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Efficacy of topical cadexomer iodine treatment in chronic wounds: Systematic review and meta-analysis of comparative clinical trials

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Abstract

The aim of this study was to summarise the clinical evidence supporting almost 40 years of topical cadexomer iodine (CIOD) use in wound bed preparation by removing barriers to healing such as exudate, slough, bioburden, and infection and allowing chronic wound progression. A systematic review was conducted (Embase/PubMed, November 2020) to identify relevant comparative studies meeting inclusion criteria. Meta-analyses were performed using a fixed-effects ($I^2 < 50\%$) or random-effects model ($I^2 \geq 50\%$) depending on statistical heterogeneity. Dichotomous outcomes were reported as relative risk (RR) and continuous outcomes as mean difference (MD), with 95% confidence intervals. In total, 436 publications were identified of which 13 were comparative trials including outcomes of interest. Significant reductions in exudate, pus/debris, slough, bioburden, and infection were reported in chronic wounds treated with CIOD, compared with standard of care (SOC). Meta-analyses highlighted the positive impact of CIOD on mean wound area reduction (MD = 2.35 cm^2, 95% CI = 0.34–4.36, $P = .0219$) after eight weeks treatment and overall wound healing events compared to SOC; wounds including venous leg ulcers, diabetic foot ulcers, and pressure ulcers treated with CIOD were more than twice as likely to heal than those receiving SOC (RR = 2.30, 95% CI = 1.54–3.45, $P < .0001$). This meta-analysis demonstrates the efficacy of CIOD on chronic wounds through removal of barriers to healing. CIOD should be considered in wound bed preparation and treatment protocols.

KEYWORDS

cadexomer iodine, desloughing, exudate, infection, wound healing

Kevin Woo and Caroline Dowsett are co-first authors.

1 | INTRODUCTION

In addition to the comorbidities of the patient, a chronic wound may contain various local factors, which may act as barriers to successful wound healing. These can include the following: excessive wound exudate, non-viable tissue or cellular debris (slough and pus or purulence consisting of dead white blood cells and bacteria with tissue debris and serum), and high bacterial bioburden including biofilm and infection. The presence of biofilm represents a significant clinical challenge, particularly their enhanced tolerance to antimicrobials[1,2] and ability to evade the host immune response.[3,4] Control or removal of these barriers is important to allow host repair and for the wound to progress to healing as part of an effective wound bed preparation protocol.[5,6]

One intervention that has been reported to help reduce and remove these barriers to healing is cadexomer iodine (CIOD). This treatment consists of biodegradable spherical hydrophilic beads (size range 100-315 μm) of cadexomer starch, which incorporate 0.9% w/w iodine, and is available in powder, gel/ointment, and dressing formats. The dual mode of action of CIOD combines physical and antimicrobial attributes, which work together to address many of the barriers to healing found particularly in chronic wounds, namely excessive exudate, slough, and bioburden.[7] The cadexomer beads have been shown to absorb up to seven times their own weight in fluid,[8] resulting in effective exudate management in wounds.[8-13] This physical absorption by the starch beads provides a further de-sloughing action[8-10,12-16] removing debris, purulence,[11,16] and bacteria[17] from the wound into the dressing. The physical swelling of the cadexomer beads upon contact with fluid allows the sustained availability of iodine, which kills bacteria and biofilm within the dressing for up to 72 hours[18-20] with subsequent minimal impact in toxicity[21,22] This mode of action is illustrated in Figure 1. These barriers to healing such as excess exudate, slough pus and debris, and bioburden including biofilm all have an increasingly recognised role in delaying wound healing. Effective management or removal of these barriers supports a wound environment conducive to healing, thereby allowing wound healing to progress. Successful healing outcomes following the use of CIOD have been demonstrated across a large number of high-level clinical studies spanning almost 40 years, culminating in a positive Cochrane review for faster rates of healing than standard of care (SOC) in venous leg ulcers (VLU).[23,24]

The aim of this systematic review and meta-analysis was to examine the clinical evidence for the use of CIOD over the last four decades, building on the previous Cochrane review analysis in VLU, with the additional assessment of published data on diabetic foot

Key Messages

- systematic review and meta-analysis of published clinical data highlights the wealth of clinical data and successful outcomes spanning almost 40 years with cadexomer iodine (CIOD) in chronic wounds
- CIOD was found to significantly reduce many of the barriers to wound healing such as excess exudate, slough, debris, and bioburden across multiple high-level studies compared to standard of care (SOC) subsequently allowing wound healing to progress
- meta-analysis of wound healing data demonstrated wounds were greater than two times more likely to heal with CIOD treatment compared to SOC ($P < .0001$)

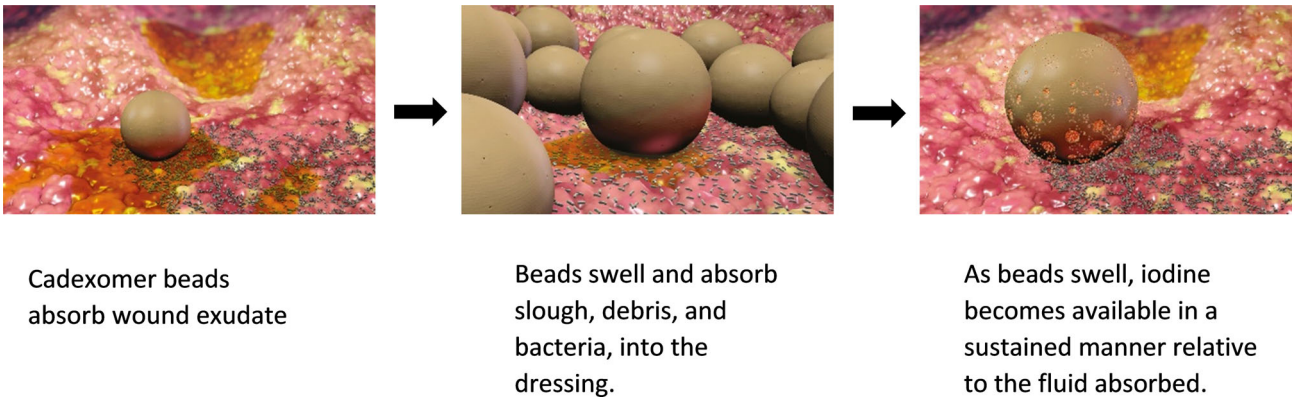

FIGURE 1 Schematic to illustrate the mode of action of cadexomer iodine[8-20]

