

Third-generation cryotherapy reduces time to surgery and local complications in patients with ankle fractures: a prospective randomised controlled trial

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Third-generation cryotherapy reduces time to surgery and local complications in patients with ankle fractures: a prospective randomised controlled trial.

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ABSTRACT***Background***

Ankle fractures are common, and cryotherapy is routinely used to reduce pain, swelling and local skin complications, both before and after surgery. The aim of this study is to report the results with the use of pre-operative third-generation cryotherapy (Z-One®, Zamar, Italy) in the management of patients with ankle fractures. We investigated the time to surgery, pain, opioid intake, and local skin complications.

Methods

169 patients with ankle fracture were randomised into two groups, the cryotherapy group (89 patients) and the control group (C: 80 patients). The time-to-surgery, Visual Analogue Scale (VAS) and the analgesic drug demands (Morphine Sulfate 10 mg/ml solution for injection) were recorded. The development of skin complications was assessed on a daily basis. BMI and the number of cigarettes smoked were also recorded.

Results

The mean time-to-surgery was shorter in patients treated with cryotherapy compared to the control group (34.78 hrs. vs. 91.44 hrs., $p<0.001$). Significant differences between treatments and controls were found for VAS, morphine intake (number of vials), and skin complications. The mean preoperative VAS and morphine consumption were lower in the cryotherapy group compared to controls (mean VAS 2.04 vs. 5.9, mean morphine consumption 0.1 mg vs. 0.83 mg). In the cryotherapy group, 4.5% of patients developed a skin complication compared to 28.7% of the control group; 85% of skin-related problems occurred in the non-cryotherapy group ($p<0.001$).

Conclusion

Preoperative third-generation cryotherapy is effective in reducing time to surgery, preoperative pain, and opioid intake in patients hospitalised for ankle fractures. It is also effective in reducing the occurrence of skin complications. No major complications related to the use of the device were reported. Third-generation cryotherapy is useful in the perioperative management of patients necessitating surgery for ankle fractures.

International Clinical Trial Registration Number: NCT06396364

90 ***Level of evidence:*** I (RCT)

91 ***Keywords:*** cryotherapy, ankle fractures, ankle surgery, time to surgery

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93 INTRODUCTION

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95 Ankle fractures are common, accounting for about 10% of all fractures [1]. They
96 are common in young and active patients, with a reported prevalence of 15%-
97 25% of all sports-related injuries [2], but their incidence is also increasing in
98 elderly patients, being the third most common fracture after the 6TH decade of
99 life [3]. Wound complications such as dehiscence and surgical site infections
100 are frequent local complications, leading to poor functional outcomes and
101 increasing healthcare costs by more than 300% [4]. Local complications may be
102 related to the time to surgery, although the literature is not univocal.

103 Cryotherapy is routinely used to reduce pain and swelling both before and after
104 surgery [5]. It is commonly used to manage pain and swelling in several
105 musculoskeletal disorders [6,7], as well as an adjuvant treatment in systemic
106 disorders [8]. Cryotherapy acts by decreasing blood flow, reducing painful
107 stimuli, and preventing local inflammation; in addition, it has antiproliferative
108 and chondroprotective effects [8].

109 Conventional cryotherapy consists of ice gels or packages that are directly
110 applied to the area of pain and soreness. Second-generation cryotherapy
111 involves the use of cuff devices, with iced water flowing through, on which
112 constant pressure can be applied [9]. The increased external pressure reduces
113 the pressure gradient between blood vessels and tissues, and discourages
114 leakage from capillaries. A common problem is the development of reactive
115 vasodilation, consequent to the rapid increase in the local temperature after the
116 procedure. Third-generation devices deliver water-free computerised
117 cryotherapy, which maintains a constant temperature through different
118 anatomical layers, while allowing progressive changes in temperature and
119 pressure to avoid reactive vasodilation [10]. Independent of the location and
120 the type of device used, cryotherapy is generally well tolerated and increases
121 patient satisfaction [9,10].

122 Although the use of cryotherapy is traditionally believed to reduce pain,
123 swelling, local skin complications, and the need for analgesia, its effects on
124 ankle surgery are contradictory. Furthermore, no studies on third-generation
125 devices have been conducted on ankle fractures.

