CHAPTER 8

Role of monochloroacetic acid application for common and plantar warts in primary care: a randomised controlled trial

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Submitted

ABSTRACT

Background

Cryotherapy or salicylic acid (SA) application for the treatment of cutaneous warts often fails. The aim of this study is to compare the effectiveness of topical monochloroacetic acid (MCA) with cryotherapy in patients with common warts, and with cryotherapy combined with salicylic acid (SA) in patients with plantar warts.

Methods

Consecutive patients with new common or plantar warts were recruited in 53 general practices in the Netherlands. Patients were randomly allocated to office-applied MCA or liquid nitrogen cryotherapy every two weeks for patients with common warts, and to MCA or cryotherapy combined with daily SA self-application for patients with plantar warts. The primary outcome was the proportion of patients in whom all warts were cured at 13 weeks, as assessed by trained research nurses during home visits. Secondary outcomes included treatment adherence, side effects and treatment satisfaction.

Results

Loss to follow-up was 2%. In the common wart group (185 participants), cure rates were 43% (95% confidence interval [CI] 34-54) for MCA and 54% (95% CI 44-64) for cryotherapy. In the plantar wart group (221 participants), cure rates were 46% (95% CI 37-56) for MCA and 39% (95% CI 31-48) for cryotherapy combined with SA. MCA caused less pain than cryotherapy, especially during treatment. Cryotherapy combined with SA was associated with considerable treatment burden.

Conclusion

For common warts, MCA is an effective alternative for cryotherapy to avoid pain during treatment. For plantar warts, office-applied MCA is preferred over cryotherapy combined with SA, based on effectiveness, side effects and treatment burden. (Dutch trial registration: NTR1771)

INTRODUCTION

Cutaneous warts are highly prevalent benign papillomas of the skin.[1] Because they have an unsightly appearance and cause pain,[2] 2% of the general population and 6% of school children yearly present their warts in family practice.[3] Worldwide, the usual treatments are cryotherapy and/or salicylic acid (SA).[4] The 2012 update of the Cochrane review on the treatments for cutaneous warts did not draw firm conclusions since data on the effectiveness of cryotherapy and SA remain contradictory.[5] However, that review highlighted the apparent difference in response to treatment between common warts (mostly located on hands) and plantar warts (located on the sole of the foot). Our recent randomised controlled trial showed that for common warts cryotherapy is more effective than a wait-and-see policy or SA treatment.[6] Nevertheless, cryotherapy did not cure half of all patients with common warts and was the cause of several side effects such as pain, blistering and scarring. For plantar warts, the trial showed that both cryotherapy and SA monotreatments were not effective; this was confirmed by another large trial.[7] However, there is some evidence for the treatment of plantar warts that SA combined with cryotherapy could be more effective than either treatment alone.[8,9]

In addition to these widely used treatments for warts, several specialised treatments such as pulsed dye laser or intralesional bleomycin are available in a hospital setting. Evidence for these treatments is limited and large-scale use in primary care is not feasible.[10] However, an exception may be monochloroacetic acid (MCA) which is a powerful irritant that has been used by dermatologists and podiatrists for several decades.[11,12] A trial from the UK, and two small unpublished pilot studies from the Netherlands, showed promising results of MCA in primary care with few side effects.[13-15] It should be stressed, however, that treatment with MCA should only be administered by experienced healthcare professionals. Therefore, we conducted a multicenter, randomised, parallel group trial to compare the effectiveness and side effects of MCA with the most effective usual treatments, i.e. in common warts compared to cryotherapy, and in plantar warts compared to cryotherapy combined with SA. Since the protocol was similar to our first trial, this also gave the opportunity to compare these treatments with cryotherapy and SA monotreatments and a wait-and-see policy.[6]

METHODS

Patient inclusion, study design and outcome assessment were identical to our previous trial to allow comparison between the treatment arms of the two trials. For details on the methods of the previous trial, including treatment protocols, we refer to the original publication.[6]

Participants

Between September 2009 and September 2010, 53 general practices in the Leiden region of the Netherlands invited all patients aged 4 years and older with one or more newly diagnosed common or plantar warts to participate. We excluded patients that were treated by a physician or dermatologist in the previous year, as well as pregnant, breast-feeding or immunocompromised patients, and patients with genital warts, seborrheic warts or warts ≥ 1cm in diameter. A trained research nurse visited eligible patients at home, confirmed eligibility, obtained informed consent (both child and parental consent for patients aged ≤ 18 years), provided information on warts and wart treatment, and collected baseline characteristics for a maximum of 10 warts per patient.