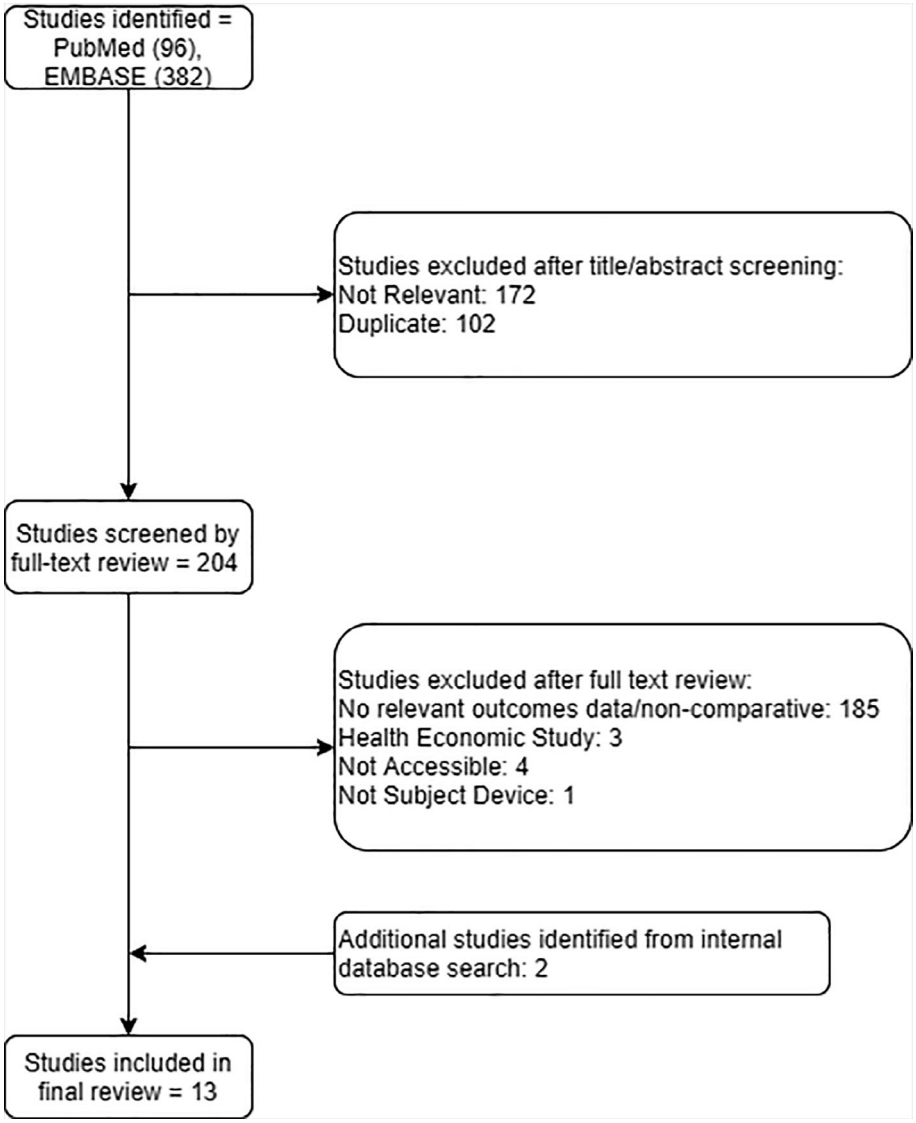

FIGURE 2 A PRISMA flow diagram mapping out the number of records identified, included and excluded, and the reasons for exclusions

ulcers (DFUs) and pressure ulcers (PUs). Furthermore, this review provides a more in-depth analysis of the impact of CIOD in reducing some of the barriers to healing such as exudate, slough, and bioburden, which subsequently may contribute to wound progression and enhanced healing.

2 | METHODS

2.1 | Search strategy

A systematic literature search was performed using the following search terms "IODOSORB" OR "IODOFLEX" OR "Cadexomer iodine" OR "CADEX" OR (("Cadexomer beads" OR "Iodine beads" OR "Iodine starch") AND ("wound healing" OR "chronic wound")), and no lower date limit was conducted on Embase and PubMed to identify relevant studies on 24 November 2020. To increase the sensitivity of the searches, search terms were intentionally left open and did not include words related to specific outcomes, patient populations, or adverse events. Reference lists of included articles were hand-searched to identify any further studies along with internal database searches. Searches were restricted to English-language articles. The inclusion of studies into the review is illustrated in Figure 2.

2.2 | Inclusion and exclusion criteria

Interventions with CIOD in any of its preparations (powder, dressing, or ointment/ gel) were assessed. Comparative studies (including prospective and retrospective design) that evaluated the use of CIOD along with relevant wound healing outcomes in patients of any age or with any risk factors for complications were included. A comparator was defined as standard or routine care

appropriate for that wound type such as compression for VLUs, and basic (non-antimicrobial) wound dressings such as paraffin, gauze, or hydrocolloid dressings, which varied according to local practices. Non-comparative trials and case reports, case series, retrospective observational studies, review articles, letters, commentaries, and notes were excluded.

2.3 | Outcome measures of interest

Outcome measures included the following: exudate management, reduction in pus (more recently termed purulence), slough and cellular debris, bioburden (including biofilm), infection, pain and wound area, and wound healing.

2.4 | Study selection and data extraction

Review of the publications that met the eligibility criteria was performed by two independent reviewers (SE and EW). Data were extracted by use of standardised spreadsheet tables. Study quality and bias was assessed, the quality of included studies were independently assessed by BC and SE (Supplement 1). Quality criteria were taken from Centre for Reviews and Dissemination guidelines for the assessment of risk of bias in RCTs. Wherever available, data recorded included general study characteristics such as year of publication, duration of follow up, number of participants, mean age of participants, and SOC (Supplement 2). Furthermore, the primary outcome measures and adverse event data were also extracted.

2.5 | Data synthesis and statistical analysis

Overall effect estimates were calculated using the meta package in R 3.5.0 (R Core Team, 2018). The inverse variance weighted method was adopted for continuous outcomes and the Mantel–Haenszel method for binary outcomes, using either a fixed-effects model or a random-effects model. Individual risk ratio estimates and summary estimates were displayed graphically in forest plots. Heterogeneity was quantified with the I^2 statistic. The method for calculating the SD of the mean difference (MD) for continuous outcomes was undertaken using the following for formula: $\sigma_d = \text{sqrt}\,(\sigma_1{}^2/n_1 + \sigma_2{}^2/n_2)$. $\sigma_1{}^2$ corresponds to the SD in population 1 and $\sigma_2{}^2$ corresponds to the SD in population 2. N_1 and n_2 correspond to the total sample sizes in population 1 and 2, respectively. Where the SD was not specifically indicated, we classed the corresponding number after the mean as the SEM and converted this to an SD. This assumption was made as a result of similar publications in that time period reporting data in this way. This was conducted by multiplying the SEM by the square root of the number of patients. Studies which reported a relevant outcome which could not be included in the pooled analysis because of methodological or reporting issues are discussed qualitatively.

3 | RESULTS

3.1 | Study selection

In total 480 publications were identified, 96 from PubMed, 382 from Embase, and 2 from additional searches. After screening the studies based on the exclusion/inclusion criteria, 13 comparative trials were reviewed and 12 comparative trials demonstrated data suitable for further analysis (Figure 2).

