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ORIGINAL RESEARCH

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Hypochlorous acid in a double formulation (liquid plus gel) is a key prognostic factor for healing and absence of infection in chronic ulcers. A nonrandomized concurrent treatment study

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Abstract

Background and Aims: Diverse protocols prevent infection and/or improve ulcer epithelialization. *The existing* protocols tend to antagonize the risk factors that *promote* the chronicity of this type of wound. Hypochlorous acid (HOCl) is used to treat ulcers and wounds because of its antiseptic and noncytotoxic properties. Its liquid form is effective but has little residual effect, while in gel it has more residual power.

Methods: An experimental nonrandomized study has been carried out treating 346 chronic ulcers of various etiologies in 220 patients. Ulcer outcomes were *originally* classified as: "complete healing," "incomplete healing without infection," and "incomplete healing with infection." Various antiseptic solutions were used as ulcers cleaning solutions: liquid HOCl, gel HOCl, polymeric biguanide, or chlorhexidine. Only one was applied to the lesion as monotherapy. But, in other cases, we used a combined HOCl (liquid then gel: bitherapy). Bivariate (Chi-square and variance tests) and multivariate studies (logistic regression) evaluated associations of ulcer characteristics and mono or bitherapy outcomes.

Results: Four factors reduce the probability of complete ulcer healing: patient age (odds ratio [OR]: 0.97); weeks of ulcer evolution (OR: 0.99); poor granulation on admission (OR: 0.35); and need for antibiotic therapy (OR: 0.41). One factor favored healing: combined HOCl therapy with liquid plus gel (OR: 4.8). Infections were associated with longer times of evolution (OR: 1.002) and bad odor of the ulcer on admission (OR: 14), but bitreatment with HOCl reduced the risk of infection (OR: 0.3).

Conclusion: A double HOCl formulation (liquid plus gel) reduces the probability of poor healing and infection, in chronic ulcers of various etiologies.

KEYWORDS

chronic ulcers, healing, HOCl (liquid plus gel), infection

1 | INTRODUCTION

Chronic ulcers are those that have not anatomically and/or functionally healed within 3 months. They can have multiple etiologies including arterial or venous vascular problems, diabetes, pressure, neoplasms, neurological pathologies, and so on. It is assumed they can affect more than 10% of the population, especially individuals over 70 years of age with any of the pathologies listed above.[1–7] Up to half of all ulcers may be infected at the time that treatment is begun. Healing procedures are protocolized in most centers. However, protocols vary from one center to another depending on whether an attempt is made to prevent infection or to improve epithelialization using debridement techniques employing surgical, enzymatic, or mechanical cleaning, addition of epithelial growth factors, use of a moist cure, and so on,[1–7] and antagonize the risk factors that may favor the chronicity of this type of injury.

Hypochlorous acid (HOCl) has been used in the treatment of ulcers and wounds of various etiologies (arteriovenous problems, neurologic difficulties, diabetes, trauma, etc.), since it combines antimicrobial properties with those of noncytotoxicity to the underlying tissue, which is a key to the healing of these injuries. In addition, the treatment has anti-inflammatory and antipruritic effects, which also help alleviate underlying conditions. Many of the HOCl formulations are of the liquid type, but some are also in gel form, which gives them more versatility as they can be applied to wounds, bedsores, ulcers, and so on, creating a hydrated medium that also maintains an antimicrobial effect for a long time (one or more days), which is very important to achieving healing.[6–18]

Using an in vitro model based on a germ carrier with or without biofilm, we concluded in 2020[19] that a more concentrated and stable formulation of HOCl was more effective than other antiseptics, such as iodines, surfactants, and biguanides. The broad-spectrum antimicrobial activity of HOCl has been experimentally confirmed both in vitro and in vivo by Palau et al.[20]

We then wondered if a faster, more effective, and safer healing of ulcers could be achieved by treating them with two different formulations of HOCl in two successive steps. The first step would be cleaning the ulcer with a moderate concentration of liquid HOCl (100–500 mg/L), a very effective microbicide but with little residual effect; and a second step, applying a gel formula with approximately 60 mg/L of HOCl to the wound. Although the gel formulation had little microbicidal power, it would serve to maintain a residual antimicrobial and noncytotoxic effect in the ulcer. For the study purposes, we named this double application "HOCl liq + gel."