Study design and randomization

Patients were assigned to two parallel groups: the plantar wart group (patients with warts on the soles of the feet) or the common wart group (patients with warts on hands or other locations). Patients with both common and plantar warts were assigned according to the type of the majority of warts and, in case of equal numbers, according to the warts causing the most discomfort. After stratification based on the number of warts (< 6 vs. ≥ 6 warts), we randomly allocated patients to MCA treatment or cryotherapy in the common wart group, and to MCA treatment or cryotherapy combined with SA in the plantar group. All warts of one patient received the allocated treatment irrespective of location. Opaque, sealed envelopes delivered by an independent statistician based on computerised randomization secured concealment of allocation. The study protocol was approved by the Medical Ethical committee of the Leiden University Medical Center.

Treatment protocols

Allocated treatments were reported to patients' own general practices where the treatments were explained and carried out. In addition to written protocols, one of the authors (PE) trained all participating general practitioners (GPs) and their practice assistants by visiting the practices and demonstrating all tools and techniques in a one-hour interactive session. All patients were instructed not to use any other treatments other than the allocated treatment during the 13-week protocols.

For topical application of MCA in the common and plantar wart group, the research pharmacy provided practices with a saturated concentration of 76%. The GP or practice assistant applied the MCA every two weeks until all warts were completely cured. The removal of callosity and protection of surrounding skin with petroleum jelly preceded each application of MCA solution on the wart with a cotton swab. In case not all applied MCA

was absorbed by the wart, excess MCA was removed with a tissue. After application, the wart was covered with tape and patients were instructed to keep the wart dry for at least 12 hours. We refer to http://www.youtube.com/watch?v=cTzkPCZaGW8 for an instruction video.

For cryotherapy in the common wart group, three subsequent freeze-thaw cycles were applied in the general practice every two weeks until all warts were completely cured. One cycle consisted of application of a wad of cotton wool saturated with liquid nitrogen on the wart until a frozen halo of 2 mm around the base of the wart appeared (usually 2-10 seconds per application). For the cryotherapy combined with SA in the plantar wart group, the above protocol for cryotherapy was applied, combined with daily self-administration of petroleum jelly containing 40% SA until all warts were completely cured. Patients were instructed to daily pare softened surface area of the wart with a file, cover the surrounding skin with tape for protection of healthy skin, and apply SA on top of the wart with another piece of tape.

Outcome assessment

Independently of the treating physician, trained research nurses assessed outcomes during home visits at 4 and 13 weeks follow-up. The visit at 4 weeks was mainly to verify and support adherence to the treatment protocol. The primary outcome measure was the proportion of patients with all common and plantar warts cured at 13 weeks. A wart was considered cured if it was no longer visible (skin favour and skin lines reestablished) and could not be palpated any more. Secondary outcome measures included reported side effects, treatment adherence, treatment burden, and treatment satisfaction. We considered adherence adequate if patients did not use treatments other than the allocated treatment, had received MCA at least every three weeks and kept the wart dry at least 8 hours after applications, had received cryotherapy at least every three weeks, and had self-administered SA at least 3 days a week. Patients rated treatment burden (yes vs. no) and treatment satisfaction on a 5-point scale (1 = very unsatisfied, 5 = very satisfied); those with a score of 4 or 5 reported to be satisfied. Research nurses, GPs and participants were not blinded to treatment allocation.

Statistical analysis

We calculated sample sizes for the common wart and plantar wart group separately, which would provide 80% power at a significance level of 5% to detect a clinically relevant absolute increase in cure rate of 20% for the MCA arms. Considering a 50% cure rate in the cryotherapy arm of the common wart group and a 30% cure rate of a wait-and-see policy in the plantar wart group,[6] 91 patients were required per treatment arm for each

wart group. Assuming a loss-to-follow of 10%, we needed 200 patients for the common wart group and 200 patients for the plantar wart group.