3.2 | Study characteristics

Thirteen studies were identified as meeting the inclusion criteria (Figure 2, Supplement 2). The majority of the studies comprised of VLU patient populations, followed by one study focusing on PUs and two studies with DFU patients, all of which covered a range of different clinical outcomes. SOC varied across studies reflective of local protocols, including dressings such as paraffin gauze or hydrocolloid dressings. In addition, lower extremity compression therapy was used across all of the VLU studies for both CIOD and SOC groups, and an offloading boot used in one of the two DFU studies.

3.3 | Outcomes measures of efficacy

3.3.1 | Reduction in excessive wound exudate

Eight RCTs were identified to report on exudate levels, measured using a visual analogue scale, following treatment with CIOD compared to SOC in VLUs. Harcup and colleagues[25] highlighted a significant reduction in exudate levels by week 4 of treatment ($P < .001$), with similar findings demonstrated by Lindsay and colleagues[10] with significant reduction in exudate levels by 4 weeks for CIOD compared with SOC ($P < .002$). Laudanksa[26] reported a significantly faster reduction in exudate levels with CIOD treatment following 1 and 2 weeks ($P < .01$),

and 4 and 6 weeks of treatment compared to SOC ($P < .001$), whereas Skog and coworkers[11] reported that treatment with CIOD for 6 weeks was significantly more effective for reducing exudate compared to SOC ($P < .005$). Also within 6 weeks of treatment, Troeng et al reported that wounds became significantly less exudative following CIOD.[9] Hansson and team reported that following a 12-week intervention with CIOD, 70% of the ulcers had no exudate, compared to 52% and 44% in the hydrocolloid and paraffin gauze groups, respectively.[13] Finally in two further randomised crossover trials,[12,15] obvious improvements in exudate levels were observed with trends favouring CIOD.

3.3.2 | Reduction in cellular debris: wound slough and purulence

Hansson and colleagues[13] reported a significant reduction in the percentage of slough in chronic wound using CIOD compared with SOC ($P < .05$), whereas Skog et al[11] observed a marked debriding effect on VLU wounds due to reduction of pus (purulence) and removal of cellular debris from the wound bed.

Nine RCTs across both VLU and PU indications identified a reduction in purulence and cellular debris after use.[9-12,15,16,25-27] Significant reductions in pus and cellular debris following 4 weeks of treatment with CIOD vs SOC were demonstrated in VLUs by Lindsay[10] ($P < .002$) and Troeng[9] ($P < .005$)—with significant reductions observed at also weeks 2 and 6 in the latter study ($P < .025$/$P < .001$). Similar results were reported in VLUs at 6 weeks ($P < .001$) compared with SOC by Hillstrom et al.[27] In an RCT crossover study, Harcup[25] demonstrated a significant improvement in pus and debris in the wound by 4 weeks of CIOD treatment compared with SOC ($P < .05$). The reduction in pus and debris was shown to be more rapid following CIOD intervention in VLUs compared to SOC by Laudanska and colleagues.[26] Improvements were also highlighted in randomised crossover trials by both Holloway[15] and Troeng[9] with trends favouring CIOD, but results were not significant. Finally, an 8-week RCT in PUs highlighted CIOD to be superior compared to SOC in removing purulence and debris ($P < .005$).

A meta-analysis of these studies that contained the required information for statistical pooling, Figure 3, demonstrated a statistically significant difference between CIOD and SOC in the reduction of pus and debris assessed by visual analogue scale at 6–8 weeks (MD = 9.52, 95% CI: 5.27–13.77, $P < .0001$).

3.3.3 | Reduction in wound bioburden

Challenges of non-standard measures and outcomes across studies ranging from elimination of specific bacteria to reduction in bacterial load resulted in the available data being insufficient for a meta-analysis; however, comparative data within the studies identified are summarised later.

Significant reductions in wound pathogens were noted following CIOD intervention compared to SOC in RCT's, within 6 or 8 weeks of treatment. Hillstrom[27] reported a significant reduction in *Staphylococcus aureus* ($P < .001$) using semi-quantitative methods with an improvement in infection (classified here as heavy growth in semi-quantitative culture) in 16 of 23 patients in the CIOD group compared with 0 of 18 groups in SOC group. Significant reductions in *S aureus* were also reported in the other three RCTs[9-11]; Lindsay et al highlighted that CIOD treatment resulted in elimination

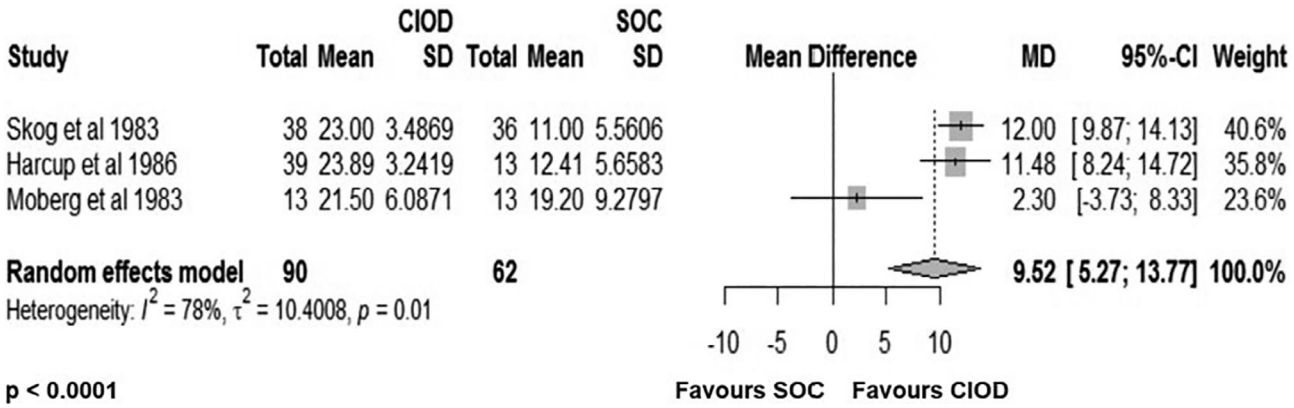

FIGURE 3 Reduction in ulcer pus and debris (visual analog scale) after 6–8 weeks for CIOD experimental group vs SOC control group. Ulcer pus and debris after 6–8 weeks was significantly reduced in CIOD experimental group as compared to the SOC control group ($P < .0001$). CIOD, cadexomer iodine; SOC, standard of care

or decrease of organisms in most cases, and this was associated with reduced odour and improvement of the ulcer.[10] In addition to significant reductions in *S aureus* reported by both Skog and Troeng following 6 weeks of intervention with CIOD compared with SOC,[9,11] significant reductions in streptococci, enterococci, and enterobacteriaceae such as *Proteus* and *Klebsiella* species were noted ($P < .001$ and $P < .01$, respectively) in these two trials.

One further study in DFU compromised by biofilm highlighted the significant reduction in biofilm numbers, as indicated by biopsy enumeration, using CIOD compared with the non-antimicrobial control following 2 weeks of treatment ($P = .063$).[28]

In addition, various studies emphasised reductions in other factors linked to infection or high bioburden following CIOD treatment; wound odour reduction has been linked to bioburden reduction, with a specific reduction in coliforms and *S aureus* in one study associated with a significant reduction in wound odour ($P < .002$).[10] Finally, Skog et al[11] reported a correlation between the time taken to reduce or eliminate *S aureus* and the rate of healing, which was much faster in the CIOD group compared with SOC as detailed in the healing section later.

