WHAM evidence summary:Traditional hypochlorite solutions

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CLINICAL QUESTION

What is the best available evidence for use of traditional hypochlorite solutions for reducing wound infection and/or improving wound healing?

KEYWORDS

Traditional wound management, hypochlorite, Eusol, Dakin's® solution, Milton® solution

SUMMARY

Traditional hypochlorites have been used to manage local wound infection since their introduction in the early 1900s[1]. Traditional hypochlorite solutions are those that have a high pH varying from 7.5 to 11.8[2-5]. In contrast, recently developed hypochlorite solutions are pH-neutral, making them more appropriate for application to healing wound tissue. *Level 5* bench research has demonstrated that traditional hypochlorite solutions have anti-bacterial properties;[6-8] however, the effect may be short-lived[9]. Although *Level 5* bench research has suggested that traditional hypochlorite solutions are toxic to cells and may delay wound healing,[6, 8, 10, 11] *Level 1 and 2* evidence[2, 12-16] showed that acceptable healing outcomes can be achieved using traditional hypochlorite solutions, with one study demonstrating superior outcomes compared to an inert solution.[17]

Level 1 and 4 evidence[12, 13, 16-20] indicated that traditional hypochlorite solutions are associated with reduction in signs and symptoms of local wound infection. *Level 1 and 2* evidence[13, 14, 16] showed that topical phenytoin[13, 16], honey[14] and nanocrystalline silver gel[16] achieved better outcomes than a traditional hypochlorite solution, and these options could be considered in settings with access. The risk of delaying healing of the wound should be considered in the context of managing local wound infection and reducing the risk of spreading and systemic infection, when alternative less cytotoxic antiseptics are not available in the setting.

CLINICAL PRACTICE RECOMMENDATIONS

All recommendations should be applied with consideration to the wound, the person, the health professional and the clinical context.

Traditional hypochlorite solutions could be applied to infected wounds in low resource settings in which less cytotoxic antiseptic solutions are not accessible (Grade B).

SOURCES OF EVIDENCE

This summary was conducted using methods published by the Joanna Briggs Institute.[21-23] The summary is based on a literature search combining search terms related to hypochlorites /EUSOL/ Dakin's® solution/ Milton® solution and wound infection. Searches were conducted in the

Table 1: Levels of evidence for clinical studies

Level 1 Evidence	Level 2 Evidence	Level 3 Evidence	Level 4 Evidence	Level 5 Evidence
Experimental Designs	**Quasi-experimental Designs**	**Observational – Analytic Designs**	**Observational –Descriptive Studies**	**Expert Opinion/ Bench Research**
1.c RCTs[2, 12-15]	2.c Quasi-experimental prospectively controlled study[16]	Nil	4.d Case studies[18, 19, 20, 24]	Level 5.c Bench research[6, 8, 9, 11, 25-27]

Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed®, Google Scholar and Health Internetwork Access to Research Initiative (Hinari) databases and in the Cochrane Library for evidence conducted in human wounds reporting the use of traditional hypochlorite preparations published to October 2022 in English. Levels of evidence for intervention studies are reported in Table 1.

BACKGROUND

Traditional hypochlorites are preparations that occur as a reaction between chlorine and an alkaline salt, most commonly sodium or calcium [28, 29]. They typically have a pH from 7.5 up to 11.8.[2-5] Commonly used traditional hypochlorites include household bleach, Dakin's® solution, Edinburgh University Solution of Lime (EUSOL) and Milton® solution. (N.b., no evidence on the use of Milton® solution for wound healing was identified).

Dakin's® solution is a preparation of bleach diluted in distilled water to 0.5% concentration for clinical use. In some reports of its use, traditional Dakin's® solution is diluted to half or quarter strength by mixing with additional water[19]. The preparation was developed by Henry Dakin on the war fields in France in 1915 to manage wound infection and to improve clinical outcomes for bullet and shrapnel wounds[28, 30, 31]. Bench research has demonstrated Dakin's® solution has action against a range of microorganisms and biofilms, including (but not limited to) *S. aureus*, *C. albicans*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*[6, 8, 9, 17, 25, 27] (*Level 5*).

