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The role of collagenase ointment in acute burns: a systematic review and meta-analysis

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Abstract

Aims: Clostridial collagenase ointment (CCO) is the only FDA-approved product for enzymatic debridement in the United States. Its efficacy in the burn patient has not been extensively examined. A systematic review and meta-analysis was performed to summarize the state of the literature in regard to the efficacy and uses of CCO in the burn patient.

Methods: A systematic review of articles available on PubMed, Scopus, and OvidSP Medline was performed. Keywords utilized in the search process included: burns; thermal injury; collagenase; enzymatic debridement; wound care. Excluded articles included reviews, case reports, independent abstracts, consensus and opinion papers. A meta-analysis was performed for articles fitting inclusion criteria.

Results: Six relevant articles were identified for systematic review. Few studies, with limited sample sizes, argue that collagenase ointment may be an effective debriding agent. CCO may also accelerate wound healing and avoid the pain associated with mechanical debridement. CCO lacks anti-microbial activity but the risk of burn wound infection does not appear to be significantly different than when using silver-impregnated products. CCO is more expensive than traditional wound care products but may halt burn depth conversion and prevent the need for surgery.

Conclusions: CCO may be a safe and effective debridement agent for burn wounds with respect to decreasing wound healing time and minimizing pain without increasing the risk of infection. It should be used on a case-by-case basis due to its financial cost. The financial cost of CCO may be off-set by its ability to manage burns non-operatively.

Keywords

burns; thermal injuries; enzymatic debridement; santyl; Novuxol; collagenase

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INTRODUCTION

Enzymatic debridement for burn wounds is an attractive alternative to surgical excision, yet the current options available in the United States are limited. Globally the two most popular products are derived from bacterial collagenase and bromelain, an enzyme found in pineapple stems. Bromelain-based products have attained widespread use^{1–10} and have demonstrated superiority over traditional wound care with silver-impregnated products¹. A recent review¹¹ has recently examined the evidence behind bromelain-based products. At this time, however, bromelain is not approved for use in the United States, although clinical trials are underway.

Clostridial collagenase ointment (CCO), sold under the trade name Santyl (Smith&Nephew), is currently the only FDA-approved enzymatic debridement agent in the United States..Despite its widespread use in burn care, the evidence to support its use has not been critically examined. Others have evaluated the uses of CCO in patients with chronic wounds but none focused on the use of CCO in burn patients. Burn injuries can occur in a more heterogeneous patient population than pressure, venous, or arterial ulcers (i.e. patients with chronic diseases) and may have varying microbial compositions and complications owing to their acute nature. Therefore, the aim of this systematic review and meta-analysis was to evaluate the published uses and efficacy of clostridial collagenase ointment (CCO) in burn patients when compared to traditional methods of wound debridement.

METHODS

A systematic literature search was performed through PubMed, Scopus, and OvidSP Medline databases as well as manually checking the reference lists of retrieved articles and reviews once relevance was determined. Permutations of the following keywords and free text were included in all search strategies: burns; thermal injury; collagenase; enzymatic debridement; Santyl; Novuxol; Iruxol. The search was restricted to English language, those with English translations, full text availability, primary source, and human subject only. The final search was conducted on October 31st, 2017. Articles were included if they:

1. presented original quantitative data
2. defined the patient population being evaluated with respect to demographics and burn severity
3. specifically used clostridial collagenase (i.e., streptococcal, bacillus, and bromelain-based enzyme products excluded)
4. incorporated statistical analysis to support conclusions

The titles, abstracts, and full text of identified articles were independently reviewed by four researchers (CP, AH, ZC, JG) to determine eligibility. Excluded studies included reviews, case reports, independent abstracts, consensus and opinion papers. All studies that used enzymes not derived from *Clostridium spp.* were excluded since the mechanisms differ and may affect wound healing and anti-microbial outcomes. In all instances, differences of opinions were resolved by discussion. Data were extracted regarding study design, patient

demographics and burn injury characteristics (e.g., age, race, gender, TBSA, number of subjects, depth of burn).