2 | MATERIAL AND METHODS

Our hypothesis is that a double application of two HOCl formulations must counteract, better than monotherapy antisepsis, the poor-prognostic factors in so far as ulcer infection or noncure.

An experimental, but nonrandomized study, carried out at the "Centro Multidisciplinar de Ulceras Cronicas" (CMUC Clinics) treated 346 chronic ulcers in 220 patients. All participants gave informed consent to this new treatment, which was also approved by the CMUC Ethical Committee. The study took place over three time periods: before 2018; 2018–2019, and 2020–2021 (with 50, 104, and 192 ulcers, respectively, included in each period).

The reference treatment consisted of cleaning the ulcers with "single or monotherapy antiseptic," a liquid HOCl (Clortech® 100-500 mg/L Clortech Lab, Spain), polymeric biguanide (Prontosan® B Braun Lab, Germ), 2% aqueous chlorhexidine (Lainco Lab), or HOCl-gel (Microdacyn60, Oculus Innovative Sciences, Inc); if the initial treatment was ineffective it was replaced by another. All monotherapy results were compared to HOCl liq + gel (bitherapy).

Other data studied were "descriptive" variables of patient clinical history such as study period, age, sex, previous diseases, nutritional status, and mobility. After calculating the BMI of each patient, we divided this numerical variable into four categories. Two of them conform to those of the WHO (overweight and obesity) but in the other two, we introduced a modification to investigate whether a very low body weight hindered the healing of ulcers. The cut-off points are indicated in the Results table, so the reader can correlate our categories with the usual ones in the WHO BMI classification.

Other variables corresponded to each ulcer at the beginning of the study, such as its anatomical site, its evolution over time, grade, dimensions, as well as some clinical signs (heat, edema, odor, pain when changing the dressing on a subjective scale from 0 to 10, etc.). In addition, the concomitant use of general antibiotic therapy during the local treatment of ulcers and the duration of both therapies were recorded. Last, some variables that described the healing process such as those that referred to the speed of healing, both in absolute or relative measurements (mm/week or % of ulcer that heals per week with respect to the total of the corresponding ulcer) were also recorded.

2.1 | Wound treatment

Wound treatments were carried out according to the protocols of the CMUC clinics, in which a vascular examination is performed on admission for each patient and the ankle-brachial index is calculated. Then, the ulcer is photographed, its dimensions calculated, and the tissue at the base of the lesion assessed. All procedures always respect the three "H's" of the skin (Hydration, Hygiene, and Humidity) and the TIME-RS concept (T = assessment of nonviable tissue, I = infection control, M = exudate control, E = stimulation of edges of the wound, R = use of advanced products, and S = social, i.e., involving the patient in cures).

Treatment begins by cleaning the ulcer with soap made from ozonized oils (Ozoaqua Lab) and drying it thoroughly, paying much attention to more difficult areas such as the interdigital spaces. Next, the wound is cleaned with the antiseptic of choice to remove the debris that is present on its surface. If there is devitalized tissue, an attempt is made to eliminate it by means of mechanical and/or enzymatic debridement. Once debridement is complete, an antiseptic

TABLE 1 Distribution of the 346 ulcers studied by degree of recovery at discharge (Only Qualitative Variables).

