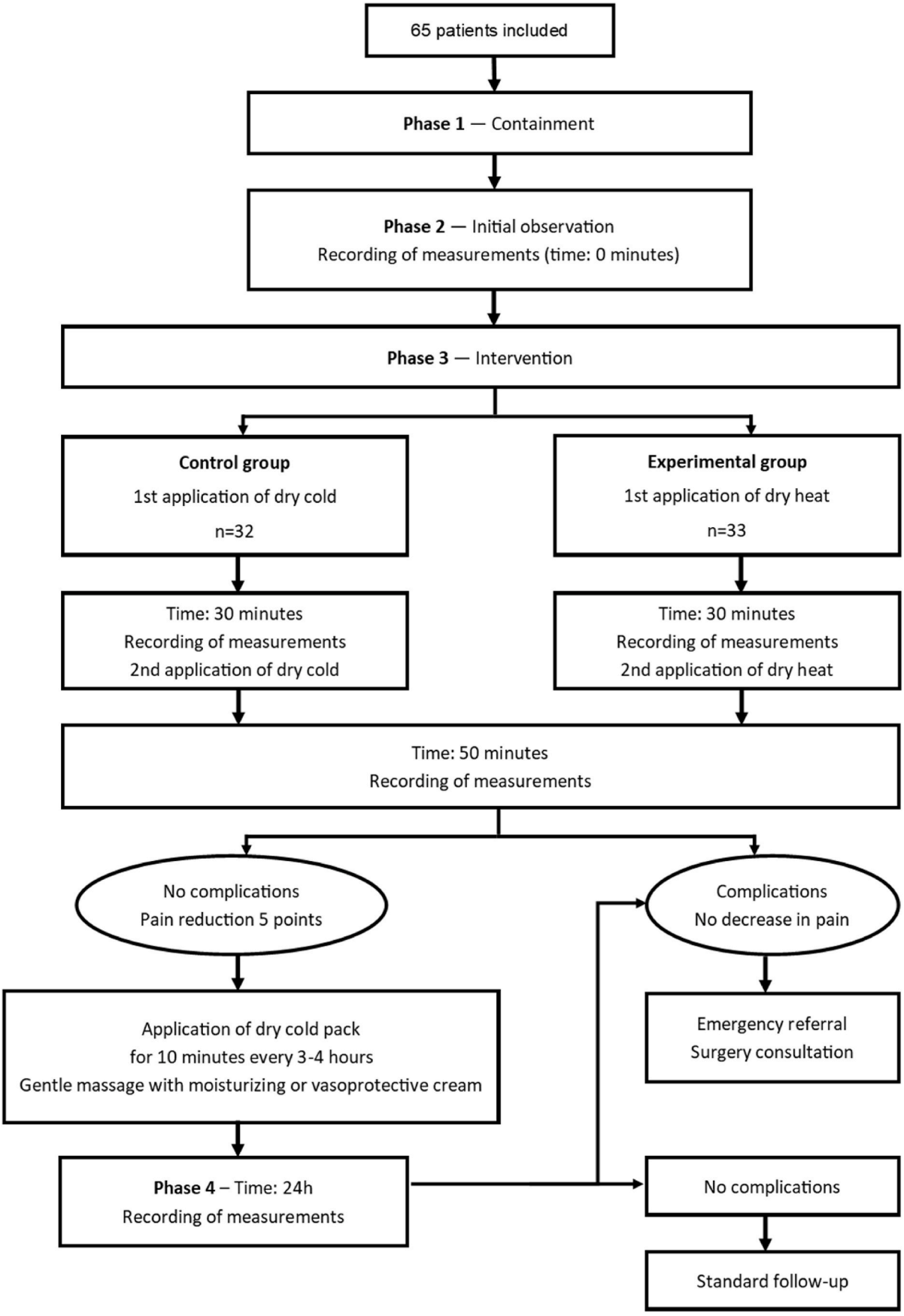

Fig. 2. Procedure flow chart.

Table 1
Sociodemographic, clinical and contrast administration data.