126 We report the results of using third-generation cryotherapy (Z-One®, Zamar,
127 Italy) in the preoperative management of ankle fractures. The primary aim was
128 to assess the time to surgery. We investigated treatment efficacy based on
129 reported pain, morphine consumption, and preoperative local skin
130 complications. The safety and tolerability of the procedure were also studied.
131 The working hypothesis is that third-generation cryotherapy reduces time to
132 surgery and is useful in the surgical management of ankle fractures.
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MATERIAL AND METHODS

We analysed the prospectively collected data of 169 patients with ankle fractures, treated with open reduction and internal fixation (ORIF). Patients were randomly grouped into two groups in the Emergency Department at the time of diagnosis. The cryotherapy group (89 patients) were treated with a third-generation cryotherapy device (Z-One®, Zamar), which was applied daily for two hours two times a day up to the day of surgery. The leg was immobilised in a walking boot, which was removed when the cryotherapy device was applied. The control group (80 patients) did not use cryotherapy before surgery, the leg was immobilised in a below-knee back slabs, and elevation of the injured limb was implemented. Patients were admitted into two hospitals (Azienda Ospedaliera San Camillo Forlanini -Roma and Ospedale San Paolo - Civitavecchia) between 2021 and 2023 (NCT06396364). All patients had signed a written consent, and the study was approved by the local ethics committee. The details of the CONSORT statement allocation are reported in Figure 1.

Inclusion and exclusion criteria

Patients admitted to the Emergency Department with an ankle fracture were included in the current study. Exclusion criteria were open fractures, fracture-dislocations which required external fixation, patients with one or more associated fractures and polytrauma patients. Patients who were not able to comply with the pre- and post-surgical indications were also excluded.

Patients' assessment and randomisation

A detailed physical examination was conducted in all patients by local orthopedic surgeons. All patients underwent standard radiographs to diagnose the fracture, and computed tomography for preoperative planning if indicated. After the diagnosis was made and surgical treatment was indicated, patients were admitted to the Department of Orthopedic and Trauma Surgery. Patients were randomised into two groups (cryotherapy and control group) by blocked randomisation with random block sizes to ensure that the patients were balanced. The randomisation of participants was conducted by the authors G.F. and R.A., who didn't operate on the participants. Other authors (R.M.L, C.D.A.,

R.A.) opened the envelopes, assessed the preoperative local skin condition, assessed a positive wrinkle sign and determined that patients were eligible for surgery. Operating surgeons (C.D.A., M.S., A.G.V.) were blinded to the group allocation. Other Authors validated the outcomes.

Sample size calculations were conducted using the G-power program (IBM Inc., Armonk, NY, USA). Patients in the cryotherapy group were immobilised in a walking boot to allow the use of the cryotherapy device (Figure 2). Patients in the control group were immobilised in below-knee back slabs. Pain was evaluated according to the Visual Analogue Scale (VAS) and analgesic drug consumption (mg of morphine). The Body Mass Index (BMI), number of cigarettes smoked, and presence of preoperative skin complications were assessed.

Surgical technique

The wrinkle sign was chosen as the clinical criteria to plan surgery. As the swelling receded and the skin began to wrinkle both on the lateral and medial sides, the patient was eligible for surgery. Under loco-regional anesthesia, the patient was positioned supine with a sandbag under the ipsilateral buttock, or prone if a posterolateral surgical approach was indicated. A tourniquet was applied at the thigh, the lower limb was prepared and draped in the usual sterile fashion, exsanguinated, and the tourniquet was inflated. The lateral malleolus was approached first, reduced and fixed with a plate and screws. Then, the surgical technique varied depending on the fracture pattern, the presence of syndesmosis injury and associated soft tissue injury. The skin was sutured with non-absorbable sutures, and the ankle was immobilised in a walking boot. All patients received intraoperative antibiotic treatment, intravenous controlled analgesia 24 to 48h after surgery, and standard thromboembolic prophylaxis with low molecular weight heparin (LMWE) for up to complete weight bearing. The ankle was immobilised in a walking boot, but passive ankle motion was encouraged from the first post-operative day.

Statistical analysis

An a priori power analysis was performed using preliminary data based on the time-to-surgery variable. The initial estimate suggested a minimum of 4 units

per group to achieve 90% power. Subsequent analysis of the full dataset indicated higher variability; under these conditions, the minimum required sample size per group would be 8. Univariate descriptive analysis of the variables under study was carried out by calculating the centrality and variability indices for the quantitative variables and frequency tables for the variables.