In primary analysis, we calculated cure rates including 95% confidence intervals (CIs) to compare treatment arms. For the common wart group MCA and cryotherapy arms were compared, and for the plantar wart group MCA and cryotherapy combined with SA arms were compared. These treatment arms were also compared to the cryotherapy, SA, and wait-and-see arms in the respective groups of patients from our previous trial with identical design.[6]

In addition, we compared the secondary outcomes (percentages of patients with side effects, considerable treatment burden, and the percentages of patients satisfied with treatment) between arms using the χ^2 test. Furthermore, subgroup analyses on effectiveness were pre-planned for age clusters (4-12 years vs. ≥ 12 years), number of warts per participant, and duration of warts (≤ 6 months v. > 6 months). In sensitivity analyses, we compared cure rates between treatments arms per wart group (a) with patients lost to follow-up considered not cured, (b) using per protocol analysis based on adequate treatment adherence, (c) after excluding patients who had both plantar and common warts, (d) only including the warts on the hands in common wart group, and (e) with individual warts instead of patients as unit of analysis.

RESULTS

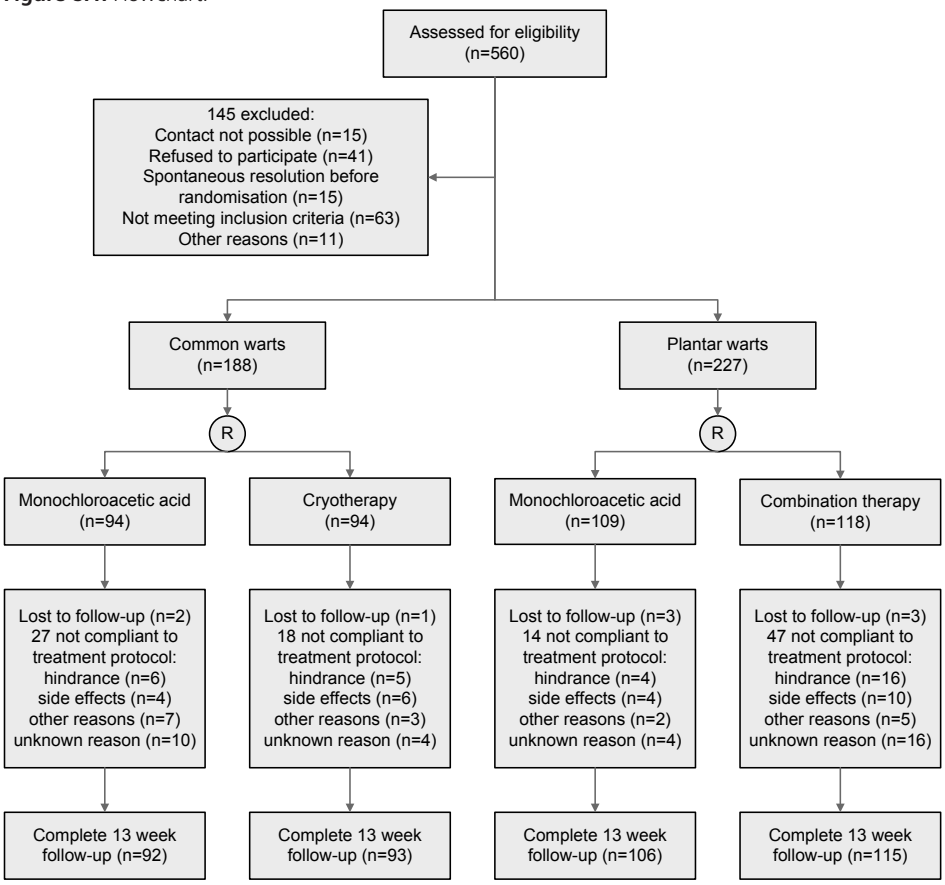
Patient characteristics

Of the 560 initially selected patients with warts, 145 were excluded mainly because they had already been treated in the past year or they did not want to participate (Figure 8.1). The remaining 415 patients were stratified into the common wart group (n=188) and the plantar wart group (n=227) before randomization. Within both groups, baseline characteristics did not differ between treatment arms (Table 8.1), and also did not differ from the baseline characteristics of the previous trial (data not shown).[6] For the common wart group, median age and median duration of warts were higher than in the plantar wart group. In total, the study contained 790 plantar warts and 611 common warts, of which 526 warts (86%) were located on hands and 85 warts (14%) were located on other body sites.

