

# Effectiveness of hyaluronic acid in post-surgical cures following partial matricectomies with the phenol/alcohol technique: A randomized clinical trial

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## ABSTRACT

**Background:** Post-operative cures with hyaluronic acid (HA) could potentially shorten the period recovery involved in the phenol technique for ingrown toenail. The aim of this study was therefore to compare a standard healing protocol with the experimental one based on hyaluronic acid cream.

**Material and methods:** 70 patients who had undergone phenol technique surgery for ingrown toenail were divided into two groups – control (n = 35) who received post-operative cures following the standard protocol with povidone iodine gel, and experimental (n = 35) who received cures with HA in the first 3 visits. Bleeding, total healing time, and perceived pain were assessed.

**Results:** Patients in the control group recovered from the intervention in a total of  $26.17 \pm 7.75$  days, while those in the HA group recovered in a significantly shorter time –  $22.42 \pm 2.41$  days ( $p = 0.007$ , effect size 0.653). However, there were no between-group statistical differences in bleeding or perceived pain over the course of the post-surgery visits.

**Conclusions:** The use of low molecular weight hyaluronic acid is effective in reducing the phenol-technique healing time by 4 days compared with the standard cure. However, no extra effects such as reductions in bleeding or perceived pain can be expected in choosing this healing protocol.

## 1. Introduction

The phenol/alcohol technique is probably the best known and most frequently applied for the surgical resolution of ingrown toenails. This technique combines removal of the nail's spicule with partial chemical matricectomy using phenol [1]. The advantages of phenol ablation include having been associated with 49 fewer recurrences per 1000 patients than other modalities [2], being applicable in the presence of sepsis, involving less post-surgical pain because of its anaesthetic properties, and having superior cosmetic results than surgical matricectomy [3]. It has also been shown to be safe for the general population, children, and people with diabetes [4]. However, it has a number of disadvantages resulting from the chemical cauterization of the tissue,

including delayed healing, prolonged serous drainage due to the acute reaction to the chemical agent, and increased risk of infection [5]. Various studies have tried to reduce the long recovery period through different types of cures such as honey, paraffin gauze, and povidone iodine [6] or nanosilver drainage [7]. Although improvements have been found in final wound healing (by a few days) with controlled flux electrolysed acid solution [8], there is as yet no strong scientific evidence that any of these protocols improve healing after segmental matrix phenolization.

There are many products currently on the market with creams based on different concentrations of hyaluronic acid (HA). HA is a non-sulfated glycosaminoglycan which is synthesized in the body mainly by dermal fibroblasts and epidermal keratinocytes. It is a major component of the

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extracellular matrix, is a biodegradable polymer, has an axial hydrophobic part and a central hydrophilic part, and is polyanionic [9]. Products with high HA concentrations, between 20 and 24 mg/ml, absorb water because they are below their hydration equilibrium. There has been growing interest recently in investigating drugs based on HA given its biocompatibility, physiological properties such as muco-adhesion, and ease of chemical modification (molecular weight changes) which have given rise to its application in tissue regeneration, anti-ageing, as an anti-inflammatory, and in wound healing [10].

When a phenol/alcohol matricectomy technique is carried out, one is facing a third-degree wound in which apparently healthy tissue is immersed in a chemical product that burns the nail matrix. But there is also loss of epidermis, involvement of the dermis, and destruction of skin appendages [11]. Wound healing is the body's natural and normal response to injury. It is a complex dynamic process of rapid recovery of damaged tissues and normal function. This process comprises four strongly interconnected and overlapping phases – haemostasis, inflammation, proliferation, and remodelling [12]. Cures with HA have been shown to be particularly effective in hydrating the skin of the foot so as to provide a physiological environment that can speed up the wound's tissue remodelling process [9]. But even though their use is becoming popular in clinical settings and they are often applied in the phenol technique's healing protocol, there is as yet no scientific evidence for their efficacy. If the phenol technique could be improved by shortening its recovery period, it would stand out as the gold standard to choose. To the best of the authors' knowledge, there has been no randomized controlled trial assessing the healing and recovery time when using a hyaluronic acid cream in phenol matricectomy. The objective of this study was therefore to compare the efficacy of a post-surgical treatment protocol with a hyaluronic-acid based ointment compared with a control protocol (using povidone-iodine gel) in partial chemical matricectomies with the phenol/alcohol technique.