All studies in the systematic review that reported (1) control cohorts (non-CCO) and (2) variance were included in the meta-analysis. Combined effect size estimates and odds ratios (ORs) were computed with 95% confidence intervals (CI) for the outcomes that fit criteria for meta-analysis.

RESULTS

Study Selection

The electronic database search initially produced 706 articles (Figure 1). Screening titles and abstracts for duplicates and eligibility to the research question resulted in the exclusion of 660 articles. After full text review of the remaining 36 articles, 30 were excluded and six were included for data extraction. Twelve articles were excluded due to the use of non-clostridial collagenase enzymes. Seven articles were excluded due to the animal study design. Five articles were excluded after being unable to retrieve the full-text. Six articles were excluded due to a focus on pressure ulcers only. Of these six articles, five used Santyl (Smith & Nephew) and one used Novuxol (Knoll Landmark Arzneimittel GmbH). The active ingredient in both of these enzymes was collagenase derived from *Clostridium histolyticum*.

DISCUSSION

The active ingredient in Santyl derives from the collagenase of *Clostridium histolyticum* (*C. histolyticum*), and the first experiments with it date back to 1951 in which Altemeier et al.¹² tested *C. histolyticum* in full-thickness burns on guinea pigs. Traditional wound management involves using silver-impregnated products such as silver sulfadiazine (SSD), which is one of the most commonly used silver products for wound care and possesses antimicrobial activity through the disruption of bacterial metabolism¹³. Drawbacks to SSD include delayed wound healing and eschar separation as well as the formation of a pseudoeschar. The delays in wound healing are thought to be due to local inhibition of keratinocyte and fibroblast growth¹³, and delays in eschar separation are due to the antimicrobial properties of SSD that prevent bacterial growth and release of bacterial collagenases and proteases¹³.

Collagenase acts by breaking down the denatured collagen molecule that is present in burned tissue. The degradation products can then be mechanically removed from the wound bed with the goal of hastening wound debridement and healing. [Rashaan] A prospective study of 15 burn patients (11.7% TBSA, mean) compared CCO (Santyl) to SSD and found that wounds treated with CCO (Santyl) had significantly shorter durations of time-to-clean (TTC) wound bed (6 vs. 12 days, $p=.0012$) and time-to-healed (TTH) (10 vs. 15 days, $p=.0007$) compared to wounds treated with SSD.¹⁴ Another multi-center prospective study¹⁵ of 79 patients (13.6% TBSA, mean) using non-contiguous wounds on individual burn patients as both study and control compared CCO (Santyl) with polymyxin B sulfate powder against SSD and demonstrated significantly faster TTC (9.3 vs. 11.6 days, $p<.001$) and TTH

(19 vs. 22.1 days, $p<.001$) durations as well as fewer days of treatment (6.5 vs 7.3 days, $p=.036$) when wounds were treated with CCO (Santyl) and polymyxin B sulfate. Although not statistically significant the authors also showed that more non-CCO-treated (non-Santyl) burn sites required surgery (15.4% vs 19.2%, $p>0.05$) and CCO-treated (Santyl) burns had less eschar and pain than non-CCO-treated (non-Santyl) burns ($p>0.05$)¹⁵. Both studies demonstrated a faster rate of wound healing, and this is hypothesized to be due to bioactive extracellular matrix peptides released by collagenases¹⁵. Recent laboratory evidence has shown that collagenase-liberated protein fragments increase endothelial and fibroblast proliferation, which results in greater formation of granulation tissue than saline-treated controls¹⁶. This is thought to be mediated by novel collagen fragments and collagen-associated peptides (thrombospondin-1, multimerin-1, fibronectin, transforming growth factor-beta induced protein ig-h3, and tenascin-C) produced by CCO¹⁶.

Another advantage of CCO over SSD is the ease of application and dressing maintenance. The same nurses (9.4 years of experience, mean) in the Ostlie et al. study were surveyed regarding the use of CCO (Santyl) vs. SSD, with 83% preferring CCO (Santyl) because of the cleanliness of dressings, lack of pseudoeschar, and appearance of less pain during dressing changes.¹⁷ The formation of a pseudoeschar is a well-known consequence of SSD use and mandates daily – sometimes more than daily -- dressing changes. This results in more pain and analgesia requirements for the patient, both of which can be minimized with the use of CCO.