Follow-up and treatment adherence

At 13 weeks, 3 patients from the common wart group and 6 patients from the plantar wart group were lost to follow-up because they refused further participation or could no longer be contacted (Figure 8.1). Of the remaining 406 patients, 106 (26%) did not fully

Figure 8.1. Flowchart.



comply with treatment protocol; 92 did not adhere to minimal treatment frequencies and 14 started other treatment in general practice in addition to the protocol. The cryotherapy combined with SA arm showed lowest adherence to treatment protocol (68/115, 59%); the most frequently reported reason was treatment burden such as time-consuming visits to the general practice and daily hassle with SA and tape (Figure 8.1). During follow-up, only one patient was referred to a dermatologist because the wart was growing larger than 1 cm in spite of treatment and the patient had considerable pain.

Effectiveness of treatment

For the common wart group, the cure rate at 13 weeks of MCA was 43% (95% CI 34-54) which was comparable to the cure rate of cryotherapy of 54% (95% CI 44-64, p=0.16) (Table 8.2). When the treatment arms were compared with the treatment arms of the previous trial,[6] both cryotherapy and MCA were more effective than the wait-and-see

Table 8.1. Baseline characteristics of patients with common warts and patients with plantar warts (n=415).

	Common wart group		Plantar wart group	
Characteristic	MCA (n=94)	Cryotherapy (n=94)	MCA (n=109)	Cryotherapy with SA (n=118)
Sex, female	54 (57)	43 (46)	69 (63)	76 (64)
Age, median (IQR)	14 (9-44)	16 (8-42)	10 (7-29)	11 (6-38)
Age, years				
4-12	35 (37)	35 (37)	59 (54)	60 (51)
≥ 12	59 (63)	59 (63)	50 (46)	58 (49)
Number of warts, median (IQR)	2 (1-4)	1 (1-3)	1 (1-3)	2 (1-4)
Number of warts				
1 up to 5	83 (88)	79 (84)	94 (85)	97 (82)
6 or more	11 (12)	15 (16)	16 (15)	21 (18)
Size of warts, mm, median (IQR)	4 (3-6)	4 (3-6)	4 (3-5)	4 (3-5)
Both common and plantar warts	13 (14)	10 (11)	17 (16)	21 (18)
Duration of warts, mo, median (IQR)	12 (6-24)	12 (4-24)	6 (3-24)	6 (3-24)
Duration of warts, mo				
< 6	20 (21)	30 (32)	47 (43)	52 (44)
≥ 6	74 (79)	64 (68)	62 (57)	66 (56)
Hindrance of warts*	64 (68)	76 (81)	90 (83)	99 (84)
Previous self-treatment†	37 (40)	30 (32)	45 (41)	46 (39)
OTC cryotherapy	18 (19)	17 (18)	26 (24)	23 (19)
OTC salicylic acid	20 (21)	16 (17)	24 (22)	18 (15)
Other self-treatment	5 (5)	5 (5)	11 (10)	15 (13)
Treatment preference at baseline				
MCA	33 (35)	41 (44)	48 (44)	45 (38)
Cryotherapy	7 (7)	8 (8)	-	-
Cryotherapy+SA	-	-	14 (13)	14 (12)
No preference	54 (58)	45 (48)	47 (43)	59 (50)

Values are numbers (%) unless stated otherwise; mo = months IQR = Interquartile range, OTC = over-the-counter, MCA = monochloroacetic acid, SA = salicylic acid.

* Presence of pain or esthetic annoyance

† More than one self-treatment possible

policy or SA treatment (Figure 8.2). Stratification by age or by duration of warts yielded similar findings (Table 8.2).