The homogeneity between the cryotherapy group and control group for the variables sex, age, type of fracture, diabetes, hypercholesterolemia, venous insufficiency, and BMI class was checked. Depending on the nature of the variables, a t-test or a chi-square test was used.

Any significant differences between the cryotherapy and control groups were assessed using independent samples t-tests for quantitative variables and chi-square tests for qualitative variables. Where the sample size was not sufficient, the non-parametric Mann-Whitney test for independent samples was used.

An alpha significance level of 0.05 was used in all analyses mentioned. For the statistical analysis of data, IBM SPSS Statistics software version 28 was used.

RESULTS

Basic characteristics of the study population are reported in Table I.

From the power analysis, the minimum sample size to obtain a statistical power of at least 0.9 with a significance level of 0.05 is at least four units for each group. Specifically, the power reached is 0.978.

The chi-square test showed no association between belonging to a group and the variables sex, type of fracture, diabetes, hypercholesterolemia, chronic venous insufficiency, and BMI. Therefore, the groups were homogeneous concerning these variables. The mean age of the cryotherapy group was 50.63 years (SD 16,271; Std. Error Mean 1.725), and the mean age of the control group was 53.25 (SD 14,541; Std. Error Mean 1.626), with no significant differences.

The mean time to surgery was shorter in the cryotherapy group. The mean time to surgery in the cryotherapy group was 34.78 hrs. (median 36.0 hrs., S.D. 12.31, Mean Std. Error 1.30). In comparison, in controls, it was 91.44 hrs. (median 78.5 hrs., S.D. 42.25, Mean Std. Error 4.72) (Figure 2). The t-test was

performed according to the different subtypes of fractures. Given the low sample size of the two groups, the non-parametric Mann-Whitney test was used. Third-generation cryotherapy significantly decreases time to surgery independently of the type of fracture (Table II).

A significant difference between the groups was also investigated for the secondary outcomes: VAS, morphine consumption (mg), and skin complications. The mean preoperative VAS and morphine consumption were lower in the cryotherapy group compared to controls. (mean VAS 2.04, S.D. 0.865, Mean Std. Error 0.092, and 5.9, S.D. 1.88, Mean Std. Error 0.210 respectively; mean morphine assumption 0.1 mg, S.D. 0.106, Mean Std. Error 0.011, and 8.3 mg, S.D. 1.652, Mean Std. Error 0.185, respectively) Figure 3.

The chi-square test was used to investigate the development of preoperative skin complications. We recorded four skin complications in the cryotherapy group (4 serous blisters; 4/89, 4.5%), and 23 skin lesions in the control group (6 severe edema, 13 serous blisters, 4 hemorrhagic blisters; 23/80; 28.7%). 85.2% of skin complications occurred in the control group (Table III). The difference was statistically significant ($p\text{-value} < 0.001$). No side effects were reported in the cryotherapy group.

257 **DISCUSSION**

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259 Ankle fractures are frequent, with an overall incidence rate ranging from 45 to
 260 107/1.000 person-years, accounting for about 10% of all fractures [11,12]. They
 261 are more common in men below 50 years of age, then females became
 262 predominant and the age-specific incidence rates decreased in both sexes [11,
 263 12]. The incidence of ankle fractures has increased by up to 300% in the last 30
 264 years, especially in the elderly population. Unfortunately, complications
 265 following surgical treatment are common, ranging from 10% to 30% of cases,
 266 with rates increasing to 40% in the elderly [4, 13]. Deep infections represent
 267 the most serious complications, increasing the risk of poor functional outcome,
 268 and may increase the healthcare costs by more than 300% [4, 14]. Time-to-
 269 surgery may influence the development of local skin complications [15],
 270 although information about the influence of delayed surgery is still ambiguous.
 271 Cryotherapy decreases swelling, joint effusion, and relieves pain. It induces
 272 local vasoconstriction, reduces capillary leakage, and diminishes blood flow to
 273 the joint and soft tissues [8]. It can moderate the inflammatory cascade by
 274 decreasing pro-inflammatory cytokines (IL-6, IL-1, VEGF, PG-E2, NF-kB-p65) in
 275 the synovial fluid, and increases the synthesis of pyruvate, which has an
 276 antioxidant effect [16]. It also decreases the electrical conduction speed
 277 through nerves and limits transmission of the electrical impulses to the sensory
 278 neurons in the posterior horn of the medullary canal, thus reducing pain [15].
 279 In vitro cryotherapy regulates the intracellular pH, which reduces muscular
 280 fatigue and increases the synthesis of alanine, which has a chondroprotective
 281 effect [16, 18]. Finally, it decreases the proliferation rate of cells, including
 282 bacteria, hence it may prevent wound infection in foot and ankle surgery [6].
 283 Independent of the location and the type of device used, cryotherapy is
 284 generally well tolerated and increases patient satisfaction [7,10,19,20,21].
 285 Conventionally, cryotherapy is delivered through ice packs, which have been
 286 proven effective in reducing edema and pain in ankle fractures. A common
 287 burden of ice pack cryotherapy is the development of reactive vasodilation,
 288 consequent to the rapid increase in the local temperature after the procedure.
 289 Seemingly, the risk of frostbite in the ankle and foot region is extremely rare,