3.3.4 | Reduction in pain

In total, six studies that reported on pain measured using a visual analogue scale (VAS) scoring following CIOD intervention compared with SOC; four in VLUs including significant pain reductions following 6[11,26] and 8 weeks[10,25] of treatment and one study in PU demonstrating a significant reduction in pain ($P < .02$) during the 8 weeks of study.[16]

A further study conveyed a trend towards less pain and was reported by Holloway and team with CIOD compared with SOC in VLUs; however, the difference was not statistically significant.[15]

Meta-analysis of relevant data, Figure 4, conveys a statistically significant difference in pain reduction measured using VAS between CIOD and SOD at 6–8 weeks (MD = 14.73, 95% CI: 3.75–25.71, $P = .0086$).

3.3.5 | Wound area reduction and wound healing

Considerable improvements in wound area reduction or complete healing events in chronic wounds (VLU, DFU, and PU) were demonstrated in 10 RCTs in the published literature following CIOD intervention.[9-13,15,16,25-27]

Specifically, significant reductions in wound area in VLUs have been reported by Hansson et al[13] who showed a 66% reduction in ulcer area over the 12 weeks study compared to only 18% in the SOC group ($P = .0127$), with a significantly higher rate of healing compared to SOC ($P = .0353$). Similarly, venous ulcers were observed to heal more than twice as rapidly using CIOD compared to SOC ($P = .0025$) in a randomised crossover trial.[15] Accelerated wound healing was also reported by Hillstrom[27] who demonstrated a significant reduction in VLU wound area with CIOD after only 1 week of treatment, and continued up to the end of the study (week 6). Similarly, Troeng and colleagues[9] also showed significant reduction in ulcer size compared to SOC at weeks 1, 2, 4, and 6 ($P < .01$, $P < .005$, $P < .01$, $P < .02$, respectively). Furthermore, the significant reduction in ulcer size by 1 and 2 weeks highlighted by Skog et al[11] ($P<.02$ and $P < 0.005$, respectively) equated to a 34% reduction in ulcer size by 6 weeks compared to an increase in ulcer size by 5% in the SOC group. Comparable reductions in VLU area following 8 weeks of CIOD treatment were also noted in a crossover trial by Lindsay et al[10] (33.6% vs 4.2% for SOC

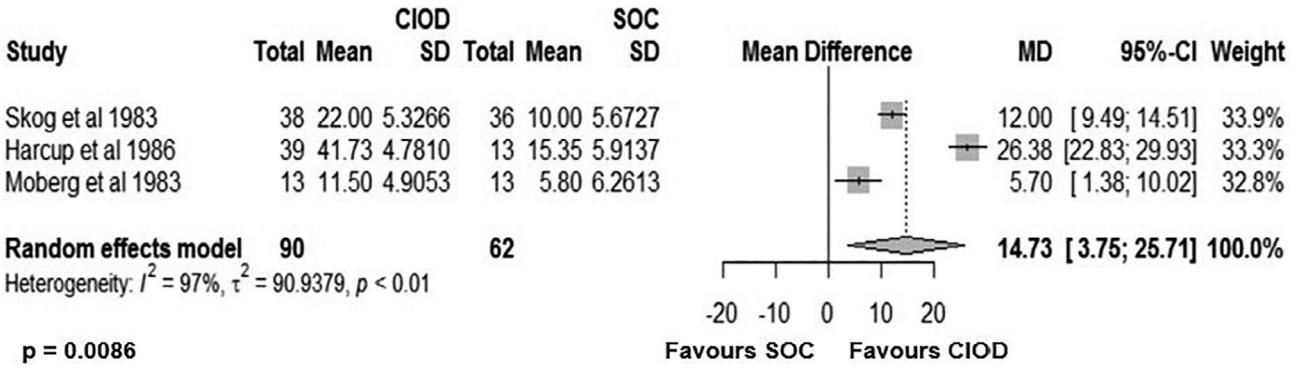

FIGURE 4 Reduction in ulcer pain (visual analog scale) after 6–8 weeks for CIOD experimental group vs SOC control group. Ulcer pain after 6–8 weeks was significantly diminished in the CIOD experimental group as compared to the SOC control group ($P = .0086$). CIOD, cadexomer iodine; SOC, standard of care

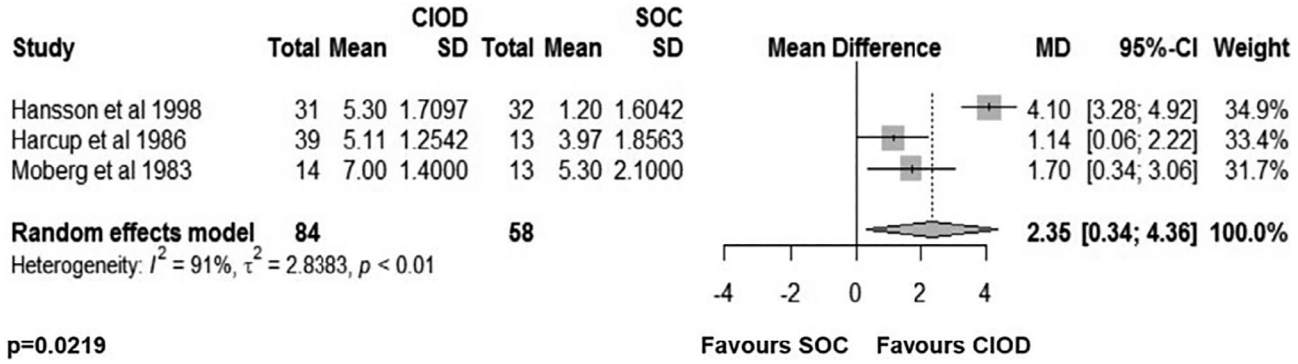

FIGURE 5 Reduction in ulcer area (cm^2) after 8 weeks for CIOD experimental group vs SOC control group. Ulcer area reduction after 8 weeks was significantly greater in CIOD experimental group as compared to the SOC control group ($P = .0219$). CIOD, cadexomer iodine; SOC, standard of care