	Total N = 65 n (%)	Dry cold N = 32 n (%)	Dry heat N = 33 n (%)	p
Sociodemographic data				
Gender (female)	34 (52.4%)	17 (53.1%)	17 (51.5%)	1.0
Age (years) [mean (SD)]	69 (13.0)	69 (13.0)	68 (13.1)	0.791
Body Mass Index [mean (SD)]	25 (4.1)	26 (4.1)	25 (4.1)	0.345
Medical history				
Diabetes	17 (26.2%)	9 (28.1%)	8 (24.2%)	0.783
Raynaud syndrome	1 (1.5%)	0 (0%)	1 (3.0%)	–
Capillary fragility	14 (21.5%)	7 (21.9%)	7 (21.2%)	1.0
Thrombosis	14 (21.5%)	8 (25.0%)	6 (18.2%)	0.558
Lymphedema	4 (6.2%)	2 (6.3%)	2 (6.1%)	1.0
Cancer	32 (49.2%)	16 (50%)	16 (48.5%)	1.0
Radiation therapy	7 (10.8%)	1 (3.1%)	6 (18.2%)	0.105
Chemotherapy	12 (18.5%)	6 (18.8%)	6 (18.2%)	1.0
Contrast administration details				
Right upper limb	27 (41.5%)	14 (43.7%)	13 (39.4%)	–
Injection speed (ml/s) [mean (SD)]	3.3 (1.1)	3.3 (1.1)	3.3 (1.2)	0.949
Pain with contrast injection	45 (69.2%)	19 (59.3%)	26 (78.7%)	<0.001
Initial pain score (scale 0–10)[mean (SD)]	5 (2.9)	5 (2.6)	5 (3.2)	–
Density ≥350 mg/ml	35 (53.8%)	17 (53.1%)	18 (54.5%)	1.0
Contrast heating 37 °C	60 (92.3%)	30 (93.7%)	30 (90.9%)	–
Extravasated volume estimate (ml) [mean (SD)]	62 (30.6)	68.9 (31.8)	55.6 (26.3)	0.085

next participant was assigned to the control treatment. A randomized criterion was followed to select the type of treatment for the first patient in each centre.

2.3. Sample size

Since no similar previous studies were found, the sample size was calculated according to the hypothesis and the data obtained in the pilot study [18]. Assuming a 40% difference between the two treatments, with an alpha risk of 0.05 and beta of 0.20 on bilateral testing, a minimum of 22 subjects in each group was required to detect statistically significant differences between proportions.

2.4. Procedure and interventions

The intervention protocol consisted of four phases:

1) Containment phase. When extravasation was detected, contrast administration was stopped and all possible contrast was aspirated through the same venous access line, using a syringe. The line was then removed and a small dressing was placed at the injection site.
2) Initial observation phase. The first measurement (time 0′) was taken of the extravasation area (cm^2) and the circumference (cm) of the limb at the site with the most swelling. In cases of greater extravasated volume, x-ray of the limb was considered, to see the distribution of the contrast, and a photograph of the skin was taken if there were visible erosions or bruising (Fig. 1).
3) Intervention phase (Fig. 2).
   a) Control Group. A single-use thermal pack of dry cold, wrapped in a small sheet to avoid direct contact with the skin, was applied for 10 min. After this time, the thermal pack was removed and the limb left to rest for 20 min. Subsequently, the extravasation area and the limb circumference were measured again. A second thermal pack of dry cold was applied for a further 10 min. Finally, after 10 min' rest time, a third set of measurements were taken.
   b) Experimental Group. A single-use thermal pack of dry heat, wrapped in a small sheet to avoid direct contact with the skin, was applied for 10 min. After this time, the thermal pack was removed and the limb left to rest for 20 min. Subsequently, the extravasation area and the limb circumference were measured again. A second thermal pack of dry heat was applied for a further 10 min. Finally, after 10 min' rest time, a third set of measurements were taken.

In the absence of complications, the patient was discharged with the same home care instructions for both groups. In the case of inpatients, the same instructions were provided to the healthcare team for monitoring on the ward.

4) Final phase. The patient was reviewed 24 h after the event, to measure the area of extravasation and the circumference of the limb, and assess possible complications.

For discharge, the criteria for a positive response during the intervention phase were a reduction in pain of at least 5 points and the absence of immediate complications such as compartment syndrome or reduced mobility.

The home care instructions were the same for both thermal treatments, which consisted of keeping the limb elevated, topical applications of dry cold pack for 10 min every 3–4 h, and between applications, gentle massage using moisturizing or vasoprotective creams.

