Electromicyn Solution and Hydrogel: Topical Antimicrobial Wound Healing Agent

By: Lance Gravatt

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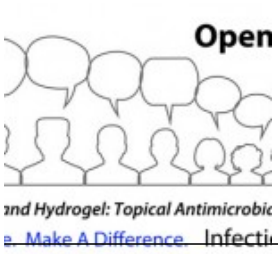

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Electromicyn Solution and Hydrogel: Topical Antimicrobial Wound Healing Agent

Application for Inclusion on 2017 WHO EML

1.

Summary

Electromicyn is a class IIb medical device containing a stabilised, pH neutral, hypotonic solution of reactive oxidising species including hypochlorous acid, peroxide, ozone and superoxide. Electromicyn has demonstrated potent antimicrobial efficacy against a wide range of bacteria, viruses, fungi, moulds, spores, biofilms and simple eukaryotes. It exerts this potent antimicrobial effect by oxidative disruption of the outer membrane followed by rapid osmotic rupture and is therefore not susceptible to the development of microbial resistance.

Electromicyn is non-cytotoxic and instead has demonstrated significant wound healing capabilities through enhancement of fibrinocyte and keratinocyte migration, mast cell stabilisation and angiogenic reperfusion.

Electromicyn is non-toxic to humans and environmentally compatible.

Electromicyn has demonstrated superior wound healing versus a range of traditional antimicrobial agents including saline, povidone-iodine, chlorhexidine, benzoyl peroxide and systemic antibiotics across a range of wounds from peritonitis, diabetic foot ulcers and venous ulcers through to sinusitis, eczema and acne vulgaris.

Electromicyn has also demonstrated superior results as a medical disinfectant.

Electromicyn is offered through the WHO at a slightly lower price mL for mL than WHO purchased povidone-iodine and a significantly lower price than WHO purchased silver sulfadiazine which recent Cochrane meta-analysis has concluded is ineffective.

3.

Supporting Organisations/Individuals

Electromicym is now included in the WHO-sponsored Antibiotic Guidelines 2015 edition for the Cook Island and Western Samoa.

4.

International Non-proprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

DO8AX07 sodium hypochorite, hypochlorous acid as a pH-neutral electrolysed water (NEW).

5.

Formulation and Strengths

Aqueous solution	80 ppm hypochlorous acid, 80 ppm sodium hypochlorite, sodium chloride
Aqueous Hydrogel	80 ppm hypochlorous acid, 80 ppm sodium hypochlorite, sodium chloride, sodium magnesium fluorosilicate, sodium phosphate

6.

Individual Medicine

Electromicyn is also available under the tradenames Microcyn, Dermacyn, MicroSafe, Microdacyn and Oxum in North America, Central America, South America, Middle East, India, Europe, Pacific Islands, and Asia.

Electromicyn is classified by FDA, EMA and TGA as a Class IIb Medical Device.

7.

Treatment Details

The solution is applied topically to disinfect, sterilise, irrigate, debride, and remove biofilms associated with wounds.

The solution may be used as a multi-surface disinfectant.

The Hydrogel is applied topically along with gauze or compression bandage for wounds that need to remain moist. Initially, in severe wounds the Hydrogel may need to be applied several times a day. Once healing is progressing,

Hydrogel applications may only be necessary 2-3 times a week.

The Hydrogel may be used as a hand sanitiser.

8.

Public Health Relevance

Chronic wounds and the infections associated with them are responsible for a considerable increase in morbidity, mortality and cost of healthcare.

The use of biocides is an essential preventative control measure against the spread of nosocomial infections and multi-drug resistant bacteria within hospital and other healthcare and community settings. The general mechanism of action of biocides involves multiple target sites, compared to that of antibiotics which usually only have a single target site, making them highly efficacious as antimicrobials. This reduces the risk of developing resistance to these agents. Acquired resistance to antibiotics is of particular concern as the number of antibiotic prescriptions is increasing worldwide. Frequent use of several existing biocides, such as povidone-iodine, can cause respiratory or dermatological health problems in hospital workers. [26] Moreover, some biocides (e.g. acidic bleach) have the potential to cause corrosion or damage to equipment. [26] Therefore, there is a need to explore alternative biocides, particularly since there is evidence for resistance to existing biocidal agents. [28] Furthermore, Cochrane meta-analysis of some topical antimicrobial agents, such as silver sulphadiazine, has found “there is insufficient evidence to establish whether silver-containing dressings or topical agents promote wound healing or prevent wound infection.” [29]

From out of this need for more effective, safe, and non-cytotoxic topical antimicrobial agents, a class of pH neutral electrolytically activated water solutions (NEW) have been developed. [1]