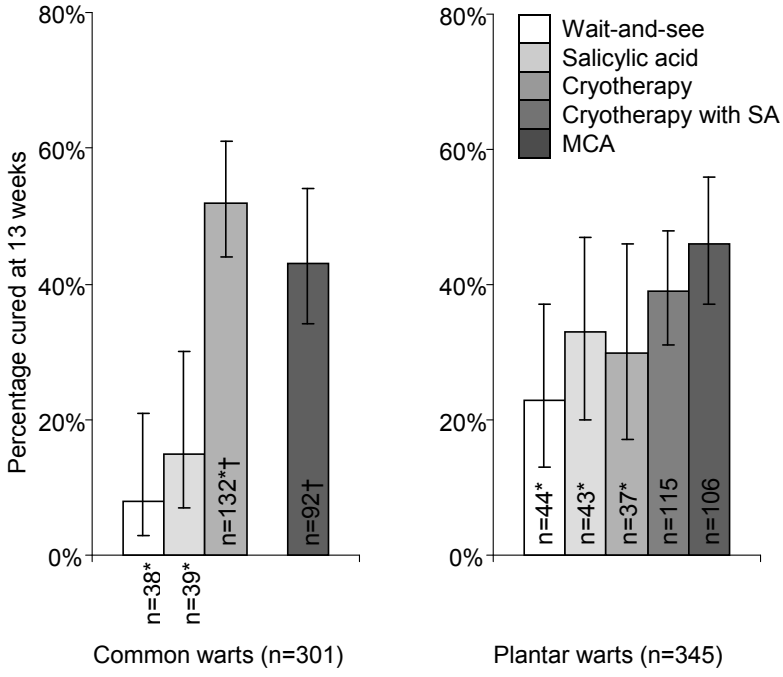
For the plantar wart group, the cure rate at 13 weeks of MCA was 46% (95% CI 37-56) which was comparable to the cure rate of cryotherapy combined with SA of 39% (95% CI 31-48) (p=0.29) (Table 8.2). When these treatment arms were compared with the treatment arms of our previous trial,(6) all CIs of the active treatment groups of MCA, cryo-

Table 8.2. Effectiveness of treatments for patients with common warts (n=185) and patients with plantar warts (n=221).

	Common wart group				Plantar wart group			
	MCA		Cryotherapy		MCA		Cryotherapy with SA	
Variable	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)
All patients	40/92	43 (34-54)	50/93	54 (44-64)	49/106	46 (37-56)	45/115	39 (31-48)
Age, years								
4-12	15/34	44 (29-61)	20/35	57 (41-72)	39/57	68 (56-79)	34/59	58 (45-69)
≥ 12	25/58	43 (31-56)	30/58	52 (39-64)	10/49	20 (11-34)	11/56	20 (11-32)
Duration of warts, months								
< 6	13/19	68 (46-85)	22/30	73 (56-86)	30/46	65 (51-77)	34/51	67 (53-78)
≥ 6	27/73	37 (27-48)	28/63	44 (33-57)	19/60	32 (21-44)	11/64	17 (10-28)

Values are numbers of participants cured/number of participants in intention-to-treat analysis at 13 weeks, and percentages of participants cured with 95% CI. A participant was considered cured when all warts present at baseline had disappeared at follow-up. MCA = monochloroacetic acid, SA = salicylic acid, CI = Confidence interval

Figure 8.2. Effectiveness of treatments with 95% confidence intervals of the current trial and the previous trial at 13 weeks for patients with common warts and patients with plantar warts (n=646). * Patients originate from previous trial. † Patients originate from current trial



therapy combined with SA, and cryotherapy and SA monotreatments overlapped (Figure 8.2). Compared to a wait-and-see policy, MCA for plantar warts was the only treatment reaching the predefined clinically relevant risk difference (RD 23%, 95% CI 8-39; RR 2.0, 95% CI 1.1-3.6) (see Appendix 8.1).

All sensitivity analyses were in line with primary analysis (see Appendix 8.2). The cure rate of cryotherapy combined with SA in the plantar wart group was increased in the per protocol analysis (60%, 95%CI 48-71), but remained comparable with the cure rate of MCA (53%, 95%CI 43-63).

Side effects and treatment satisfaction

Pain was the most frequently reported side-effect for all treatment arms (Table 8.3). We found a lower proportion of patients reporting pain *during* MCA application compared to cryotherapy for both common and plantar wart groups. However, similar proportions of

Table 8.3. Side effects reported during the 13-week follow-up per treatment group (n=406).