2.5. Study variables

The study variables were collected in a purpose-designed data sheet that was filled in during the various phases, grouped as:

a) Independent variables – Application of a dry cold or dry heat in the first hour of treatment.
b) Dependent variables – Pain (0–10 numerical scale), extravasation area (cm^2), and limb circumference (cm).
c) Anthropometric data – Gender (male/female), age (years), weight (Kg), height (cm), and body mass index (BMI).
d) Medical history – Vascular disease, diabetes, cancer, chemotherapy and radiotherapy.
e) Radiological procedure – Timing and site of cannulation, catheter size (G), professional experience (<5 or ≥5 years), contrast density (mg/ml), contrast preheating (yes/no), injection speed (ml/s), volume administered (ml), and extravasated volume estimate (ml).

2.6. Statistical analysis

Statistical analysis was carried out using IBM SPSS STATISTICS V.25.

Descriptive analysis was performed for all study variables. For qualitative variables, differences were analyzed with $\chi 2$ test and odds ratio calculation of risk when necessary. For quantitative variables, means were compared using Student's *t*-test and analysis of variance (ANOVA) if more than two categories. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Sample characteristics

A total of 65 patients were included, of which 32 were treated with dry cold only and 33 with dry heat then cold. The mean age was 69 years (SD:13), 52.3% of the patients were overweight and 87.7% had some relevant past medical history from the points included in the record sheet. Table 1 shows the sociodemographic, clinical and contrast administration characteristics of the study population. No significant differences in these characteristics were found between the two intervention groups, with the exception of pain during the administration of contrast which did not interfere with the outcome as can be seen in the following section.

3.2. Pain

Pain at the time of extravasation occurred in 69.2% (n = 45) of the patients, with a mean pain score of 5 (SD:2.9) on a 0 to 10-point scale; there was no statistically significant association between pain and any of the other variables studied. After the first thermal application, pain decreased by 3.6 (SD:2) points on average with both applications, the difference between hot and cold not being significant ($p > 0.5$). However, extravasations occurring outside the radiology department had a 2.4-point higher average pain score (n = 9; $p < 0.03$; 95%CI:0.31–4.53).

3.3. Inflammation

Data on limb circumference as an assessment of inflammation are shown in Table 2, where it can be observed that size increased during the first hour and decreased at 24h. Proportionally, the increase in circumference during the first hour was less in the patients who received initial heat treatment. Patients treated with heat also had a greater final decrease at 24h, with respect to starting values.

3.4. Treatment response and evolution of extravasation

The proportion of patients with complete absence of extravasation at 24h (Table 3) was more than twice as high in the group treated with heat than in the group treated with cold alone ($p < 0.001$; OR:14.6; 95% CI:3.6–58.1).

Table 4 details the outcomes at the different measurement times. Patients treated with heat had a smaller proportional increase in extravasation area during the first hour of treatment.

Of the patients who had only partial resolution of the extravasation area (Table 3), the initial mean area was 172 cm^2 (SD:67) and at 24h was 60 cm^2 (SD:56). In patients treated with cold pack only, the mean residual area was 67 cm^2 (SD:58) and in patients treated with heat pack first, the mean residual area was 16 cm^2 (SD:12), this difference being not statistically significant ($p = 0.153$).

3.5. Intravenous line

The most-used catheter during the administration of contrast was 20G (44.6%), followed by 22G or less (29.2%) and 18G (26.2%). Extravasation area was associated with the size of the catheter (ANOVA: $F = 4.017$; $p = 0.023$) and injection speed (ANOVA: $F = 24.56$; $p < 0.001$) (Fig. 3).

In the 62 patients for whom the data were reported, cannulation was performed by nursing staff with more than five years' professional experience in 61.3%. Cannulation was done at the time of the procedure in 74.2%.

3.6. Contrast density and speed of administration

Contrast density was grouped as a dichotomous variable, either 300 mg/ml or equal to or greater than 350 mg/ml.

An increase in the extravasation area was found with higher contrast density (300 mg/ml area: 116.1 cm^2; ≥350 mg/ml area: 161 cm^2) with a mean difference of 45.56 cm^2 ($p = 0.02$; 95%CI:10.27–80.84). Likewise, it was observed that the higher density contrast was administered at a higher speed [300 mg/ml, 2.5 ml/s (SD:0.48); ≥350 mg/ml, 4 ml/s (SD:1.1), with an average difference of 1.5 ml/s; 95% CI:1.06–1.92; $p < 0.001$].