EUSOL solution is made from chlorinated lime (calcium oxide) and boric acid (sodium salts) at a 0.25% concentration[2, 24, 32, 33].The solution, which was also developed in the early 1900s, is traditionally used as a debriding agent and to manage infection.[32, 34]

Traditional hypochlorites are unstable and have a short shelf life.[29, 34] They have a high pH[2-5], which is associated with impaired wound healing. Both full strength (0.5%) Dakin's® solution[8] and half strength (0.25%) Dakin's® solution[6] have been reported to be cytotoxic to fibroblasts in laboratory studies, raising concerns that traditional hypochlorites at their full concentration may delay wound healing[11, 16, 29-31, 34-36]. To address these limitations, hypochlorites are now prepared electro-chemically to produce contemporary hypochlorites referred to as super-oxidised solutions[29, 37]. Although super-oxidised solutions have a longer shelf-life and a neutral pH, and they appear to have a good safety profile,[29, 38] they are not universally available. In low resource settings, traditional hypochlorites are still used for managing wound infection[39, 40].

CLINICAL EVIDENCE ON DAKIN'S® SOLUTION

Studies reporting clinical outcomes of interest for treatment with traditional Dakin's® solution are summarised in Table 2.

Dakin's® solution for promoting wound healing

An RCT[17] at high risk of bias explored the use of Dakin's® solution for treating infected diabetic foot ulcers (DFUs). Ulcers were surgically debrided on admission and received evidence based DFU care in conjunction with daily 10-minute irrigation with either Dakin's® solution diluted to 0.1% concentration or normal saline, followed by application of a silver sheet dressing. Treatment was delivered in hospital for at least five days. On discharge, patients cleansed their own wounds every second day by soaking the DFU for 30 minutes in the assigned solution. Treatment continued for at least three months. Approximately 35% of DFUs treated with Dakin's® solution were totally healed compared to 4% in the control group (odds ratio 11.9, 95% confidence interval 2.53 – 55.5, $p < 0.001$)[17] (*Level 1*).

Dakin's® solution for treating signs and symptoms of wound infection

In the RCT[17] comparing Dakin's® solution to normal saline for DFUs, quantitative wound swab analysis showed DFUs treated with Dakin's solution had a reduction from baseline in microbial load of 1 log cycle or more after five days (statistically significant versus control, $p < 0.001$). Local wound infection resolved in more DFUs treated with Dakin's® solution compared to normal saline (35.6% versus 4.4%, p = not reported)[17] (*Level 1*).

There are numerous case reports[18-20] of infected wounds of various aetiologies that have been successfully treated with regimens that include regular irrigation with Dakin's® solution. Many of the wounds were reported to be extensive and deep, with exposed ligament and bone and/or necrotising tissue. Wounds were either confirmed or suspected to be colonised with anaerobic bacteria[20] or fungal

organisms[18]. To treat wound odour[19], wound exudate[19] and extensive slough[18-20] (all recognised signs and symptoms of local wound infection[41]) wounds were surgically debrided and regularly irrigated with full, half or quarter strength Dakin's® solution. Many of the regimens also included systemic antibiotics, serial surgical debridement, negative pressure wound therapy and split skin grafting. The cases were reported to achieve resolution of signs and symptoms of local wound infection and development of healthy granulation tissue or complete epithelialisation[18-20] (*Level 4*).

CLINICAL EVIDENCE EUSOL SOLUTION

Studies reporting clinical outcomes of interest for treatment with traditional Edinburgh Solution of Lime (EUSOL) solution are summarised in Table 3.

EUSOL solution for improving wound healing

Five *Level 1* studies and one *Level 2* study provided evidence on EUSOL for improving healing of wounds of various aetiologies. In the first RCT[14] (32 children with 43 wounds), which was at moderate risk of bias, open wounds (surgically excised pyomyositis abscesses) were packed twice daily with either EUSOL-soaked gauze or honey-soaked gauze. At 3-week follow-up, 55% of the EUSOL-treated abscesses achieved complete healing; compared to the 87% healing rate in the honey group ($p < 0.047$)[14] (*Level 1*). The second RCT,[2] also at high risk of bias, reported use of EUSOL dressings to treat infected traumatic wounds. In this study, EUSOL was compared with an antibiotic-impregnated collagen granule dressing. At 4-week follow-up, 53.8% of the EUSOL-treated wounds were completely healed, and the remaining wounds had healthy granulation tissue. This was not statistically significantly different from the group treated with collagen granules, of which 69% completely healed, with the remainder achieving healthy granulation ($p = 0.416$)[2] (*Level 1*).

A comparison of EUSOL-soaked gauze to sugar dressings is reported in a third RCT[12] at high risk of bias that was conducted in traumatic, contaminated wounds (n = 50). After four weeks of daily wound dressings, wounds treated with the EUSOL dressing achieved superior results to the wounds treated with sugar dressings, including wound size reduction ($p = 0.0042$), achievement of granulation ($p = 0.0048$) and wound closure rate ($p = 0.008$)[12] (*Level 1*).