	Common wart group			Plantar wart group		
	MCA (n=92)	Cryotherapy (n=93)		MCA (n=106)	Cryotherapy+SA (n=115)	
Treatment pain	70 (76)	85 (91)	*	80 (76)	92 (80)	
During application	8 (9)	77 (83)	*	17 (16)	85 (74)	*
After application	69 (75)	74 (80)		77 (73)	76 (66)	
Pain score, median (IQR)	4 (2-6)	6 (4-7)	*	4 (2-6)	5 (3-7)	*
Other side effects						
Number of other side effects						
none	33 (36)	26 (28)		43 (41)	55 (48)	
1	24 (26)	43 (46)		38 (36)	40 (35)	
≥2	35 (38)	24 (26)		25 (24)	20 (17)	
Type of other side effects						
Blistering	36 (39)	58 (62)	*	36 (34)	33 (29)	
Wound	12 (13)	9 (10)		3 (3)	2 (2)	
Infection	4 (4)	2 (2)		2 (2)	1 (1)	
Scar	8 (9)	8 (9)		4 (4)	0	
Pigmentation	7 (8)	3 (3)		6 (6)	6 (5)	
Irritation of skin	25 (27)	12 (13)	*	18 (17)	34 (30)	*
Burning sensation	12 (13)	2 (2)	*	10 (9)	0	*
Itching	12 (13)	1 (1)	*	16 (15)	5 (4)	*
Other minor side effects	0	2 (2)		5 (5)	2 (2)	

Values are numbers (%) unless stated otherwise; IQR = Interquartile range, MCA = monochloroacetic acid, SA = salicylic acid.

* $p<0.05$

patients reported pain *after* treatment. MCA showed a pain-free period after MCA application (median 1 h, IQR 10 min-7 h), whereas the pain during application for cryotherapy was immediately followed by post-application pain. Median duration of pain for all treatment arms was 1 day (IQR 2 h-3 days). The median overall treatment pain score was lower for MCA than for cryotherapy arms (Table 8.3). In the common wart group, the percentage of patients reporting treatment burden was comparable for MCA (34%, 95% CI 25-46) and cryotherapy (37%, 95% CI 27-47, p=0.76). In the plantar warts group, treatment burden was lower for MCA (30%, 95% CI 22-39) than for cryotherapy combined with SA (47%, 95% CI 38-56, p=0.009). The percentage of patients satisfied with their treatment was comparable between treatment arms and between common and plantar groups (overall 64%, 95% CI 59-68).

DISCUSSION

Summary of findings

This pragmatic randomised controlled trial in primary care showed that for common warts both MCA application and cryotherapy are effective treatments. Pain caused by MCA starts about one hour after application compared to the immediate, more intensive pain caused by cryotherapy. For plantar warts, MCA was the only treatment with a clinically relevant risk difference (23%) compared to a wait-and-see policy. Cryotherapy combined with SA also seemed effective, especially in patients compliant to treatment protocol, but caused considerable side effects and treatment burden.

Comparison with other literature

In line with the recently updated Cochrane review on cutaneous warts, the present trial was separately powered for patients with common warts and patients with plantar warts because of evident differences in response to treatment. However, in that review MCA was not investigated due to the insufficient number of trials to include. Apart from a few descriptive studies,[11,12] we found only one trial on MCA in warts.[13] That study reported that MCA combined with SA treatment resulted in a cure rate of 66% compared to 16% for placebo after 6 weeks in patients with plantar warts; however, only 59 patients were included and a MCA crystal was taped on the wart for one week. We also found two unpublished pilot studies showing that MCA saturated solution every 2 weeks was more effective than SA, and as effective as cryotherapy but with less reported pain.[14,15] Our data confirm the modest benefit for SA in plantar warts reported by the Cochrane review, but only significant when pooled. This benefit is probably enhanced when combined with

cryotherapy, but the clinical relevance of the risk differences compared with a wait-and-see policy remains questionable.