## 2. Methods

### 2.1. Participants

A randomized controlled trial was performed with a sample of 70 patients (20 women and 50 men, mean age  $22.6 \pm 8.7$  years), who presented for ingrown toenail surgery at the Podiatric Clinic of the University of Extremadura and the Clínica Podológica Gijón. The research protocol was approved by the Bioethics and Biosecurity Committee of the University of Málaga (UMalagaUEX2021) and registered in the Clinical Trials Registry (trial id: NCT04812457). The inclusion criteria were: (i) patients who require and request surgical treatment of ingrown toenails at the participating centres and are willing to participate in the study; (ii) age between 14 and 40 years old; (iii) Kline classification stage I, II, or III of unilateral or bilateral ingrown toenail or Mozena stage I or IIa [13]; (iv) no prior systemic pathology (diabetes, coagulation or immunological disorders). The exclusion criteria were: (i) ingrown toenail with significant fold hypertrophy; (ii) severe paronychia at the time of surgery; (iii) allergy to any of the substances used in the intervention or the cures.

### 2.2. Sample size calculation

The confidence level was established at 95% and the statistical power at 90%. The necessary minimum precision was 3 days (time between cures). The squared variance ( $S^2$ ) was 16 since, in a previous pilot study, the variance found between groups of cures was 4 days. The minimum size required for each group was estimated at 30 subjects, so that samples of 35 subjects were taken to allow for possible losses.

### 2.3. Design and protocol

After agreeing to participate in the study, all patients underwent

ingrown toenail surgery with the phenol/alcohol technique following a standardized protocol [14]: in a sterile and blood-free field, (a) nail spicule removal after careful separation of the surrounding tissues, (b) light curettage of the nail matrix with a Martini curette in order to remove the hyperkeratotic tissue, (c) 30-s application of phenol (88%, in sterile capsules) with a cotton swab, (d) isopropyl alcohol (70°) rinsing to dissolve the phenol present in the nail fold, (e) repetition of steps c and d, (f) liberation of the ring block, and (g) application of a non-stick dressing to facilitate fibrin formation and of a semi-compression bandage.

### 2.4. Post-operative protocol

The patients were randomly assigned to 2 groups (using Microsoft Excel's "random function between"). One of the professionals not present at the intervention (either Researcher 2 or Researcher 4) proceeded to carry out the post-surgical cures, removing the bandage, washing the area with physiological saline, and applying the cream in accordance with the group to which the subject belonged. At the first post-surgery visit (48 h after surgery), in the experimental group ( $n = 35$ ), 1 ml of Hialucic® (2% pure hyaluronic acid cream, Hialucic S.L, Valencia, Spain) was applied onto the operated nail fold, and, in the control group ( $n = 35$ ), 1 ml of povidone iodine gel was applied. The same secondary non-stick dressing (Melolin®) was used after iodine gel or HA group in every cure, followed by a gauze bandage. This procedure was continued on days 4, 6, and 8 post-surgery. After that, for both groups equally, on days 10, 14, and 20 after surgery, and successively every 4 days (if healing was not complete), cure was with povidone iodine in order for the wound to dry and recover.

### 2.5. Outcome measurements

Researchers 3 and 5, who were blinded, performed the follow-up. A checklist was used to register the outcomes for the patients' safety [15]. The primary outcome parameter was healing time, considered to be the time from ending the surgical procedure to full post-surgery resolution in accordance with the following criteria: (i) absence of exudate in the non-stick dressing, (ii) no signs of infection or inflammation in the nail folds, and (iii) no signs of erythema or hypergranulation. The secondary outcomes were inflammation, post-surgical pain, bleeding, and infection. Bleeding was assessed from the first post-surgery visit's dressing, and classified as null, light, moderate, or abundant by an independent clinician [16]. A 10-point visual analogue scale of pain (VASp) was used to assess pain at each visit after surgery [17].

### 2.6. Statistical analysis

Statistical analysis was performed with the SPSS v.28 statistical software package. The normality of the distributions was assessed by the Shapiro-Wilk test. The results are reported as means and standard deviations. Since the data satisfied normality, the null hypothesis (no differences between the HA and the control groups) was tested using bivariate parametric tests (Student's t and chi-squared). The minimal detectable change (MDC), which reflects the magnitude of change necessary to provide confidence that a change is not the result of random variation or measurement error, was determined from the  $\eta^2$  measure of effect size. Differences were considered significant if  $p < 0.05$ , with a confidence interval of 95%.