Since CCO has no intrinsic anti-microbial properties, its use alone may result in increased incidence of burn wound infections when compared with standard anti-microbial dressings. As mentioned above, traditional wound therapy with silver-impregnated products such as SSD or mafenide acetate (Sulfamylon) provides anti-microbial activity, however, relies on eschar autolysis and mechanical debridement – the former which is implicated in delayed time to wound healing¹³. In rats, clostridial collagenase has been associated with increased rates of infection, but this association was not significant and has yet to be demonstrated in humans¹⁸. Ozcan et al. prospectively showed that CCO-treated patients did not experience a significant difference in wound infections compared to non-CCO treated patients.¹⁹ In the Hansbrough et al. study 15 patients developed cellulitis but 12 experimental and 11 control burns involved with no significant difference in the incidence of wound infections¹⁵. Ostlie et al. performed a prospective study comparing CCO (Santyl) (N=50) to SSD (N=50) in partial-thickness burns (4–5% TBSA, mean) in children (9–10 years, mean) and reported more suspected infections in patients receiving CCO (Santyl) than those receiving SSD, but this did not reach significance (7 vs. 1 cases, $p > .05$).²⁰ Meta-analysis showed no significant difference in the odds of developing wound infections between CCO-treated and non-CCO treated patients (OR: 2.52); however, larger studies are required to definitively understand the effects of CCO on the development of wound infections.

Another consideration when using CCO over traditional wound care products is the financial cost. One institution estimated the cost of using CCO (Santyl) for a cohort of patients with wounds, including burns, and found an average total debridement cost of \$1,521 per patient²¹; however, they designed a protocol of Santyl plus hypochlorous acid (Vashe) that allowed them to reduce their total debridement cost to \$424 per patient²¹. Similar studies have also

examined the costs of CCO (Santyl) and while they found it to be more expensive than SSD (+\$842, $p < .001$), they believed it to be a small part of a much larger hospital bill²⁰. It has been shown that Santyl is associated with more rapid wound healing and has the potential to neutralize the need for excision and grafting. It has been posited that using CO with Bactroban to help determine depth of burns faster than traditional therapy¹⁴; this claim, however, is tempered by the fact that SSD can prolong wound healing and may confound these estimates¹⁴. Ostlie et al. found no significant differences in outcomes (need for skin graft, time-to-graft, LOS, and burn wound infection) between CCO-treated (Santyl) and SSD-treated patients²⁰. Estimating the cost-effectiveness of using Santyl is difficult because, while it is unequivocally much more expensive than most silver-impregnated products, one must consider the potential savings of (1) not needing to perform an expensive surgery, (2) foregoing the morbidity that comes with harvesting an autologous skin graft, and (3) obviating the need for mechanical debridement of pseudoeschar associated with SSD and the pain that results from this debridement.

The potential for CCO to prevent burn wound conversion may be secondary to its release of wound healing peptides from digested endothelial and fibroblast extracellular matrix (ECM) that are implicated in human dermal endothelial cell, keratinocyte, and fibroblast proliferation *in vitro* and *in vivo* in murine models.¹⁶ Hansbrough et al. found that patients treated with CCO required fewer surgeries compared to patients treated with SSD, however, this did not reach statistical significance.¹⁵ Ozcan et al. enrolled 78 patients with partial-thickness burns that were assigned to treatment with CCO-only, of which 29/78 subsequently required excision and grafting. It is not possible to discern how many of the 49 patients in the CCO-only group prevented burn depth conversion and avoided surgery due to CCO; however, the ability of CCO to prevent burn depth conversion and obviate the need for surgery is suggested by significantly fewer blood transfusions ($P < 0.05$) in CCO-treated patients vs. patients who received early excision and grafting.¹⁹