All recruited patients recovered satisfactorily, either in the first 24 h or in subsequent days without the need for further interventions. There was only one patient who, after the 24-h check, had to be sent to the emergency room due to dermal blisters. This patient had a past medical history of stasis blisters.

4. Discussion

Thermal treatment based on the application of dry heat in the first instance produced a better outcome during the first hour and at 24 h, compared to the application of cold pack alone. The initial application of cold may be up to 14 times less effective. Heat reduces contrast viscosity, increasing its area of distribution and reabsorption [16], making it more beneficial than applying only cold compresses in the management of extravasation and inflammation.

In the cases in which extravasation did not resolve fully at 24 h, the residual area was much smaller in those treated with heat than those treated with cold alone, which would indicate a trend toward better resolution also exists in these patients.

Previous studies have documented local inflammation and swelling associated with the extravasation of contrast media, however they do not provide data on how this evolved over time, probably due to their retrospective design [19–21]. In the present study, the application of heat was proposed during the first hour of treatment to favor the immediate diffusion of the extravasation area, but continuing the subsequent treatment with cold compresses every 3–4 h to manage the local inflammatory reaction. As this represents an internal aggression with the skin remaining intact, topical application of hydrating or vasoprotective creams was also recommended, to promote resolution and symptomatic relief of inflammation [22]. A smaller increase in limb circumference was observed in patients treated with dry heat in the first hour of treatment, with a 1.2% greater reduction at 24h compared to patients treated with cold only, which could be attributed to better modulation of the local inflammatory effect.

A previous retrospective study [21] considered it appropriate to treat extravasation of radiological contrast using moist compresses at room temperature with clobetasol and silver sulfadiazine. The present study shows that dry thermal application would be sufficient to reduce the

Table 2
Limb circumference at the different measurement times.

Treatment	Dry cold		Dry heat		p	n (lost)
Time	Limb circumference					
	cm (n)	%[a]	cm (n)	%[a]		
0′	26.78 (32)	100%	26.09 (33)	100%	0.563	65 (0)
30′	27.32 (29)	+2.2%	26.46 (31)	+1.4%	0.450	60 (−5)
50′	28.00 (31)	+4.4%	26.37 (32)	+1.1%	0.174	63 (−2)
24h	26.50 (32)	**- 1.1%**	25.50 (33)	**- 2.3%**	0.357	65 (0)
Total	32		33			65

[a] Percentage in relation to time 0'.

Table 3
Outcomes of both interventions in the final phase (24h).*$\mathbf{p < 0.001}$/OR:14.6/95% CI 3.7–58.1

Complete diffusion extravasation area	Treatment		Total n (%)
	Dry cold n (%)	Dry heat n (%)	
YES*	13 (40.62%)	30 (90.9%)	43 (66.2%)
NO	19 (59.4%)	3 (9.1%)	22 (33.8%)
Total n (%)	32 (100%)	33 (100%)	65 (100%)

Table 4
Extravasation area over time. *Percentages in relation to time 0'.

Treatment	Dry cold		Dry heat		p	n (lost)
Time	Extravasation area					
	cm^2 (n)	%*	cm^2 (n)	%*		
0′	152 (32)	100%	128 (31)	100%	0.183	63 (−2)
30′	187 (29)	+19%	155 (29)	+18%	0.198	58 (−7)
50′	213 (31)	+29%	163 (31)	+22%	0.105	62 (−3)
24h	39 (32)	- 75%	1.5 (33)	- 99%	<0.001	65 (0)
Total	32		33			65

unwanted effects of uncontrolled inflammation and the probable associated tissue injuries, without requiring other products. Manipulating the skin with moisture could cause maceration [16], as could the placement of occlusive bandages and containment dressings [23], which is why they were not used.

Of note was the absence of pain at the beginning of extravasation in 30.8% (n = 20) of the patients, even in some cases with an estimated extravasation volume of more than 70 ml (n = 10). This finding is in line with other retrospective studies (30% [21] and 29.7% [10]), so it would not be advisable to use pain as the only sign of alarm in case of extravasation. This could have been influenced by the previous heating of the contrast medium, which coincided with 100% of the cases that did not have pain. Heating prior to administration has been shown to prevent immediate discomfort by reducing its viscosity, especially at high contrast densities [24]. It can also help in the management of extravasation, avoiding serious complications, since viscosity is considered a risk factor [10].