## 3. Results

Total recovery days were found to be less in the HA group ( $22.42 \pm 2.41$  days) than in the control group ( $26.17 \pm 7.75$  days), with the difference being statistically significant ( $p = 0.007$ , effect size  $d = 0.653$ , Table 1). On the contrary, in none of the cases were there significant differences in pain score. Only for Times 1 (HA  $2.42 \pm 1.2$ , control 3.08

**Table 1**

Mean values (and coefficient of variation) of the control (CG) and hyaluronic acid (HA) groups' VASp pain scores and days for recovery, and the results of using Student's *t*-test for independent samples.

Variables	Group	Mean	SD	Coefficient of variation	<i>p</i> -value	Cohen's <i>d</i>
Age (years)	Control	24.19	10.15	0.42	0.679	0.287
	Hyaluronic acid	19.81	7.84	0.39		
VAS pain score Time 1	Control	3.08	1.61	0.52	0.051	0.469
	Hyaluronic acid	2.42	1.20	0.49		
VAS pain score Time 2	Control	1.94	0.92	0.47	0.07	−0.424
	Hyaluronic acid	2.42	1.27	0.52		
VAS pain score Time 3	Control	0.47	1.16	2.45	0.55	0.140
	Hyaluronic acid	0.33	0.79	2.37		
VAS pain score Time 4	Control	0.14	0.49	3.50	0.63	−0.116
	Hyaluronic acid	0.19	0.47	2.40		
Recovery (days)	Control	26.17	7.75	0.29	0.007	0.65
	Hyaluronic acid	22.42	2.41	0.100.65		

± 1.61) and 2 (HA 2.42 ± 1.27, control 1.94 ± 0.92) were the differences close to significance (*p* = 0.051 and 0.07, Table 1), in favour of the HA group for Time 1 and the control group for Time 2. This closeness to statistical significance disappeared in the following pain scores, with *p* = 0.55 and 0.63 (Table 1, Fig. 1).

Fig. 1 shows interval plots of the groups' pain scores at the first four follow-up visits. The qualitative variables infection and inflammation presented no differences according to the chi-squared analysis for any of those visits (Table 2).

**4. Discussion**

An ingrown toenail is a painful disease that generally affects young adults and limits their activities of daily life. Surgical intervention is often required for cases that are resistant to conservative treatment [18]. A variety of techniques are applicable [19], although the phenol technique is the most commonly used due to its simplicity and low recurrence rate [20]. But one of its drawbacks is the long time for total recovery from the superficial second-degree burn provoked by the acid. Given this context, the hypothesis of the present study was that performing cures with HA could reduce the total recovery time and the number of post-surgery visits.

The study's findings showed that the use of HA treatment following chemical matricectomy with 88% phenol solution improved the post-surgery healing period by around four days compared with povidone-iodine gel. In this sense, curing with HA should also eliminate one future post-surgery visit. The cream used in these cures contained low molecular weight HA in a non-aqueous base, so that it could be expected

**Table 2**

Frequencies of inflammation and presence of exudate in the two groups; chi-squared test *p*-value.

		INFLAMMATION			PRESENCE OF EXUDATE		
		Yes	No	<i>p</i> -value	Yes	No	<i>p</i> -value
TIME 1	HA	33	2	0.05	32	3	0.98
	Control	34	10.05		33	20.98	
TIME 2	HA	4	31	0.53	11	24	0.47
	Control	6	290.53		15	200.47	
TIME 3	HA	28	7	0.08	30	5	0.05
	Control	35	00.08		35	10.05	
TIME 4	HA	32	3	0.64	35	0	1
	Control	33	20.64		35	0	

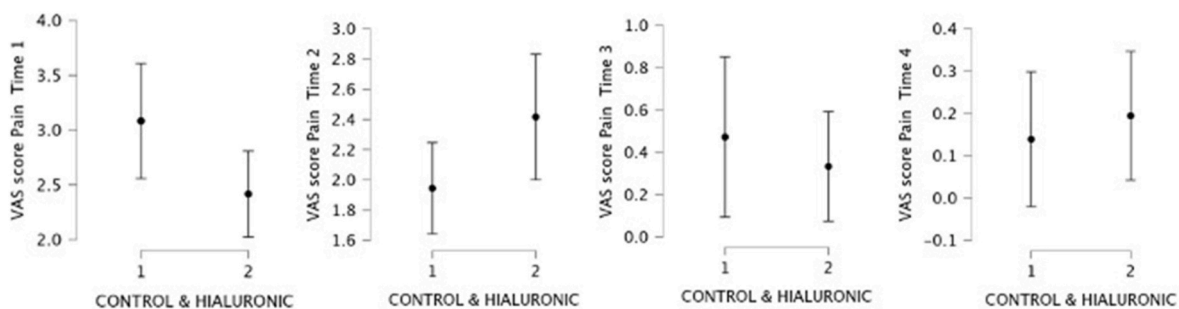
to retain moisture. For this reason, our protocol was to apply 4 equally spaced cures with HA – at 48 h post-surgery, and at 4, 6, and 8 days. We thereby avoided maceration around the wound [10], maintaining the tissue oxygenated. Low molecular weight hyaluronic acid accelerates wound healing by promoting epithelization and neovascularization, and remodelling collagen fibres [21].