This review examined the uses and outcomes of CCO in burn patients. These data suggest that CCO can be used on an individualized basis to debride burn wounds with less pain and nursing labor than traditional therapy with other silver-impregnated products such as SSD. There is no evidence that CCO leads to an increase in burn wound infections compared to traditional anti-microbial wound dressings. While CCO comes at not an insignificant financial cost, this issue is likely less worrisome than believed given the average total hospital cost for a burn patient in the United States and the potential of CCO to prevent surgery by halting burn depth conversion. Large randomized controlled trials are needed to draw definitive conclusions regarding risk differences in wound infections, cost-savings, and pain reduction with the use of CCO in burns. The bromelain-based debridement agents have much more robust data in the burn literature^{1–11} than CCO. Bromelain-based products appear to effectively prevent burn depth conversion and the subsequent need for surgery¹¹, which hints at its cost-effectiveness. Despite the promising data, however, bromelain-based products are not FDA-approved in the United States yet. We conducted this review and meta-analysis to appraise the burn literature for the evidence behind CCO while it remains the only FDA-approved product for burn care.

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Figure 1. Study selection process, PRISMA diagram.

Using the metafor package in the R programming language, a meta-analysis was performed with a random-effects model to examine ORs of wound infections (Figure 2) in CCO-treated and non-CCO treated patients. Funnel plots are shown (Figure 3) but assessment for asymmetry and publication bias is difficult due to the low number of observations. There were no significant differences found in the odds of developing wound infections between CCO-treated and non-CCO treated patients (Figure 2). Time-to-clean wound bed and time-to-healed were unable to be included in the meta-analysis due to an absence of reported variance or the full dataset in the original full-text.

Figure 2.

Meta-analysis results. Forest plots show ORs (95% CIs) for wound infection in individual studies and combined estimates is shown. There was substantial heterogeneity ($I^2=54\%$), therefore, statements made about wound infections are not definitive.

Figure 3.
Funnel plots to assess for publication bias.

Table 1.

Study Summaries.

Clostridial collagenase ointment, CCO; Silver sulfadiazine, SSD; Length-of-stay, LOS.

Study	Design	Sample Size (N)	TBSA, mean	Depth of burn	Type of enzymatic debrider	Outcome
Soroff, 1994	Prospective	15	11.7	Partial-thickness	Santyl vs SSD	Time to clean wound bed (6 vs. 12, $P=0.0012$) Time to healed (10 vs. 15, $P=0.0007$) Time-to-clean wound bed (9.3 days vs 11.6 days, $P<0.001$)
Hansbrough, 1995	Prospective, multicenter	79	13.6%	≥ 2 non-contiguous, partial-thickness, comparably sized and distributed burns	Santyl w/ polymyxin B sulfate/bacitracin powder vs SSD	Time to healed (19 vs 22.1 days, $P<0.001$) CCO wounds healed faster than SSD wounds treated on the same person ($P<0.001$) More control sites required surgery ($p>0.05$) CCO-treated sites had "thinner" eschar and less debridement pain
Ozcan, 2002	Prospective	49 (CCO) vs. 41 (early excision & grafting)	12%	NR	Novuxol	Time-to-clean wound bed (7.8 ± 2.8 vs. 8 ± 3.6) CCO patients had fewer blood transfusions, wound infections, and a shorter LOS ($P<0.05$)
Ostlie, 2012	Randomized controlled trial	50 (CCO) vs. 50 (Control)	9.4% (SSD); 9.9% (CCO)	Partial-thickness	CCO vs SSD	No significant difference in cost, need for skin graft, % grafted, total number of treatments, time-to-graft, LOS, incidence of burn wound infection
Sharp, 2014	Survey	12 RNs	NR	NR	NR	10/12 (83%) nurses preferred CCO over SSD because 1) cleanliness of dressing (12%), lack of pseudoeschar (25%), belief that there was less pain during dressing changes (8%).
Miller, 2014	Prospective	26 (51 wounds)	NR	NR	Santyl	Before protocol: Cost of CCO per patient = 1521 Cost of CCO per wound = 775 Cost of CCO per wound = 775 Total debridement cost per patient/wound = 1521/775 Expenditure for CCO/vashe = 39,544/0 After protocol: Cost of CCO per patient = 400 Cost of CCO per wound = 335 Total debridement cost per patient/wound = 424/355 Expenditure for CCO/vashe = 14,410/878