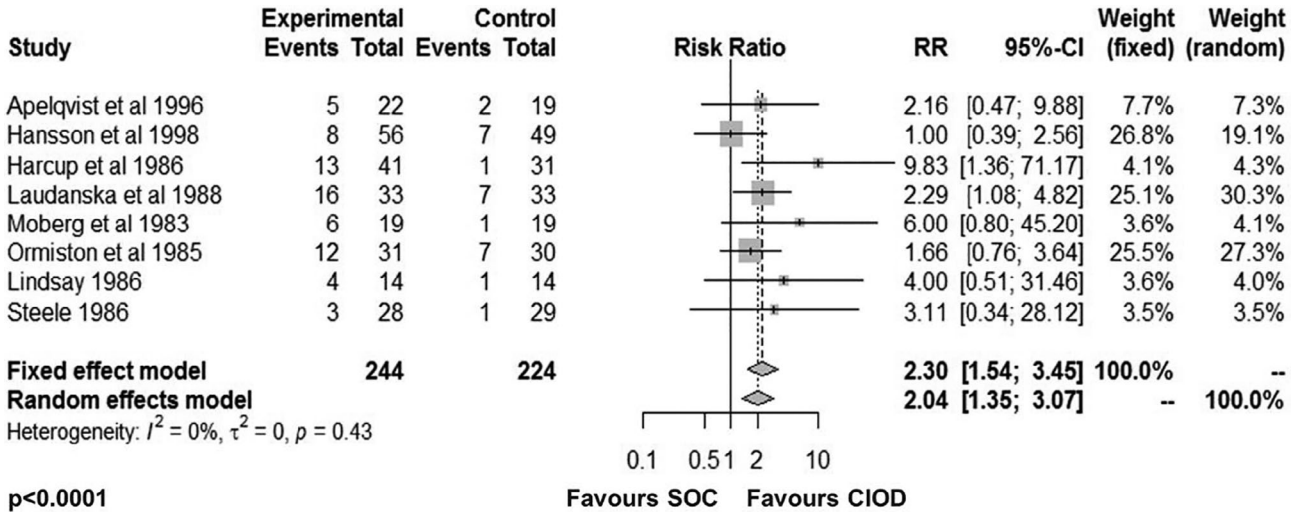

FIGURE 6 Complete healing events reported for CIOD experimental group vs SOC control group. Events are defined as complete healing by clinical observation. Complete closure events increased two-fold in the CIOD experimental group as compared to the SOC control group ($P < .0001$). CIOD, cadexomer iodine; SOC, standard of care

$P < .005$). Finally, a 71% reduction in mean ulcer area compared to 54% in SOC group ($P < .05$) over an 6-week CIOD intervention was shown by Laudanska and Gustavson.[26]

Effective reductions in ulcer area were also reported in other chronic wound indications; Moberg et al[16] demonstrated a significant reduction in PU area in 8/18 in the CIOD group compared to 1/18 in the SOC patients (31% vs 19.5%, respectively, $P < .01$). However in DFU, a 53.6% median reduction in wound area and 50% reduction in wound depth were reported following CIOD treatment compared to baseline.

Data pooling with regard to reductions in ulcer area is shown in Figure 5. This demonstrates that when using CIOD an MD of 2.35 cm^2 was observed after 8 weeks of treatment in both VLUs and PUs, significantly more than that compared to SOC (MD = 2.35 cm^2, 95% CI = 0.34–4.36, $P = .0219$).

Several studies involving participants with VLU, DFU, and PU reported complete wound healing following CIOD intervention. In VLUs, significantly more wounds were healed using CIOD compared to SOC across studies spanning 6 weeks,[26,29] 8 weeks,[10,25] and 12 weeks[12,13] intervention. Likewise in PUs, significantly more healing events were reported in the CIOD group compared to SOC in an RCT by Moberg et al.[16] Also, in an open controlled comparative study in DFU, more wounds in the CIOD group healed compared to the SOC comparison group (5/22 vs 2/19).

Furthermore, upon pooling the relevant healing data (Figure 6) when comparing CIOD to SOD with regard to complete healing events, wounds treated with CIOD

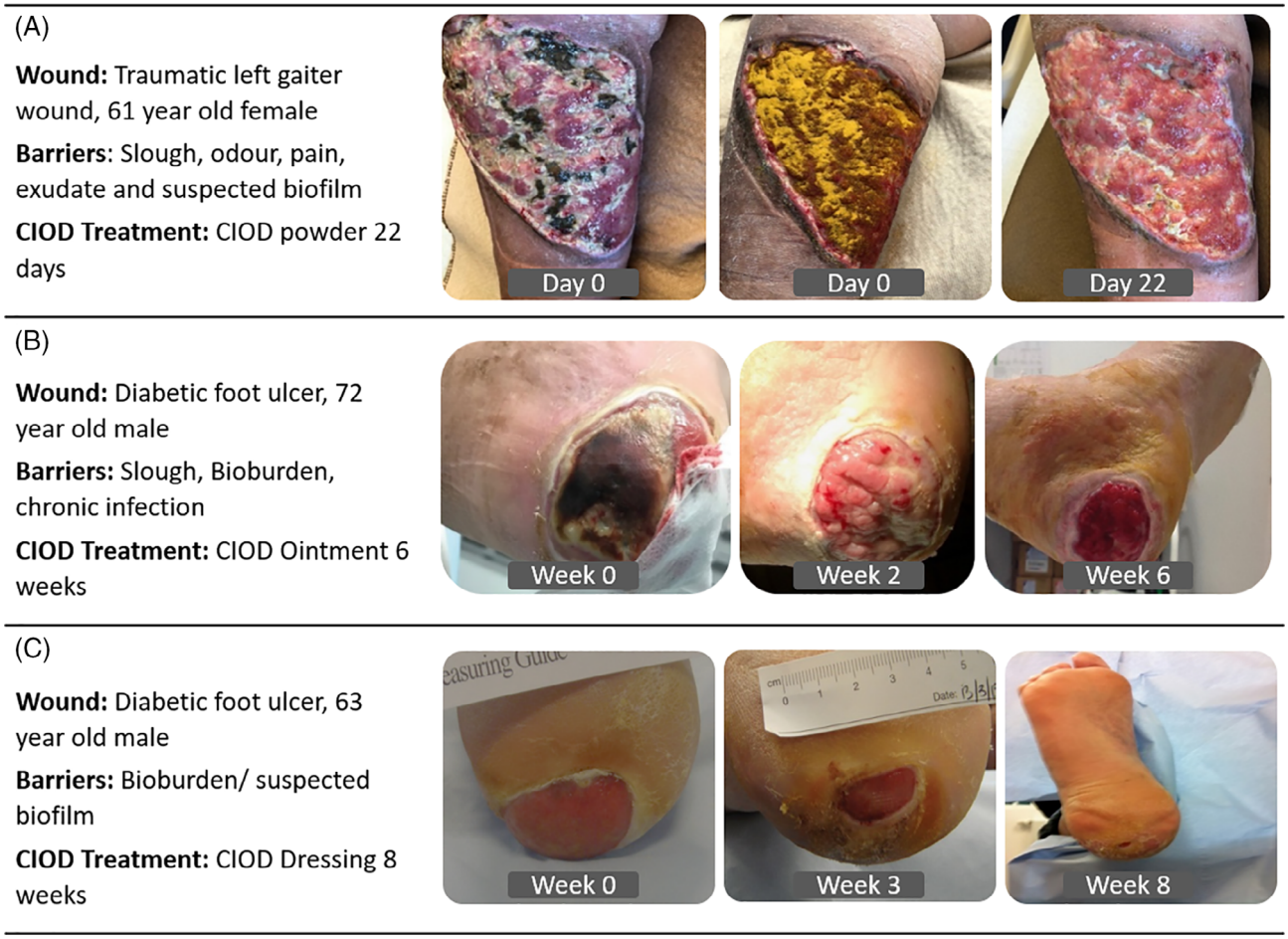

FIGURE 7 CIOD use in clinical practice; images illustrate wound condition before and after CIOD treatment in conjunction with wound bed preparation including debridement and cleansing as per local protocol in (a) traumatic leg wound, CIOD powder; (b) DFU, CIOD ointment; (c) DFU, CIOD dressing. Wound images with permission from Dr Woo, Dr Malone, and Dr Dowsett, respectively. CIOD, cadexomer iodine; DFU, diabetic foot ulcer; SOC, standard of care

were greater than two times more likely to heal than those treated with SOC across studies including VLUs, DFUs, and PUs (relative risk [RR] = 2.30, 95% CI = 1.54–3.45, $P < .0001$).