Variables (categories)	Complete healing *N* = 203	Incomplete healing without infection *N* = 119	Incomplete healing with infection *N* = 24	Chi-squared and *p* values
Year				
<2018	23 (11.3%)	24 (20.2%)	3 (12.5%)	26.85 ($p < 0.001$)
2018–2019	45 (22.2%)	46 (38.6%)	13 (54.2%)	
2020–20211	135 (66.5%)	49 (41.1%)	8 (33.3%)	
Sex				
Women	111 (54.7%)	69 (58%)	16 (66.6%)	1.41 ($p = 0.5$)
Men	92 (45.3%)	50 (42%)	8 (33.3%)	
Cleaning treatment				
HOCl (liquid and gel)	142 (70%)	51 (42.9%)	8 (33.3%)	29.3 ($p < 0.001$)
Single antiseptic	61 (30%)	68 (57.1%)	16 (66.7%)	
Diabetes				
Yes	90 (44.3%)	43 (36.1%)	7 (29.2%)	3.46 ($p = 0.17$)
No	113 (55.7%)	76 (63.9%)	17 (70.8%)	
Heart disease				
Yes	87 (42.9%)	44 (37%)	8 (33.3%)	1.59 ($p = 0.45$)
No	116 (57.1%)	75 (63%)	16 (66.7)	
Congestive heart failure				
Yes	9 (4.4%)	10 (8.4%)	5 (20.8%)	9.55 ($p < 0.01$)
No	194 (95.6%)	109 (91.6%)	19 (79.2%)	
Peripheral venous disease				
Yes	99 (48.8%)	69 (58%)	11 (45.8%)	2.91 ($p = 0.23$)
No	104 (51.2%)	50 (42%)	13 (54.2%)	
Peripheral arterial disease				
Yes	64 (31.5%)	29 (24.4%)	9 (37.5%)	2.65 ($p = 0.26$)
No	139 (68.5%)	90 (75.6%)	15 (62.5%)	
Neurologic				
Yes	39 (19.2%)	29 (24.4%)	7 (29.2%)	2.03 ($p = 0.36$)
No	164 (80.8%)	90 (75.6%)	17 (70.8%)	
Malignancies				
Yes	9 (4.4%)	8 (6.7%)	1 (4.2%)	0.85 ($p = 0.65$)
No	194 (95.6%)	111 (93.3%)	23 (95.8%)	
Other comorbidities				
Yes	29 (14.3%)	26 (21.8%)	6 (25%)	3.92 ($p = 0.43$)
No	174 (85.7%)	93 (78.2%)	18 (75%)	
Ulcer location				
Sacrum	7 (3.4%)	12 (10.1%)	1 (4.2%)	7.70 ($p = 0.41$)
Upper leg	6 (3%)	3 (2.5%)	0 (0%)	

(Continues)

TABLE 1 (Continued)

Variables (categories)	Complete healing $N = 203$	Incomplete healing without infection $N = 119$	Incomplete healing with infection $N = 24$	Chi-squared and p values
Lower leg	126 (62%)	72 (60.5%)	17 (70.8%)	
Foot	55 (27.1%)	28 (23.5%)	5 (20.8%)	
Others	9 (4.4%)	4 (3.4%)	1 (4.2%)	
BMI				
Underweight (BMI < 17)	8 (3.9%)	2 (1.7%)	2 (8.3%)	7.28 ($p = 0.30$)
Healthy Weight (BMI: 17–25)	83 (40.9%)	45 (37.8%)	7 (29.2%)	
Overweight (BMI: 25–30)	64 (31.5%)	44 (37%)	12 (50%)	
Obesity (BMI > 30)	48 (23.6%)	28 (23.5%)	3 (12.5%)	
Mobility				
Normal	151 (74.4%)	80 (67.2%)	17 (70.8%)	18.05 ($p < 0.02$)
Seated patient	20 (9.9%)	18 (15.1%)	2 (8.3%)	
Bed-ridden patient (>1h walking/ sitting)	25 (12.3%)	17 (14.3%)	2 (8.3%)	
Bed-ridden patient (<1h walking/ sitting)	7 (3.4%)	4 (3.4%)	2 (8.3%)	
Bed-ridden patient (no walking/ sitting)	0 (0%)	0 (0%)	1 (4.2%)	
Weeks of evolution of the ulcers on admission				
0–16 weeks	154 (75.8%)	54 (45.4%)	5 (20.8%)	48.70 ($p < 0.001$)
17–52 weeks	29 (14.3%)	34 (28.6%)	9 (37.5%)	
>52 weeks	20 (9.9%)	31 (26%)	10 (41.7%)	
Ulcer origin				
Vascular: arterial	37 (18.2%)	22 (18.5%)	8 (33.3%)	13.41 ($p = 0.34$)
Vascular: venous	82 (40.4%)	54 (45.4%)	10 (41.7%)	
Pressure	24 (11.8%)	19 (16%)	3 (12.5%)	
Surgical	7 (3.4%)	5 (4.2%)	0 (0%)	
Diabetic foot	29 (14.3%)	14 (11.8%)	3 (12.5%)	
Traumatic (Other than burn)	20 (9.9%)	5 (4.2%)	0 (0%)	
Burn	4 (2%)	0 (0%)	0 (0%)	
Exudate (quantity)				
Abundant	53 (26.1%)	33 (27.7%)	1 (4.2%)	19.36 ($p < 0.01$)
Moderate	79 (38.9%)	66 (55.4%)	13 (54.1%)	
Scarce	71 (35%)	20 (16.8)%	10 (41.7%)	
Exudate (characteristics)				
Serous liquid	189 (54.6%)	108 (90.7%)	18 (75%)	19.89 ($p < 0.001$)
Purulent	3 (5%)	16 (8%)	3 (3.5%)	
Bloody	7 (3.4%)	2 (1.7)%	0 (0%)	