but its consequences might be devastating, requiring active surveillance and prompt treatment [22,23].

Second-generation cryotherapy involves the use of cuff devices, with iced water flowing through, on which constant pressure can be applied [24]. The increased external pressure reduces the pressure gradient between blood vessels and tissues, and discourages leakage from capillaries. Thanks to the effect of compression, these devices are effective in reducing edema and ankle swelling after trauma. Compressive cryotherapy is well tolerated and efficacious in decreasing the use of analgesic after knee and ankle surgery, and it is becoming a standard of care in postoperative rehabilitation of patients with ankle fractures [25]. However, it does not decrease the development of postoperative complications, including infections [26]. No differences in pain reduction and ROM were reported using second-generation compared to first-generation devices following total knee arthroplasty [27]. Furthermore, second-generation cryotherapy devices are not able to maintain a constant cold temperature for a long time.

To avoid these problems, third-generation devices use computed cryotherapy to deliver gradual changes in pressure and temperature. The software produces a progressive drop in temperature and a controlled, slow return to a room-temperature environment, avoiding reactive vasodilation (Figure 4).

Despite the above-mentioned beneficial results of cryotherapy in the pre- and postoperative care of ankle surgery, the lack of standardised protocols and few level 1 studies make it difficult to appreciate its benefits. In addition, there's scarce evidence on the benefits of the preoperative use of cryotherapy [14].

Third-generation cryotherapy is effective in reducing time-to-surgery, pain and wound complications. Mean VAS score and morphine consumption were significantly lower in the cryotherapy group compared to controls. The reduction of morphine intake reduces their dose-related side effects, and improves patient satisfaction [20,28]. Cryotherapy significantly reduces the prevalence of preoperative skin complications, which are common in ankle trauma. The most common are local erythema, severe edema, blistering, and necrosis, which are predictors of negative outcomes [4]. Notably, 95.5% of the cryotherapy group did not show skin complications compared to 71.3% of the control group. When we considered all patients with skin injuries, 85.2% of

these patients belonged to the control group. We hypothesise that the reduction of time to surgery is due to the faster reduction of swelling and a significant reduction of preoperative local skin complications. BMI, cigarette consumption and acetaminophen intake did not affect primary and secondary outcomes. Finally, no side effects such as deep venous thrombosis, frostbite, excessive pain, or compartmental syndrome were reported. We found only a recent retrospective study comparing the effect of ice pack and third-generation cryotherapy after unicompartmental knee arthroplasty surgery, reporting significant improvements in postoperative pain control and knee function [29]. However, the study's retrospective design and lack of well-designed studies make further level I studies necessary to validate these promising results. Our study certainly had some limitations. Firstly, there was no standardised protocol that could define the best timing and frequency of cryotherapy. The patients were not blinded about the treatment, because the cryotherapy group was immobilised in a walking boot, while the control group was immobilised in a back slab. However, the surgeon was blinded about the patients' allocation because the immobilisation was removed before entering the surgical theatre. Thirdly, literature results on pre-operative cryotherapy are scarce, and some have reported a paradoxical increase in time-to-surgery with cryotherapy. Some patients might have taken other analgesics, including NSAIDs, which were not reported in the study. No investigation has been done on the total length of stay, as most of our patients are discharged the day after surgery, in functional outcomes, or in the development of postoperative complications (i.e. wound dehiscence and surgical site infection). We are aware that a full health economics analysis has not been performed and was not planned. However, the favourable impact on pre-operative length of stay is likely to result in cost savings for our healthcare system.