Figure 7 illustrates the obvious impact of reducing barriers such as slough, exudate, and bioburden in clinical practice following CIOD treatment, with images of wound condition before and after CIOD treatment in conjunction with a wound bed preparation protocol including debridement and cleansing as per local protocol.

4 | DISCUSSION

Chronic wounds impart a high human and financial cost.[30] From a patient's perspective, wounds can lead to pain, distress, social isolation, anxiety, extended hospital stay, chronic morbidity, or even mortality.[30] Furthermore, recent data from the United Kingdom demonstrates that an estimated 4.5% of the total UK adult population (2.2 million people) are living with a wound and up to £5.3 billion spend annually on managing these wounds.[31] Similarly reported health expenditure related to wound care in the United States is far greater than previously recognised.[32] In addition, the patient care cost of an unhealed wound further adds to this burden; reported to be a mean of 135% more than that of a healed wound.[33]

An essential part of any treatment protocol for a chronic wound is to minimise or remove the barriers to healing by performing appropriate wound bed preparation as described by wound experts using the T.I.M.E acronym (Tissue (non-viable), Infection, Moisture imbalance, Edge (not advancing or undermining)).[5-7] This systematic review of clinical studies highlights how CIOD treatment can manage and reduce many of these barriers, helping the wound to progress. The existing evidence for CIOD use in clinical practice spans almost 40 years indicating

consistent successful outcomes compared to SOC. Although some of the studies using CIOD were published nearly 40 years ago, the SOC is mostly reflective of current clinical practice with compression or offloading still used frequently today when managing VLUs and DFUs, respectively, as per various current guidelines and pathways.[34-36] In addition the outcomes of more recent studies are aligned to these older trials also. Although research trends in recent years have focussed more on silver use in wound care, our understanding of the efficacy of iodine, in particular CIOD, against new challenges such as biofilm has re-ignited the interest in this intervention.

Excessive exudate, often containing elevated levels of inflammatory mediators may slow down or prevent cell proliferation,[37] interferes with growth factor availability,[38,39] it can lead to peri-wound skin maceration and loss of skin integrity.[40] Exudate production may continue and be excessive due to ongoing infection or inflammatory processes (localised and/ or systemic).[40] CIOD can absorb up to seven times its own weight in exudate,[8] a benefit reflected in many clinical studies in this review, demonstrating a reduction in exudate levels following CIOD treatment[8-14,21,25,26,41] and helping to optimize moist wound environment that is conducive to healing.

The presence of slough in chronic wounds, defined as non-viable adherent fibrous material derived from proteins, fibrin, and fibrinogen, is a barrier to healing as it may prevent migration of cells, provides protection and nutrition for bacteria, and may sequester growth factors.[42,43] CIOD demonstrates effective desloughing properties in chronic wounds,[8-10,12-16] with significant reductions of slough, pus, and debris compared to SOC ($P < .05$), which is demonstrated across multiple studies in VLUs.[10,13,25,26] More detailed exploration of the available data by meta-analysis in this study highlighted a statistically significant MD in pus and debris reduction (assessed by visual analogue scale), which is observed in favour of CIOD compared to SOC at 6 to 8 weeks of MD = 9.52, 95% CI: 5.27–13.77, $P < .0001$). The removal of slough as a barrier to healing through autolytic debridement is vital to wound bed preparation.

High bioburden and wound infection are associated with overproduction of pro-inflammatory cytokines and matrix metalloproteinases (MMPs) leading to a prolonged inflammatory stage. The wound may then enter a chronic state and fail to heal.[44-46] In addition to the fast and effective broad spectrum antimicrobial activity demonstrated in clinically relevant *in vitro* tests and animal models,[18,47] many clinical studies using CIOD demonstrate the removal/reduction of bioburden as described in this review.[9-11,27,48] According to a previous review by Sundberg et al,[14] CIOD was also found to be more effective than SOC in reducing bioburden and infection.[14] Furthermore, significant reductions compared to baseline in total bioburden counts in DFU wounds compromised by biofilm highlighted by Malone and colleagues were correlated to reductions in MMP-9 and MMP-2 ($P = .03$).[49]

More recently, the role of biofilms as causes of chronic wound infections and delay in wound healing have been reported,[50-52] with over 78% of chronic non-healing wounds demonstrated to contain biofilms.[53] The presence of biofilm represents a significant clinical challenge, particularly their enhanced tolerance to antimicrobials[1,2] and the ability to evade the host immune response.[3,4] CIOD has demonstrated to be effective against mature biofilms in multiple *in vitro* models incorporating various clinically relevant conditions and substrates such as porcine tissue[1,19,20]; in addition, animal models show promising results with CIOD against biofilm in a wound.[19,20]

Recently, a systematic review on the efficacy of topical agents used in wounds for managing chronic biofilm infections identified a large disparity in the translation of laboratory studies to clinical research.[54] Published clinical studies on CIOD are now starting to bridge the wound biofilm evidence gap from laboratory to clinic. These studies demonstrate an ability to affect/reduce microbial load and community cohesion (biofilm and planktonic) in DFUs with biofilm following CIOD treatment.[28,49] In addition, the physical impact of the cadexomer beads reported previously from experimental work[17,18] has been observed clinically with a visual reduction in biofilm architecture on the tissue samples from the DFUs.[49] Moreover, a recently published meta-analysis of topical antimicrobial treatments against biofilms has concluded that CIOD was the only agent that reduced total microbial load including biofilm in human clinical studies.[54] Many of the older studies in this review report significant outcomes within 6 to 12 weeks of treatment. This longer treatment may be explained today in part by the increasing understanding of persistent biofilm communities in wounds that may require longer antimicrobial intervention to ensure effective activity[55] although further research is yet to define this clearly.

Increasing pain, malodour, friable tissue, and excessive exudate production are some of the clinical symptoms that have been used to indicate localised and spreading wound infection.[56-59] Increasing pain specifically is reported to be indicative of infection in a wound.[56,58] Thus, it follows that when wound bioburden and/or infection are reduced in a wound, a concurrent reduction in pain may also be reported. A reduction in pain was observed in six studies in this review following intervention with CIOD with five studies demonstrating significant pain reductions compared to SOC. Further analysis demonstrated ulcer pain was significantly

diminished in the CIOD experimental group as compared to the SOC control group in both VLUs and PUs after 6 to 8 weeks treatment ($P = .0086$).