TABLE 1 (Continued)

Variables (categories)	Complete healing *N* = 203	Incomplete healing without infection *N* = 119	Incomplete healing with infection *N* = 24	Chi-squared and *p* values
Ulcer signs				
Heat				
Yes	114 (56.1%)	70 (58.8%)	15 (62.5%)	0.48 ($p = 0.78$)
No	89 (43.9%)	49 (41.2%)	9 (37.5%)	
Swelling				
Yes	93 (45.8%)	55 (46.2%)	11 (45.8%)	0.01 ($p > 0.99$)
No	110 (54.2%)	64 (53.8%)	13 (54.2%)	
Bad odor				
Yes	26 (12.8%)	44 (37%)	19 (79.2%)	61.49 ($p < 0.001$)
No	177 (87.2%)	75 (63%)	5 (20.8%)	
Altered granulation				
Yes	28 (13.8%)	29 (24.3%)	6 (25%)	6.43 ($p < 0.05$)
No	175 (86.2%)	90 (75.7%)	18 (75%)	
Ozone				
Yes	94 (46.3%)	68 (57.1%)	14 (58.3%)	4.10 ($p = 0.12$)
No	109 (53.7%)	51 (42.9%)	10 (41.7%)	
Compressive cure				
Yes	123 (60.9%)	66 (55.5%)	20 (87%)	6.49 ($p < 0.001$)
No	80 (39.1%)	53 (44.5%)	4 (13%)	
Antibiotics				
Yes	85 (41.9%)	74 (62.2%)	16 (66.6%)	15.05 ($p < 0.001$)
No	118 (58.1%)	45 (37.8%)	8 (33.4%)	
Antibiotic used *(when antibiotic = yes)*				
Quinolone	45 (22.3%)	38 (31.9%)	10 (43.5%)	8.41 ($p = 0.21$)
Beta-lactam	5 (2.5%)	11 (9.2%)	3 (13%)	
Others	8 (5.9%)	10 (8.4%)	1 (4.1%)	
Combinations[a]	27 (13.4%)	15 (12.6%)	2 (8.7%)	

Note: Percentages in relation to the total of the respective column.

Abbreviations: BMI, body mass index; HOCl, hypochlorous acid.

[a]Quinolone followed by beta-lactam or quinolone followed by aminoglycoside, and so on.

reinforcement is applied to the wound for 15 min to destroy its bacterial load. Last, some of the cases that were treated with liquid HOCl (100–500 mg/L) receive a second HOCl application in a gel format.

Finally, depending on the type of tissue present in the wound bed, the dressing will be placed to provide a moist environment or not and, considering the etiology of the wound, a type of bandage will be chosen. For example, in the case of patients with wounds of vascular venous etiology, compression bandages would be chosen.

In some ulcers, especially those of vascular origin, the above treatment would be accompanied by the noninvasive application of ozone, as has been done in other studies.[21]

If the wound is healing well, cures are scheduled approximately every 2 days until complete healing, or until voluntary discharge,

either due to treatment failure, hospitalization, or, in a few cases, death related to ongoing chronic diseases.

2.2 | Data analysis

Sample size estimation used SSI from the STATA package (Philip M Jones, 2010. "SSI: Stata module to estimate sample size for randomized controlled trials" Statistical Software Components S457150, Boston College Department of Economics).

We assumed that the new therapy with double application of HOCl would be at least 1.5 times more effective than the reference monotherapy. In previous years, this therapy had produced complete healing of 40% of the ulcers, so we estimated that with a 20% increase in efficacy, Statistical Power = 80% and 95% confidence level, the number of ulcers to be studied should be at least 264.