CONCLUSION

Third-generation cryotherapy is effective in reducing time-to-surgery, pre-operative pain and opioid intake in patients undergoing surgery for ankle fractures. It is also effective in reducing the occurrence of skin complications. The patients themselves administer it, and patient monitoring is not needed. It is safe, with no major complications related to its use. Third-generation cryotherapy may be useful in perioperative treatment of patients hospitalised for ankle fractures, as it may reduce the hospital stay. However, standardised protocols and further studies are required to confirm these encouraging results.

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364 **DECLARATIONS**

365

366 **Author Contributions:** Conceptualisation, R.M.L. and C.D.A.; methodology,
 367 G.F. and R.A.; investigation, G.F., S.D.S., F.A.; data curation, R.M.L., G.F. and
 368 S.D.S.; wrote original draft preparation, F.A. and A.G.V.; review and editing,
 369 G.V.A.; supervision, M.S., G.P.; final review and supervision, F.M., N.M; All
 370 authors have read and agreed to the published version of the manuscript.”

371

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374

375 **Ethics approval:** The study was conducted in accordance with the Declaration
 376 of Helsinki and approved by the Institutional Review Board (or Ethics
 377 Committee) of A.O. San Camillo-Forlanini, Rome, Italy (Comitato etico Lazio 1,
 378 protocol code 12/2021, 28 February 2021).

379

380 **Informed Consent Statement:** Written informed consent was obtained from
 381 all subjects involved in the study.

382

383 **Data Availability Statement:** All data generated or analysed during this study
 384 are included in this
 385 published article. The datasets used and/or analysed during the current study
 386 are also available
 387 from the corresponding author on reasonable request.

388

389 **Conflicts of Interest:** All the authors declare no conflicts of interest. The
 390 company that founded the APC had no role in the design of the study, in the
 391 collection, analyses, or interpretation of data, in the writing of the manuscript,
 392 or in the decision to publish the results. “

393

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507 **LIST OF ABBREVIATIONS**

508

509 ORIF: open reduction and internal fixation

510 VAS: Visual Analogue Scale

511 BMI: Body Mass Index

512 LMWE: Low Molecular Weight Heparin

513 NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

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516 **FIGURES AND TABLES**

517

		Group			
		Cryotherapy		Control	
		Count	%	Count	%
Sex	M	56	62.9%	45	56,3%
	F	33	37.1%	35	43,8%
Fracture type *	Trimalleolar fracture	26	29.2%	19	23,8%
	Bimalleolar fracture	29	32.6%	36	45,0%
	Tibial malleolus only	0	0.0%	0	0,0%
	Malleolar fracture only	17	19.1%	15	18,8%
	Trimalleolar fracture with syndesmotic disruption	17	19.1%	10	12,5%
Skin injuries	No	85	95.5%	57	71.3%
	Yes	4	4.5%	23	28.7%
Diabetes	No	73	82.0%	70	87.5%
	Yes	16	18.0%	10	12.5%
Hypercholesterolemia	No	73	82.0%	67	83.8%
	Yes	16	18.0%	13	16.3%
Venous insufficiency	No	82	92.1%	76	95.0%
	Yes	7	7.9%	4	5.0%
BMI	Underweight	0	0.0%	0	0.0%
	Normal	42	47.2%	46	57.5%
	Overweight	35	39.3%	23	28.7%
	Obesity I stage	12	13.5%	7	8.8%
	Obesity II stage	0	0.0%	3	3.8%
	Obesity III stage	0	0.0%	1	1.3%

518

519 **Table I.** Basic characteristics of the study population. (*Fracture type: ankle
 520 fractures were classified according to the Weber and Lauge-Hansen
 521 Classification).

522

523

524

			Group						
			Cryotherapy				Control		
			Time to surgery (h)			Time to surgery (h)			
			Mean	Median	Standard Deviation	Mean	Median	Standard Deviation	p-value°
Type of fracture	Trimalleolar	36.23	39.00	8.66	102.26	90.00	42.73	<0.001	
	Bimalleolar	33.79	30.00	11.94	79.94	75.00	24.60	<0.001	
	Medial malleolus	.	.	.	.	.	.		
	Lateral malleolus	31.65	24.00	11.32	93.33	72.00	63.43	<0.001	
	Trimalleolar with TPA dislocation	37.35	28.00	17.79	109.40	111.50	47.61	<0.001	

Table II. Cryotherapy reduces the time to surgery for all types of ankle fractures compared to controls.