In searching for similar studies in the literature, we found a difference in the healing time reported in a work by Dovison et al. [7]. Those workers used different products (10% povidone iodine, an amorphous hydrogel dressing, and a control paraffin gauze) following segmental nail ablation and phenolization, but found no shortening of the time of healing. One major difference with the present study is that their mean time of healing was around 33 days as compared with the average 24 days of our study considering both of our protocols together. Although group ages between studies are different (younger in both groups in our sample, 22 years for the 38 of Dovison et al.), and this could be an important factor in wound recovery, seems that with our HA protocol, healing time was 10 days shorter than that reported in the fore cited work [7].

Post-surgical healing with the phenol/alcohol technique, or any other chemical matricectomy, is usually slower than with the incisional technique [22]. Phenolization causes controlled necrosis of the matrix epithelium and the underlying connective tissue, a prerequisite for successful therapy, and, since a third-degree burn occurs, the phenol application time directly affects the healing time [20].

The phases of healing are homeostasis, inflammation, proliferation, and remodelling [12]. HA acts directly during the proliferation and remodelling phases as it favours increased collagen synthesis and the exit of fibroblasts to the basal bed [21]. This is why the statistically significant changes were observed in the total days for recovery, since no phase study was made.

There are few studies in the literature that evaluate the efficacy of cures in this type of surgery. We did, however, find work in which total cure times varied according to the phenol application time. Application for 30 s gives the fastest healing [20]. In contrast, Ramesh et al. [23] applied 88% phenol for 3 min, performing cures with antiseptic



**Fig. 1.** Mean values (and coefficient of variation) of the control (CG) and hyaluronic acid (HA) groups' VASp pain scores and days for recovery, and the results of using Student's *t*-test for independent samples.

ointment and 5 days of oral antibiotic, leading to wound-healing times of  $40.5 \pm 3.7$  days, values longer than those of our sample. The small sample size of the phenol group ( $n = 5$ ) and again, the older age of the sample of Ramesh et al. [23], that was around 33 years (for our 22) could have influenced the lengthening of the recovery period.

For the pain variable as measured on a visual analogue scale (VAS), we found no significant differences between groups in any of the healing phases. The type of cure performed may not influence the pain perceived by the patient. However, we did find in the literature [24] differences in the pain reported following incisional techniques with VAS scores of more than 7/10, although that work does not specify at what time the measurements were made. These scores contrast with our sample in which the highest pain score was at the first cure with values of  $3.08 \pm 1.61$  in the control group and  $2.42 \pm 1.20$  in the experimental group.

The present study has been the first to assess the application of HA cream in the post-surgery protocol for the phenol technique. However, a possible limitation is that the experimental protocol was only applied during the first week (every 2 days, for a total of 4 cures) in order to avoid tissue maceration which could lead to swelling, infection, and delayed healing. After this week, the protocol of the control group was also applied to the experimental group. Other factors, such as the age of the patients, may play a role in healing time. It would be desirable to evaluate a similar protocol with longer application of the HA cream.

This longitudinal study has several limitations, although there were matching of the groups after random allocation in terms of age, 24 for control and around 20 in the HA (Table 1), other factors, as activity levels or footwear could influence the wound healing in the follow up period. So these non-measured variables could be a bias interpreting the results, as more activity level or poor footwear (of non-breathable materials) could be affect in a bit longer recovery period.

## 5. Conclusions

The use of low molecular weight hyaluronic acid in post-surgical cures after ingrown toenail surgery using the phenol/alcohol technique reduces healing time and eliminates one post-surgery visit compared with the standard cure. No differences can be expected in post-surgical pain, infection rates, or amount of inflammation.

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