Data on each ulcer was initially collected by nurses from the CMUC clinics in a protocol (defined at the beginning of the study) and then reviewed by their Nursing Director.

The critical variable of interest was the degree of curation, which was classified into three possible outcomes: "complete healing," "incomplete healing without infection," and "incomplete healing with infection."

A descriptive analysis was carried out using cross-tabulations of the different variables by cleaning treatment category (mono or bitherapy) to determine their distribution. Statistical associations were calculated using the Chi-square test when variables were qualitative. For quantitative variables, differences between the cleaning treatments were assessed through an analysis of variance with Bonferroni correction to obtain the mean, standard deviation, and internal comparison between the three categories of the key variable.

Finally, multivariate logistic regression was used to assess the efficacy of the cleaning products used after controlling for other variables that also influence ulcer healing or infection and may act as confounders of these antimicrobials. In this analysis, two dependent variables were used, "complete healing" and "infection," both with two categories: 0 versus 1.

All analyses have been performed using SPSS, version 25, with anonymized data.

3 | RESULTS

The results are detailed in Tables 1 (qualitative variables), 2 (quantitative variables), and 3 (multivariate logistic regression equations).

(1) Descriptive epidemiology:

Tables 1 and 2 show the "descriptive" variables for patient clinical history, which have been associated with the three final results for the ulcers (*p* values on the right margin of the tables) such as congestive heart disease, or the grade (predominately VI or

TABLE 2 Quantitative variables of the 346 ulcers studied regarding the three types of results at discharge.

Variable	Complete healing (*N* = 203)	Incomplete healing without infection (*N* = 119)	Incomplete healing with infection (*N* = 24)	Variance analysis F (and *p*) values
Baseline status				
Age (years)	72 (15.1)	75 (13.5)	75 (12.1)	2.2 ($p = 0.11$)
Ulcer evolution (weeks)	27.7 (69.9)	72 (116)	91.4 (125)	11.5 ($p < 0.001$)
Ulcer perimeter (mm)	123 (169)	171 (182)	324 (298)	13.5 ($p < 0.001$)
Ulcer necrosis area (%)	27.2 (39.8)	21.9 (34.3)	27.3 (36.3)	0.79 ($p = 0.45$)
Ulcer granulation (%)	36.6 (37.6)	27.9 (30.7)	18.4 (22.4)	4.4 ($p < 0.05$)
Ulcer pain scale (0–10)	3.4 (3.5)	4.6 (3.2)	6.9 (3.2)	10.4 ($p < 0.001$)
Dressing change pain scale (1–10)	4 (3.6)	5.1 (3.2)	7.1 (3.4)	10.7 ($p < 0.001$)
Follow-up status				
Antibiotic treatment (days)	11.7 (4.5)	14.4 (20.2)	24.3 (14.2)	16.5 ($p < 0.001$)
Antiseptic treatment (weeks)	14.7 (20.3)	25.1 (33.1)	23.1 (23.3)	6.5 ($p < 0.01$)
Healing speed (% ulcer perimeter/week)	12.9 (9.3)	3 (7.7)	0.8 (44)	61.1 ($p < 0.001$)
Wound healing speed (mm/week)	13.7 (19.2)	5.4 (9.6)	2.8 (5.5)	12.5 ($p < 0.001$)
Nonhealed residual ulcer (%)	0 (0)	67.9 (59.7)	78.1 (43.9)	150.5 ($p < 0.001$)

Note: Mean (and standard deviation).

TABLE 3 Prognostic factors of the 346 ulcers studied regarding the results at discharge.