Cutaneous Complications Crosstabulation

			Skin lesions		Total
			No	Yes	
Group	Cryotherapy	Count	85	4	89
		% within Group	95.5%	4.5%	100.0%
		% within skin lesions	59.9%	14.8%	52.7%
	Controls	Count	57	23	80
		% within Group	71.3%	28.7%	100.0%
		% within skin lesions	40.1%	85.2%	47.3%
Total	Count		142	27	169
	% within Group		84.0%	16.0%	100.0%
	% within skin lesions		100.0%	100.0%	100.0%

535 **Table III.** Cutaneous Complications Crosstabulation. 95.5% of the cryotherapy
536 group did not report skin complications with respect to 28.7% of the controls.
537 Among all skin lesions reported, 85.2% belong to the control group.

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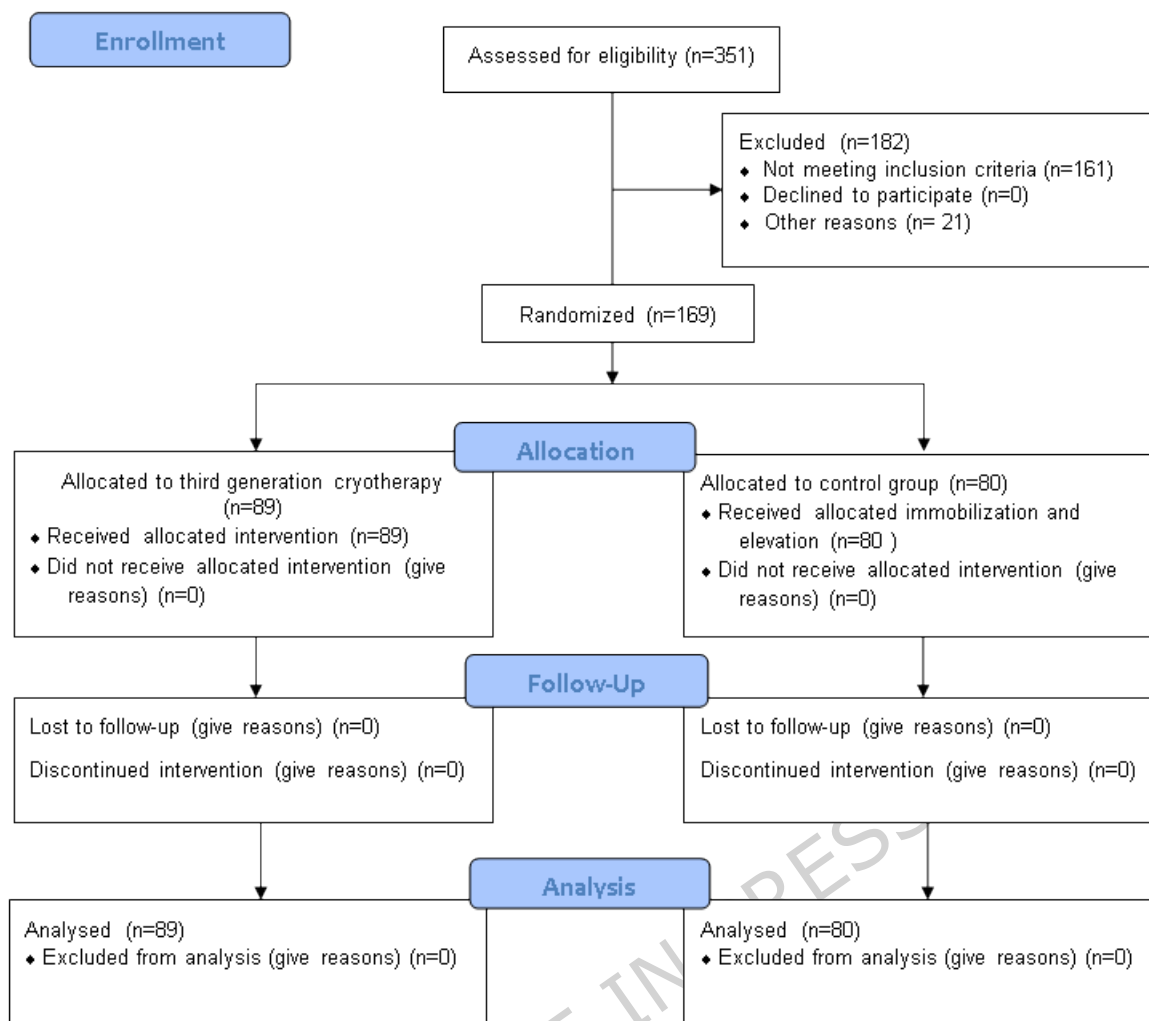
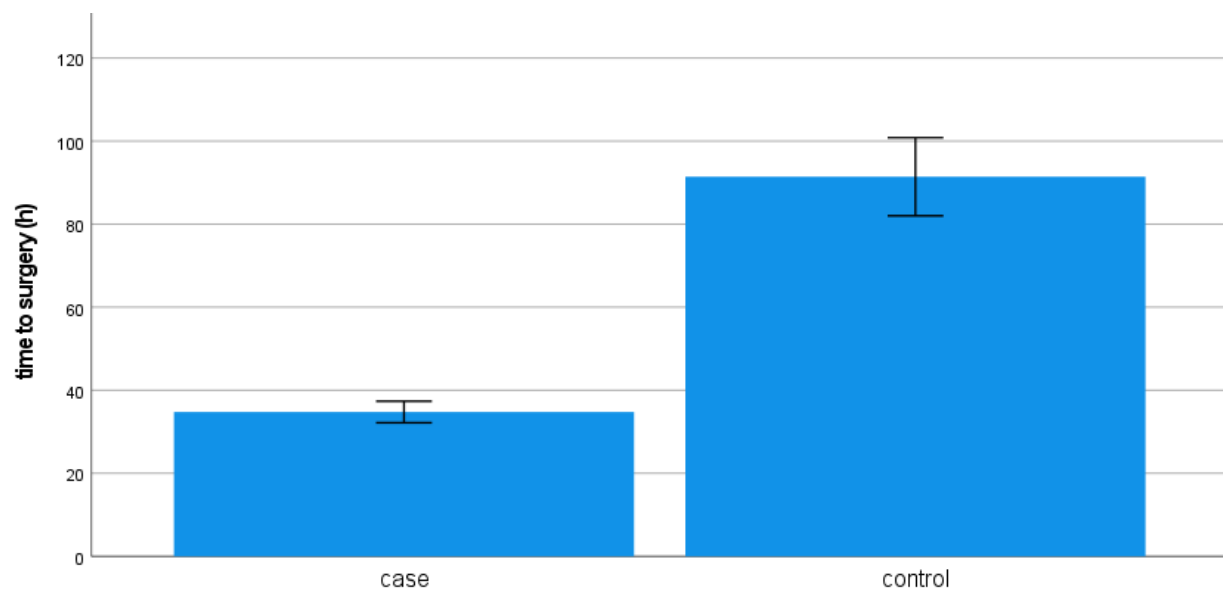