The effective outcomes reported in relation to the removal of barriers to healing described earlier help to provide a wound environment conducive to healing. It is no surprise therefore that many of the clinical studies using CIOD in chronic wounds also report improved healing outcomes with 11 RCTs demonstrate these benefits. Furthermore, a recent meta-analysis (Cochrane review) highlighted with these findings, suggesting that CIOD generates higher healing rates than SOC in VLUs,[23] and as a result, CIOD has been incorporated in treatment guidelines for management of VLUs.[60] The costs savings using CIOD as a result of the faster rate of healing with CIOD compared with SOC have also been highlighted.[61]

Meta-analysis of quantifiable data in this review identifies that the ulcer area after 8 weeks of treatment is significantly decreased in persons receiving treatment with CIOD as compared to the SOC ($P = .0219$). Moreover, complete wound healing events increased 2-fold in persons treated with CIOD as compared to the SOC ($P < .0001$). This suggests that wounds treated with CIOD are at least two times more likely to heal compared to SOC (across VLUs, DFUs, and PUs). This faster healing following CIOD treatment can lead to substantial cost savings in patient care.[61]

5 | CONCLUSIONS

Systematic review and meta-analysis of published clinical data highlight the wealth of clinical data spanning over 40 years with CIOD. The data demonstrate consistent positive outcomes that CIOD treatment has on chronic stalled wounds through the removal of barriers that impede wound healing. The data presented in this systematic review and meta-analysis confirm that treatment with CIOD should be considered as part of wound bed preparation and treatment protocols in persons with chronic non-healing wounds. Moreover, further real-world investigations of CIOD as part of wound bed preparation and infection management protocols would show the impact of these benefits to the patient and resources, translating observations from clinical research into clinical practice.

5.1 | Limitations of the study

For numerous outcomes, the meta-analysis revealed a high I^2 value (>90%), indicating the presence of statistical heterogeneity or that over 90% of the observed variance reflects differences in effect size between studies. One explanation for this could be the fact that the meta-analysis pooled data across different wound types. As a result of this, the random-effects model was reported in these instances. Additional comparative studies particularly in PU and DFU would allow statistical differentiation for each wound type similar to that already demonstrated in VLUs. Additionally, the power of the test to detect true heterogeneity was low due to the presence of small numbers of studies; however, the findings of the statistical analysis were in agreement with the wider literature, that is, the studies not included specifically within the meta-analysis that were discussed qualitatively. Building on the results in this analysis and review, further research may consider comparative studies in the increasingly important area of wound biofilms.

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CONFLICT OF INTEREST

CD, KW, and MM are consultants for Smith+Nephew. MM has received investigator funding from Smith+Nephew for research on the efficacy of CIOD against biofilm *in vivo*. EW, BC, and SE are employees of Smith+Nephew.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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REFERENCES

1. Phillips PL, Yang Q, Davis S, et al. Antimicrobial dressing efficacy against mature *Pseudomonas aeruginosa* biofilm on porcine skin explants. *Int Wound J*. 2015;12:469-483.
2. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *Lancet (London, England)*. 2001;358:135-138.
3. Jesaitis AJ, Franklin MJ, Berglund D, et al. Compromised host defense on *Pseudomonas aeruginosa* biofilms: characterization of neutrophil and biofilm interactions. *J Immunol*. 2003;171:4329-4339.
4. Bjarnsholt T, Jensen PØ, Burmølle M, et al. *Pseudomonas aeruginosa* tolerance to tobramycin, hydrogen peroxide and polymorphonuclear leukocytes is quorum-sensing dependent. *Microbiology*. 2005;151:373-383.
5. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen*. 2003;11(Suppl 1):S1-S28.