Complete healing. Multivariable equation				
Variables	**Beta coef**	**SE-B**	***p* Value**	**OR (95% CI)**
Age (years)	−0.029	0.009	0.001	0.97 (0.95–0.98)
Ulcer evolution (weeks)	−0.005	0.002	0.001	0.995 (0.992–0.998)
Unhealthy granulation	−0.954	0.329	0.001	0.38 (0.2–0.73)
Antibiotics used (Ref. No antibiotics)	−0.948	0.267	<0.001	0.39 (0.23–0.65)
HOCl (liquid plus gel) vs. "single antiseptic"	1.57	0.27	<0.001	4.8 (2.83–8.1)
Hosmer–Lemeshow goodness-of-fit = 0.903				
Infection. Multivariable equation				
Variables	**Beta coef**	**SE-B**	***p* Value**	**OR (95% CI)**
Bad odor	2.64	0.51	<0.001	14 (4.9–39.6)
Ulcer evolution (weeks)	0.002	0.002	0.19	1.002 (0.997–1.006)
HOCl (liquid plus gel) vs. "single antiseptic"	−1.118	0.4	0.01	0.3 (0.12–0.78)
Hosmer–Lemeshow goodness-of-fit = 0.79				

Note: Multivariable study by logistic regression.

Abbreviations: Beta-coef, beta-coefficient; CI, confidence intervals; OR, odds ratio; SE-B, standard error beta coefficient.

IV, respectively, in venous or arterial ulcers), lesion dimensions (123–324 mm diameter), as well as some clinical signs (bad odor or pain when changing the dressing). In addition, the concomitant use of general antibiotic therapy (especially quinolones) during the treatment of ulcers and the duration of both therapies (antiseptic and antibiotic) were significant.

The speed of healing, in absolute or relative terms, was two to four times faster in the ulcers that healed completely and slower in those that eventually became infected, so, healing speed is a good prognostic factor for healing.

Last, we consider the effect of the cleaning solution on the ulcers. The most used was the combination HOCl-liquid + gel: *N* = 201 (58.1%) versus "one antiseptic" *N* = 145 (41.9%). The latter group are composed of distinct treatments: HOCl (liquid) *N* = 60; polymeric biguanide *N* = 20; chlorhexidine, *N* = 20; HOCl-gel, *N* = 22 (6.4%) or, consecutively two of the above, in monotherapy, *N* = 23.

When HOCl liquid is added to the HOCl gel treatment (combined or double therapy), the ulcers healed better (70%) than when only one antiseptic was used, including when either HOCl (liquid) or HOCl gel were used alone, because all of them, individually, obtained a much lower healing frequency (around 40%). For this reason, we have thought it more convenient to group all these antiseptics as "single antiseptic" (because all were applied as a monotherapy) and they are considered the reference category versus HOCl-liq + gel.

(2) Analytic epidemiology:

Table 3 shows the multivariable analysis. In our Logistic Regressions, we have only included two equations, since they represent the most interesting prognostic results: cure or infection. In the "healing equation" the ulcers that evolved correctly are compared with those that evolved poorly (regardless of whether they became infected or not) and the "infection equation" compares ulcers that suffered infection with those that did not become infected (regardless of whether they healed completely or not).

Four factors have been found that reduce the probability of the complete healing of ulcers: patient age (odds ratio [OR]: 0.97; 95% confidence interval [CI]: 0.95–0.98); weeks of ulcer evolution before the beginning of treatment in CMUC clinics (OR: 0.995; 95% CI: 0.992–0.998); ulcers with poor granulation on admission (OR: 0.38; 95% CI: 0.2–0.73); and need for antibiotic therapy (OR: 0.39; 95% CI: 0.23–0.65). Moreover, one factor favored healing: the use of the double ClHO formulation (liquid plus gel) (OR: 4.8; 95% CI: 2.8–8.1).

Otherwise, infection was associated with longer times of ulcer evolution (OR: 1.002; 95% CI: 0.99–1.006) and bad odor of the ulcer at enrollment (OR: 14; 95% CI: 4.9–39.6). The double formulation treatment with HOCl (liquid plus gel) reduced the risk of infection (OR: 0.3; 95% CI: 0.12–0.78). A variable that was nonsignificant by itself (ulcer evolution in weeks) was included because it helped to improve equation fit.

4 | DISCUSSION

Classic factors that influence the good or bad evolution of chronic ulcers[2–6] are patient age and the time of evolution until the start of treatment; in our study, healing time is multiplied by two, or three, when the evolution is not good (incomplete healing or infection). Pain

(spontaneous or when the dressing is changed) and size are less in ulcers that end up healing well. Likewise, those ulcers that evolve well, as is logical, require a shorter duration of antibiotic treatment and cleaning sessions and also heal faster.