In a fourth RCT[13] at high risk of bias, chronic leg ulcers (n = 102) were treated daily with debridement followed by application of either EUSOL or topical phenytoin. Ulcers that achieved uniform granulation were treated with skin grafts. Wound surface area and presence of granulation tissue were evaluated weekly

Table 2: Summary of the evidence for Dakin's® solution

Study	Country	Dakin's® treatment and comparators (number wounds)	Type of wounds	Treatment duration	Clinical outcome measures	Level of evidence
Jaber et. al. (2022)[17]	Jordan	Surgical debridement, in-patient treatment: irrigation for 10 minutes with solution, after discharge: second daily 30-minute soak, silver sheet dressing: 0.1% Dakin's® solution	Diabetic foot ulcer	24 weeks	• Complete healing • Ulcer depth • Change in bacterial load • Signs and symptoms of local wound infection	1
Duarte et. al. (2017)[20]	Portugal	Debridement, 8-hourly Dakin's® solution irrigation, concurrent systemic antibiotics (n = 1)	Necrotising diabetic foot ulcer	6 weeks	Wound tissue	4
Cornwell et. al. (2010)[19]	USA	Debridement, negative pressure wound therapy, Dakin's® solution irrigation and/or soaked gauze dressing (n = 5)	Post-surgical chronic wounds, post-amputation wound, pressure injury, trauma wounds	3 weeks - 21 months	• Wound size • Signs and symptoms of local wound infection	4
Lewandowski et. al. (2013)	USA	Surgical debridement, serial debridement and wound irrigation with Dakin's® solution (n = 3)	Traumatic wounds, post-amputation wounds	21-50 days	• Signs and symptoms of local wound infection	4

during the 28-day treatment period. The ulcers treated with EUSOL showed a mean reduction in surface area of about 60% over 28 days; this improvement appeared to be inferior to the topical phenytoin group (p = not reported). Although 86% of the ulcers receiving EUSOL achieved healthy granulation by 28 days, this was statistically significantly poorer outcome than the phenytoin group[13] (*Level 1*).

The final RCT[15], which was also at high risk of bias, reported a comparison of EUSOL-soaked gauze with a topical silver nitrate (0.01% w/v) liquid for treating pressure injuries (PIs) in people with spinal cord injury (n = 22). The groups were matched for severity of PIs at baseline. All Stage 1 PIs healed within two weeks of treatment. For Stage 2 PIs, those treated with EUSOL decreased in wound size by a mean of 47% after four weeks. For Stage 3 PIs treated with EUSOL, the average reduction in wound area at 4 weeks was 17%, compared with a mean size reduction of 26% for the silver-based treatment (p values = not reported). No Stage 4 PIs healed in the 4-week study duration[15] (*Level 1*).

In a comparative study,[16] which was at high risk of bias, EUSOL solution was compared to phenytoin powder and nanocrystalline silver gel for promoting healing in DFUs of Wagner grade 1 (superficial ulcer) and grade 2 (deep ulcer). The DFUs were surgically debrided as required and treated for up to four weeks with the assigned topical treatment. At 4-week follow-up, 73.33% of the DFUs treated with EUSOL solution had granulation tissue in the wound bed (p > 0.05). At baseline the mean ulcer size in the EUSOL-treated group was 16.66 cm^2 ± 7.52 cm^2, reducing to a mean of 7.7cm^2 ± 6.65 cm^2 by the end of four weeks, which may be clinically significant for patients. However, the EUSOL-treated DFUs achieved statistically significantly inferior results compared with those treated with phenytoin powder or nanocrystalline silver gel[16] (*Level 2*).

EUSOL solution for reducing signs and symptoms of wound infection

Four of the above studies[2, 12, 13, 16] reported reduction in signs and symptoms that are associated with local wound infection, including wound-associated pain, wound exudate, and a sloughy wound surface.[41]

In the study comparing EUSOL to topical phenytoin, the people with EUSOL-treated ulcers reported reduction in severe wound-associated pain and improvement in wound exudate by the second week of treatment[13]. Although the topical phenytoin group had superior outcomes at week two, there was no statistically significant difference by 28 days In the study comparing EUSOL dressings to sugar dressings, fewer wounds treated with EUSOL had a sloughy wound surface (p = 0.0034) and exudate level (p = 0.011) after four weeks.[12] The infected wounds that were treated with EUSOL in the RCT by Shah et. al. (2017) [2] showed improvement in wound exudate characteristics by the fourth week of treatment and this was not statistically significantly different (p = 0.24) to the exudate profile of the antibiotic-impregnated collagen granule group[2] (*Level 1*).