6. Moore Z, Dowsett C, Smith G, et al. TIME CDST: an updated tool to address the current challenges in wound care. *J Wound Care*. 2019;28:154-161.
7. Schultz G, Mozingo D, Romanelli M, Claxton K. Wound healing and TIME; new concepts and scientific applications. *Wound Repair Regen*. 2005;13:1-11.
8. Johnson A. A combative healer with no ill-effect. Iodosorb in the treatment of infected wounds. *Prof Nurse*. 1991;7:60-64.
9. Troëng T, Skog E, Arnesjö B, Gjöres JE, Bergljung L, Gundersen JEA. A randomised multicentre trial to compare the efficacy of cadexomer iodine and standard treatment in the management of chronic venous ulcers in out patients. In: Fox J, Fisher H, eds. *Cadexomer Iodine*. Stuttgart: Schattauer Verlag; 1983:43-50.
10. Lindsay G, Latta D, Lyons KGB. A study in general practice of the efficacy of cadexomer iodine in venous leg ulcers treated on alternate days. *Acta Ther*. 1986;12:141-148.
11. Skog E, Arnesjö B, Troëng T, et al. A randomized trial comparing cadexomer iodine and standard treatment in the out-patient management of chronic venous ulcers. *Br J Dermatol*. 1983;109:77-83.
12. Ormiston MC, Fox JA. Controlled trial of Iodosorb. *Br Med J (Clin Res Ed)*. 1985;291:308-310.
13. Hansson C. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. *Int J Dermatol*. 1998;37:390-396.
14. Sundberg J, Pharm MS, Meller R, Se B, Pharm MS. A retrospective Review of the Use of Cadexomer Iodine in the Treatment of Chronic Wounds. *Wounds A Compend Clin Res Pract*. 1997;9:68-86.
15. Holloway GA, Johansen KH, Barnes RW, Pierce GE. Multicenter trial of cadexomer iodine to treat venous stasis ulcer. *West J Med*. 1989;151:35-38.
16. Moberg S, Hoffman L, Grennert ML, Holst A. A randomized trial of cadexomer iodine in decubitus ulcers. *J Am Geriatr Soc*. 1983;31:462-465.
17. Akiyama H, Oono T, Saito M, Iwatsuki K. Assessment of cadexomer iodine against *Staphylococcus aureus* biofilm in vivo and in vitro using confocal laser scanning microscopy. *J Dermatol*. 2004;31:529-534.
18. Forest, E., Gunning, P., Coleman, D. & Fitzgerald, D.J Cadexomer iodine delivers rapid and sustained broad spectrum antimicrobial activity and substantial biofi lm disruption and kill in a clinically relevant wound model. Poster presentation. European Wound Management Association (EWMA), Gothenburg (2019).
19. Fitzgerald DJ, Renick PJ, Forrest EC, et al. Cadexomer iodine provides superior efficacy against bacterial wound biofilms in vitro and in vivo. *Wound Repair Regen*. 2017;25:13-24.
20. Roche ED, Roche ED, Woodmansey EJ, et al. Cadexomer iodine effectively reduces bacterial biofilm in porcine wounds ex vivo and in vivo. *Int Wound J*. 2019;16:674-683. https://doi.org/10.1111/iwj.13080.
21. Zhou LH, Nahm WK, Badiavas E, Yufit T, Falanga V. Slow release iodine preparation and wound healing: in vitro effects consistent with lack of in vivo toxicity in human chronic wounds. *Br J Dermatol*. 2002;146:365-374.
22. Brustolin EV, Brustolin EV, Skare TL, et al. Wound healing under the effect of iodine cadexomer in rats. *Acta Cir Bras*. 2012;27:874-879.
23. O'Meara S et al. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev*. 2014;1:CD003557.
24. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev*. 2010;CD003557. https://doi.org/10.1002/14651858.CD003557.pub3.
25. Harcup JW, Saul PA. A study of the effect of cadexomer iodine in the treatment of venous leg ulcers. *Br J Clin Pract*. 1986;40:360-364.
26. Laudanska H, Gustavson B. In-patient treatment of chronic varicose venous ulcers. A randomized trial of cadexomer iodine versus standard dressings. *J Int Med Res*. 1988;16:428-435.
27. Hillstrom L. Iodosorb compared to standard treatment in chronic venous leg ulcers—a multicenter study. *Acta Chir Scan Suppl*. 1988;544:53-56.
28. Lantis JC et al. Effects of cadexomer iodine on a biofilm in diabetic foot ulcers: a pilot study. *Poster presentation WUWHS Florence*. 2016;1.
29. Steele K, Irwin G, Dowds N. Cadexomer iodine in the management of venous leg ulcers in general practice. *Practitioner*. 1986;230:63-68.
30. Lindholm C, Searle R. Wound management for the 21st century: combining effectiveness and efficiency. *Int Wound J*. 2016;13:5-15.
31. Guest JF, Ayoub N, McIlwraith T, et al. Health economic burden that wounds impose on the National Health Service in the UK. *BMJ Open*. 2015;5:e009283.
32. Nussbaum SR, Carter MJ, Fife CE, et al. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. *Value Heal*. 2018;21:27-32.
33. Guest JF, Ayoub N, McIlwraith T, et al. Health economic burden that different wound types impose on the UK's National Health Service. *Int Wound J*. 2017;14:322-330.
34. Atkin L, Critchley A. The leg ulceration pathway: impact of implementation. *Wounds UK*. 2017;13:107.
35. Phillips CJ, Humphreys I, Thayer D, et al. Cost of managing patients with venous leg ulcers. *Int Wound J*. 2020;17:1074-1082.
36. Lipsky BA, Senneville É, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36:1-24.
37. Bucalo B, Eaglstein WH, Falanga V. Inhibition of cell proliferation by chronic wound fluid. *Wound Repair Regen*. 1993;1:181-186.
38. Trengove NJ, Langton SR, Stacey MC. Biochemical analysis of wound fluid from nonhealing and healing chronic leg ulcers. *Wound Repair Regen*. 1996;4:234-239.
39. Yager DR, Zhang LY, Liang HX, Diegelmann RF, Cohen IK. Wound fluids from human pressure ulcers contain elevated matrix metalloproteinase levels and activity compared to surgical wound fluids. *J Invest Dermatol*. 1996;107:743-748.
40. WUWHS. *Principles of best practice: Wound exudate and the role of dressings. A consensus document.*. London: Medical Education Partnership (MEP); 2007.
41. Floyer C, Wilkinson JD. Treatment of venous leg ulcers with cadexomer iodine with particular reference to iodine sensitivity. *Acta Chir Scand Suppl*. 1988;554:60-61.
42. Falanga V, Grinnell F, Gilchrest B, Maddox YT, Moshell A. Workshop on the pathogenesis of chronic wounds. *J Invest Dermatol*. 1994;102:125-127.

43. Tong A. The identification and treatment of slough. *J Wound Care*. 1999;8:338-339.
44. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. *Clin Dermatol*. 2007; 25:19-25.
45. Edwards R, Harding KG. Bacteria and wound healing. *Curr Opin Infect Dis*. 2004;17:91-96.
46. Wolcott R, Sanford N, Gabrilska R, Oates JL, Wilkinson JE, Rumbaugh KP. Microbiota is a primary cause of pathogenesis of chronic wounds. *J Wound Care*. 2016;25:S33-S43.
47. Mertz P, Davis S, Brewer L, Franzen L. Can antimicrobials be effective without impairing wound healing? The evaluation of a cadexomer iodine ointment. *Wounds*. 1994;6:184-193.
48. Danielsen L, Cherry GW, Harding K, Rollman O. Cadexomer iodine in ulcers colonised by *Pseudomonas aeruginosa*. *J Wound Care*. 1997;6:169-172.
49. Malone M, Johani K, Jensen SO, et al. Effect of cadexomer iodine on the microbial load and diversity of chronic non-healing diabetic foot ulcers complicated by biofilm in vivo. *J Antimicrob Chemother*. 2017;72:2093-2101.
50. Schierle CF, De la Garza M, Mustoe T a, Galiano RD. Staphylococcal biofilms impair wound healing by delaying reepithelialization in a murine cutaneous wound model. *Wound Repair Regen*. 2009;17:354-359.
51. Roche ED, Renick PJ, Tetens SP, Ramsay SJ, Daniels EQ, Carson DL. Increasing the presence of biofilm and healing delay in a porcine model of MRSA-infected wounds. *Wound Repair Regen*. 2012;20:537-543.
52. Zhao G, Usui ML, Underwood RA, et al. Time course study of delayed wound healing in a biofilm-challenged diabetic mouse model. *Wound Repair Regen*. 2012;20:342-352.
53. Malone M, Bjarnsholt T, McBain AJ, et al. The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. *J Wound Care*. 2017;26:20-25.
54. Schwarzer S, James GA, Goeres D, et al. The efficacy of topical agents used in wounds for managing chronic biofilm infections: A systematic review. *J Infect*. 2020;80:261-270.
55. Schultz G, Bjarnsholt T, James GA, et al. Consensus guidelines for the identification and treatment of biofilms in chronic non-healing wounds. *Wound Repair Regen*. 2017;25:744-757.
56. Haesler E, Swanson T, Ousey K, Carville K. Clinical indicators of wound infection and biofilm: reaching international consensus. *J Wound Care*. 2019;28:s4-s12.
57. Swanson T et al. Wound Infection in Clinical Practice. *Wounds Int*. 2016;5:1-32.
58. Bui UT, Finlayson K, Edwards H. The diagnosis of infection in chronic leg ulcers: A narrative review on clinical practice. *Int Wound J*. 2019;16:601-620. https://doi.org/10.1111/iwj.13069.
59. Woo KY, Sibbald RG. A cross-sectional validation study of using NERDS and STONEES to assess bacterial burden. *Ostomy Wound Manage*. 2009;55:40-48.
60. Maessen-Visch MB, de Roos K-P. Dutch venous ulcer guideline update. *Phlebology*. 2014;29:153-156.
61. Nherera LM, Woodmansey E, Trueman P, Gibbons GW. Estimating the clinical outcomes and cost differences between standard care with and without cadexomer iodine in the management of chronic venous leg ulcers using a Markov model. *Ostomy Wound Manage*. 2016;62:26-40.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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