Our multivariate analysis, when controlling for other possible risk factors, found only four that were associated with poor healing (OR <1 incomplete healing): increased age of the patient (associated to poor vascularization and concurrent diseases); weeks of evolution of the ulcer; poor granulation at admission; and a need for antibiotic therapy. The physiological mechanisms (inflammation, cellular proliferation, and tissue regeneration) altered by these risk factors, implicated in the poor ulcer healing, are very well described by several authors.[22,23]

But the same multivariate analysis shows that only one protection factor is associated with complete healing: the successive application, in each treatment session, of the two HOCl formulations, liquid and gel. This factor enhances the healing of ulcers by more than four, which is why this type of treatment is to be highly recommended in vascular, traumatic, diabetic foot ulcers, and so on in patients who are generally over 70 years of age and have many previous pathologies, like ours.

According to Santy,[24] pain in an ulcer is due to bacterial contamination or infection and its biofilm formation play a detrimental role in wound healing process and progress to closure.

On these sense, the risk of infection of the ulcers in our patients, which in the bivariate analysis can be associated with many factors, as mentioned above, but is reduced to only two risk factors in the multivariate analysis: the "time of evolution" of the ulcer, (because in torpid ulcers, healing is worse according to the infection with successive microbial colonizations, and, in some cases, repeated infections) and the most important variable, which associates diverses characteristics of the ulcer such as size, heat, bad smell, type of tissue at the ulcer bed, and so on: the "stench" from the ulcer. These negative characteristics generate a huge OR,[14] because they are strong indicators of infection on admission. Despite this, of 89 ulcers with this characteristic, only 19 became infected, thanks to the established treatment (especially with the combination of HOCl liquid plus gel, since this reduced the risk of infection by almost a third in those so treated, because as all correct treatment, modifies the prognosis of the ulcer.

This HOCl antimicrobial efficacy and increase of ulcers' healing process, was observed too by other researchers with a minor number of patients,[25] because cleans and removes the necrotic tissue and biofilm from wounds, but we must add that this acid act better when is it is in a double formulation, as we have indicated.

4.1 | Study limitations and strengths

Limitations: This is a nonrandomized study, which may have biased treatment allocation, but it has been controlled by multivariate analysis, so it can be accepted that the final result on the ulcers (complete healing or infection) is dependent on the treatment and was not affected by important biases. However, we cannot ensure that there is nonuncontrollable bias in the analysis, so it would be helpful to ratify these findings in an experimental randomized study.

Strengths: Contrary to other studies that finish within 3–4 weeks, (so they only assess processes, but not results), our study has a long follow-up as long as 12 months in some cases, which makes it possible to assess the final outcome in most patients.

The large number of ulcers studied, and their etiologies, have allowed us to assess the global efficacy of this mixture of HOCl formulations without being restricted to a specific etiology.

5 | CONCLUSION

Statistically significant factors found in the multivariate study that indicate a poor prognosis in the healing of chronic ulcers were older age, a marked delay in starting treatment, the type of tissue in the ulcer bed or poor smell of the lesion on admission and whether antibiotic treatment was employed.

The double formulation of HOCl used to heal these ulcers was the only protective factor found in this multivariate analysis; it increased the probability of complete healing by four and decreased the probability of infection at discharge by almost a third.

However, these results require larger clinical trials to confirm the effectivity of our experience with HOCl liquid plus gel to cure chronic ulcers.

AUTHOR CONTRIBUTIONS

Rafael Herruzo: Conceptualization; formal analysis; investigation; methodology; supervision; validation; writing—original draft; writing—review and editing. **Erika Fondo Alvarez**: Conceptualization; data curation; methodology; supervision; validation; writing—review and editing. **Irene Herruzo**: Conceptualization; formal analysis; methodology; writing—review and editing. **Macarena Garrido-Estepa**: Conceptualization; formal analysis; methodology; writing—original draft; writing—review and editing. **Emma Santiso Casanova**: Data curation; validation; writing—review and editing. **Silvia Cerame Perez**: Conceptualization; data curation; methodology; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Spanish law prohibits the use of raw data from patient's clinical histories. However, we have summarized and anonymized data that we can supply to qualified querents. Data available on request from the authors.

TRANSPARENCY STATEMENT

The lead author Rafael Herruzo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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