Figure 1. Study flow diagram.



541

542 **Figure 2.** Time to surgery. The time to surgery is significantly shorter in

543 patients treated with the third cryotherapy device compared to the control

544 group.

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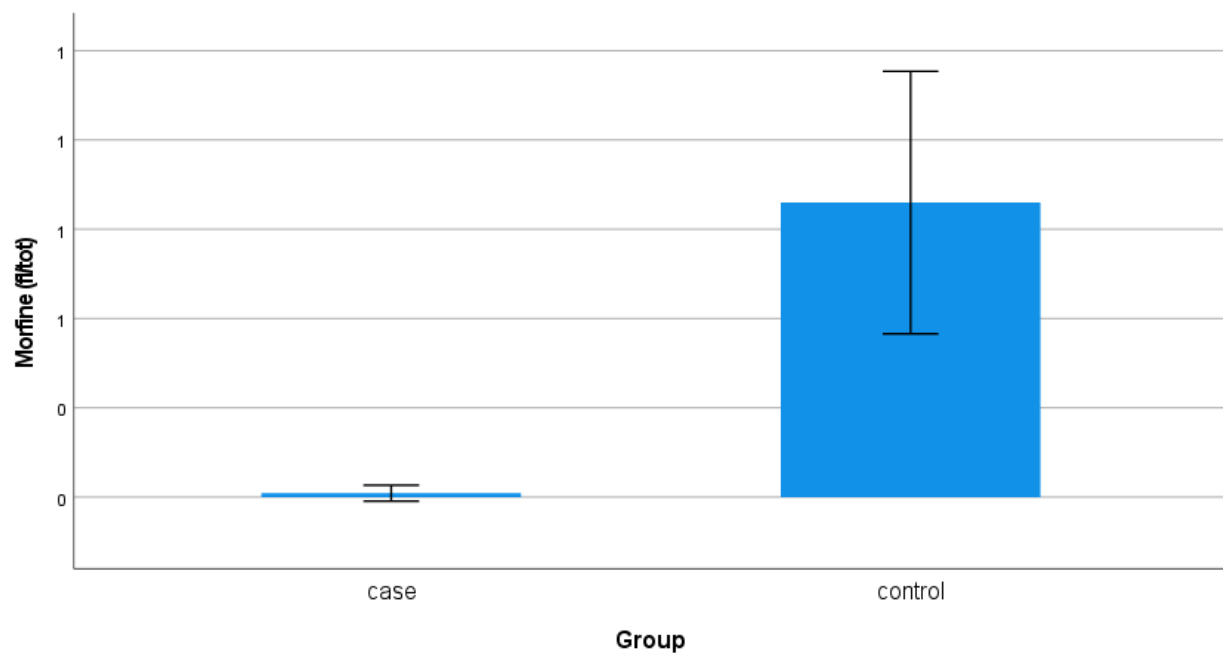
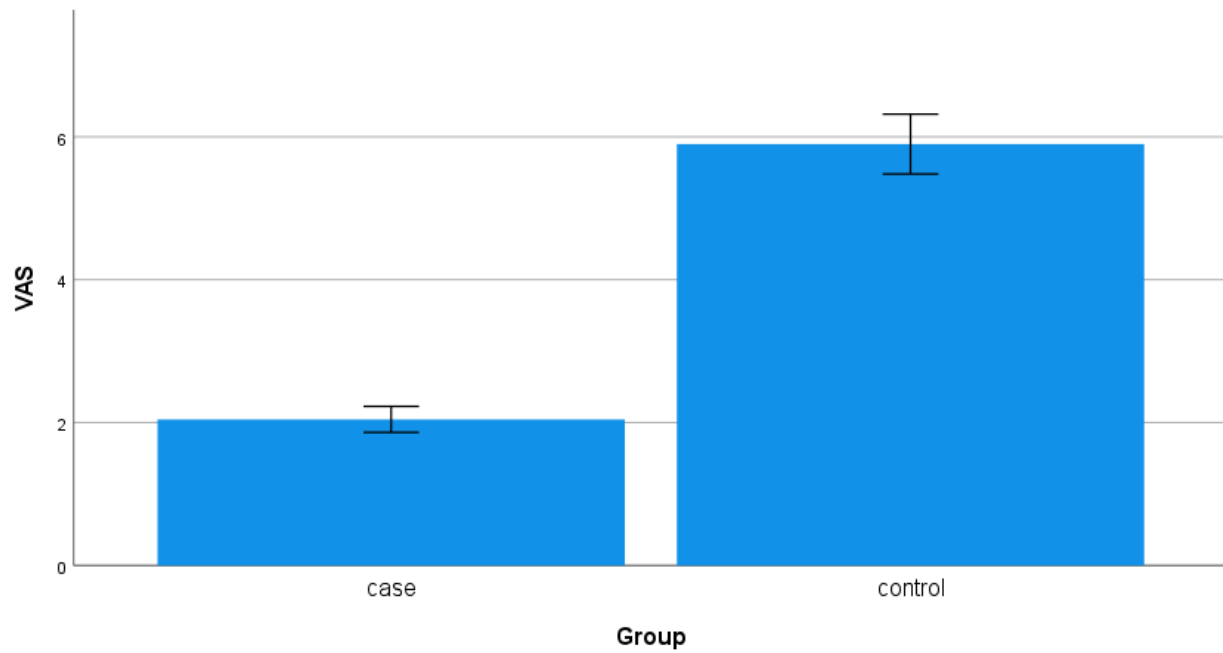


Figure 3. The mean pre-operative VAS (A) and morphine consumption (Mg of morphine - B) were significantly lower ($p\text{-value} < 0.001$) in the cryotherapy group compared to the control group.

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556 **Figure 4.** Third-generation cryotherapy device.

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Third generation cryotherapy reduces time to surgery and local complication in patients with ankle fractures: a prospective randomized controlled trial.

Patients Flow Diagram