In the study conducted in DFUs,[16] EUSOL solution was associated with a small reduction in pain after four weeks of treatment (mean pain score reduction of 1.87 ± 1.57 on a five-point visual analogue scale). This was unlikely to be clinically significant.[16] (*Level 2*).

CONSIDERATIONS FOR USE

Adverse effects reported with traditional hypochlorites

- Contact sensitivity to traditional hypochlorites has been observed in rare cases[24] (*Level 4*).
- Although skin irritation,[34] mild pain on application[9]and chemical burns with using the solution at inappropriate concentrations[16] have been associated with traditional hypochlorites, these adverse events were not observed in the studies reported in this evidence summary.

Preparation of solutions in low resource settings

- A 0.5% Dakin's® solution can be prepared with 25 mL household bleach mixed with 2 teaspoons of baking soda (bicarbonate of soda/sodium bicarbonate) in 1 L of clean water[40]. The solution has a short shelf-life,[28, 29] and bench research has suggested the solution may provide inadequate antibacterial effect within 24 hours of preparation[9]. Therefore, the solution should be prepared every 24 hours[40].

Table 3: Summary of the evidence for Eusol solution

Study	Country	Eusol treatment and comparators (number wounds)	Type of wounds	Treatment duration	Clinical outcome measures	Level of evidence
Okeniyi et. al, 2005[14]	Nigeria	Surgical draining, systemic antibiotics, twice daily dressing with solution-soaked gauze: • EUSOL (n = 20) Honey (n = 23)	Pyomyositis abscesses	21 days	• Complete wound healing • Length of hospitalisation	1
Shah et. al., 2017[2]	Nepal	Debridement, saline lavage, second daily wound dressing: • EUSOL (n = 65) Antibiotic impregnated collagen granules (n = 65)	Infected traumatic or infected postoperative wounds on limbs	28 days	• Complete wound healing • Wound exudate characteristics	1
Carneiro and Nyawawa, 2003[13]	Tanzania	Debridement, daily application of topical solution-soaked gauze: • EUSOL (n = 50) Phenytoin (n = 52)	Leg ulcers arising from trauma, inflammation or burn	28 days	• Mean surface area • Change in wound tissue type • Wound pain • Wound exudate	1
Bajaj et. al., 2009[12]	Nepal	Debridement, daily wound dressing: • EUSOL-soaked gauze (n = 24) Sugar dressing (n = 26)	Traumatic, contaminated wounds	28 days	• Wound size • Wound closure • Presence of granulation tissue • Presence of slough • Wound exudate	1
Kumar and Sinha, 2018[15]	India	Debridement, wound dressing at unknown frequency: • EUSOL containing dressing (n = 11) Silver nitrate liquid (n = 11)	Stage 1-4 pressure injuries	28 days	• Change in PUSH scale score • Mean wound surface area reduction	1
Chauhan et. al., 2019[16]	India	Debridement, wound dressing as required: • Topical EUSOL solution (n = 30) • Topical phenytoin (n = 30) Nanocrystalline silver gel (n = 30)	Wagner grade 1 and 2 diabetic foot ulcers	28 days	• Mean surface area • Change in wound tissue type • Wound pain • Duration of hospitalisation • Dressing changes	2
Salphale et. al. (2003)[24]	India	EUSOL soaks, patch testing when sensitivity signs and symptoms appeared (n = 1)	Trophic ulcers	4 years	• Adverse effects	4

- A EUSOL solution can be prepared with 12.5 g sodium hypochlorite (bleaching powder) and 12.5 g of boric acid combined in 1 L of clean, lukewarm water. The solution has a short shelf life and preparation immediately before use is recommended[2, 24, 32, 33].

CONFLICTS OF INTEREST

The author declares no conflicts of interest in accordance with International Committee of Medical Journal Editors (ICMJE) standards.

ABOUT WHAM EVIDENCE SUMMARIES

WHAM evidence summaries are consistent with methodology published in

Munn Z, Lockwood C, Moola S. The development and use of evidence summaries for point of care information systems: A streamlined rapid review approach, Worldviews Evid Based Nurs. 2015;12(3):131-8.

Methods are provided in detail in resources published by the Joanna Briggs Institute as cited in this evidence summary. WHAM evidence summaries undergo peer-review by an international review panel.

WHAM evidence summaries provide a summary of the best available evidence on specific topics and make suggestions that can be used to inform clinical practice. Evidence contained within this summary should be evaluated by appropriately trained professionals with expertise in wound prevention and management, and the evidence should be considered in the context of the individual, the professional, the clinical setting and other relevant clinical information.

PUBLICATION

This evidence summary has been published in WCET® Journal:

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