Strengths and limitations

With the pragmatic design in a primary care setting, almost complete follow-up and intention-to-treat analysis, our findings are directly applicable to daily practice. The baseline characteristics of our two subsequent trials with identical designs were similar. A sound comparison between the treatment arms across the two trials was confirmed by comparable outcomes of the two cryotherapy arms in the common wart groups.
Treatment options did not secure realistic blinding of patients and practices. Research nurses were also not blinded, because they assessed side effects, treatment burden and treatment adherence in addition to outcome assessment during home visits.
Although MCA has been locally used by podiatrists and dermatologists for treatment of warts for decades, it is not routinely obtainable in pharmacies.[11] However, it could easily become widely available at low costs if the demand increases, because MCA is produced on a large scale for the chemical industry and agriculture.[16] When carefully administered, MCA is safe for topical use on skin lesions. However, because of the strong corrosive capacity of the acid it should be stored in small quantities. It is not suitable for self-application and should always be administered by a healthcare professional.[17] In our trial, the most serious side effects MCA caused were blistering (36% of patients) and superficial wounds (8% of patients). Chemical wounds were caused by the application of too much MCA or spilling MCA on healthy skin. However, cryotherapy caused even more blistering in common warts and comparable numbers of wounds. Full-thickness chemical burns and joint deformity have been described in case reports when MCA was not carefully applied, i.e. high concentration of MCA with a long application period or large application surface.[18,19] Systemic effects may be expected when a body surface up to 5% is exposed to an 80% solution of the acid.[20]

Implications

The present trial establishes MCA as an effective treatment option for cutaneous warts. For common warts MCA is an effective alternative for cryotherapy to avoid pain during treatment. This might be appealing for treatment in children who often fear the pain during cryotherapy. For plantar warts, MCA is preferred over cryotherapy combined with SA based on effectiveness, side effects and treatment burden.
Nevertheless, optimal treatment for both common and plantar warts only cures around 50% of patients. Therefore, subgroups of patients that respond to current treatments need to be identified and new treatments should be investigated. Ultimately, an evidence-based decision tool should be developed that assists physicians in their decision concerning which treatment to use for specific patient groups.

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Appendix 8.1. Relative measures of effect comparing the treatments of the two trials with a wait-and-see policy* for patients with common warts (n=301) and patients with plantar warts (n=345).

	Common wart group		Plantar wart group	
Treatment*	Relative risk (95%CI)	Risk difference % (95%CI)	Relative risk (95%CI)	Risk difference % (95%CI)
Salicylic acid	2.0 (0.52-7.2)	7 (-7;22)	1.4 (0.72-2.9)	10 (-9;29)
Cryotherapy	6.6 (2.2-20)	44 (32-56)	1.3 (0.63-2.7)	7 (-12;26)
Cryotherapy with SA	-	-	1.7 (0.95-3.1)	16 (1-32)
MCA	5.5 (1.8-17)	36 (22-49)	2.0 (1.1-3.6)	23 (8-39)

MCA = monochloroacetic acid, SA = salicylic acid, CI = Confidence interval
* Data for wait-and-see policy, SA and cryotherapy in the plantar wart group originate from our previous trial; data for MCA and cryotherapy combined with SA originate from the present trial; data for cryotherapy in the common wart group are combined from our previous and present trial.

Appendix 8.2. Sensitivity analyses for the effectiveness of treatments for patients with common warts (n=185) and patients with plantar warts (n=221).

	Common wart group				Plantar wart group			
	MCA		Cryotherapy		MCA		Cryotherapy with SA	
Analysis	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)
Primary intention to treat analysis	40/92	43 (34-54)	50/93	54 (44-64)	49/106	46 (37-56)	45/115	39 (31-48)
Patients lost to follow-up considered not cured	40/94	43 (33-53)	50/94	53 (43-63)	49/109	45 (36-54)	45/118	38 (30-47)
Per protocol analysis based on treatment adherence	38/65	58 (46-70)	45/75	60 (49-70)	49/92	53 (43-63)	41/68	60 (48-71)
Patients with both common and plantar warts excluded	36/79	46 (35-57)	49/83	59 (48-69)	45/90	50 (40-60)	43/94	46 (36-56)
Only patients with warts located on hands	38/81	47 (36-58)	42/83	51 (40-61)	-	-	-	-
Individual warts instead of patients as unit of analysis*	145/249	58 (52-64)	170/265	64 (58-70)	150/296	51 (45-56)	155/359	43 (38-48)

Values are numbers cured/total number in treatment arm, and percentages cured with 95% confidence interval (CI). MCA = monochloroacetic acid, SA = salicylic acid.
* The total number of 514 common and 655 plantar warts in analysis at 13 weeks is lower than the reported total of 611 common and 790 plantar warts, because outcomes of individual warts were reported for a maximum of 10 warts per patient.