When comparing age groups, we observed a higher incidence in people over 65 years of age (67%), similar to previous studies [10,20,25]. No differences were observed by gender rank in the present study, although Ding et al. [25] documented in their systematic review that women had a higher risk of extravasation than men (OR:0.2891 – OR:0.5674).

In line with recent reviews [20,25], the size of the intravenous catheter used did not seem to influence the level of pain or resolution of extravasation. Hwang et al. [10] stated that there was no relationship between high speed of administration and extravasation. However, as shown in Fig. 3, the greater the caliber of the catheter and speed of administration, the greater the extravasation volume. Also, a higher density of contrast produced a greater extravasation area, which coincided with procedures with high speed of administration.

4.1. Limitations

Although a randomized clinical trial is ideal for evaluating the efficacy of a treatment, a quasi-experimental study was selected due to the low incidence of cases, available resources and time to research. Even so, this work provides higher levels of evidence than the retrospective studies published to date on the management of iodinated contrast extravasations by heat treatment. Future studies should be provided with a randomized clinical trial with a larger sample size to obtain more evidence on the efficacy of dry heat. It would have been desirable to carry out a continuous follow-up during the first 24 h, to record the evolution of the intended modulating effect over time. Another limitation was the

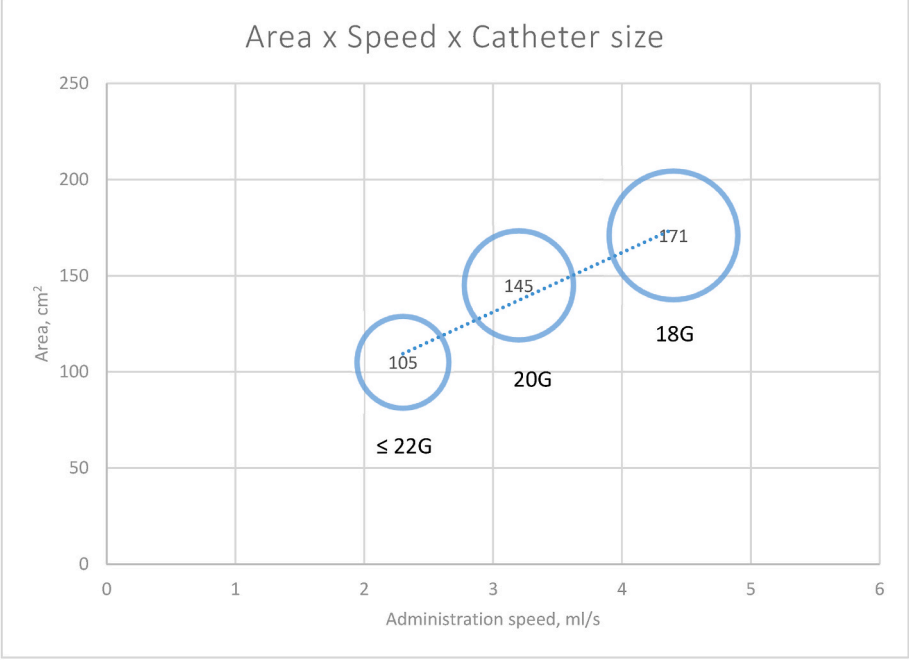

Fig. 3. Catheter size, administration speed, and mean extravasation area.

low number of extravasations in extreme distal anatomical areas, where the subcutaneous tissue and the skin itself have little margin for dilation, and topical treatment may not be sufficient for large extravasated volumes.

5. Conclusion

The initial application of dry heat improves statistically significantly the resolution of non-ionic iodinated contrast extravasation. This finding may help resolve the lack of consensus on how best to manage this adverse event, which requires immediate action to treat tissue injury and avoid associated complications.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical responsibilities

The study was approved by the different ethical committees of the centers that participated in the study and the Bioethics Commission of the University of Barcelona. The study subscribes to the principles of the Declaration of Helsinki and the legal regulations for data protection and was registered at ClinicalTrials.org (NCT 03426735).

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

To all the patients who have participated. To Carlos Lozano, for advice on the statistical analysis of this study. To Fundació Recerca Hospital Sant Pau from Barcelona for their support.

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