NEW characteristically has an oxidation reduction potential (ORP) of +800 mV to +1,200 mV, creating an environment outside the working range of important microbial processes, including energy-generating mechanisms. [28] If immersed in these solutions, the microorganisms will be exposed to powerful oxidants which will sequester electrons with high efficiency from microbial structural compounds, and cause the rupturing of biochemical bonds and subsequent loss of function. Moreover, the high ORP environment is thought to create an unbalanced osmolarity between the ion concentrations in the solution and that within unicellular organisms, resulting in further damage to the membrane structures. This will cause increased membrane porosity. [1] Thus, Microdacyn mimics the body’s natural cellular defence system in that the reactive oxygen species present mimic macrophage oxidative burst. [10]

Following the disruption of the cellular membrane, the low osmolarity of NEW, typically around 13 mOsmol/L, causes cell death by osmotic rupture. [27] Since the antimicrobial efficacy of NEW is essentially rapid osmotic shock, it is not believed to be susceptible to the development of antimicrobial resistance because of its extremely rapid physical mode of action and not cytotoxic mode of action. Furthermore, NEW has a broad biocidal effect against bacteria, viruses, fungi, spores, eukaryotes, and biofilms (Table 1).

Table 1: *In vitro* log kill per minute for NEW against various bacteria, viruses, fungi, spores, eukaryotes, and biofilms.

Target organism	**Experimental kill rates (k) of various NEW (log_{10} CFU $ml^{?1}$ reduction per minute)** [1, 2, 3, 35]
Aerobic/facultative bacteria	
Acinetobacter spp.	10.0
Actinobacillus actinomycetemcomitans	++
Aeromonas liquefaciens	13.8

Alcaligenes faecalis	13.6
Bacillus subtilis	1.7
Bacillus cereus	2.3-5.9
Burkholderia cepacia	34.5
Citrobacter freundii	13.3
Campylobacter jejuni	44.9
Escherichia coli	1.7-16.0
Enterobacter aerogenes	10.0
Enterococcus spp.	3.5-15.4
VRE	3.5-10.0
Flavobacter spp.	14.2
Haemophilus influenzae	>10.0
Helicobacter pylori	3.50
Lactobacillus spp	4.4-5.0
Legionella pneumophila	8.0
Listeria monocytogenes	1.3-16.3
Klebsiella spp.	10.0
Micrococcus luteus	10.0
Mycobacterium spp.	3.5-5.1
Proteus spp. 14.0 [54] 10.0 [52]	10.0
Pseudomonas aeruginosa	8.0-16.0
Salmonella spp.	5.2-16.0
Serratia marcescens	10.0
Staphylococcus spp.	3.9-16.0
MRSA	13.4
MRSE	3.2
Stentotrophomonas maltophilia	2.0
Streptococcus spp.	3.8-5.0
Xanthomonas maltophilia	++
Anaerobic bacteria	
Actinomyces spp.	2.9
Bifidobacterium bifidum	5.0
Bacteroides fragilis	10.0
Clostridium difficile	5.9
Eubacterium lentum	3.0
Fusobacterium nucleatum	2.9
Peptococcus niger	4.2
Peptostreptococcus anaerobius	4.1
Prevotella melaninogenica	5.8
Porphyromonas spp.	3.5
Prevotella loeschii	5.5
Propionibacterium acnes	4.6
Veillonella parvula	4.7
Viruses	
FCV 2280	4.0
Flu A H1N1	2.0
Flu A H5N1	6.0
Flu A H9N2	6.0
Flu A H3N1	2.0
HIV 1	8.0
HSV 1	2.0

HSV 2	3.0
Norovirus	3.0
Polio 1	6.0
Rhino A1	2.0
RSV	6.0
WNV	3.0
Bacterial Spores	
Bacillus anthracis	0.2
Bacillus atrophaeus	0.4-2.0
Bacillus cereus	1.32-6.98
Bacillus subtilis	1.0-15.0
Clostridium difficile	2.0
Clostridium perfringens	0.04
Streptomyces spp.	++
Eukaryotes	
Aspergillus spp.	5.25
Candida spp.	3.5-16.0
Cryptosporidium parvum oocysts	++
Various environmental fungi	++
Biofilms 24h	
Staphylococcus aureus	6.0
Pseudomonas aeruginosa	6.0
Candida albicans	6.0

NEW is not merely an effective biocidal agent. It has been shown to have potent wound healing effects through significantly increasing the skin fibroblast cell migration. In vitro a single wound was created across a keratinocyte monolayer which was then incubated with either NEW or povidone-iodine. Keratinocyte migration at 24 hours was approximately +25% versus baseline ($p<0.05$) with NEW compared to approximately -20% at 24 hours versus baseline for povidone-iodine ($p<0.05$). [2] Povidone-iodine demonstrated cytotoxic activity, while NEW demonstrated wound healing efficacy.

The measurement of metabolic activity (MTT assay) is a reliable measurement of cytotoxicity to the basal layer (BL) as it measures metabolic activity only in undifferentiated keratinocytes in the BL, in the first suprabasal layer of the epidermis, and in the fibroblasts in the dermis. A study comparing the cytotoxic effect of a range of antiseptics on skin autografts using MTT found that Microdacyn (Dermacyn) had approximately 85% MTT of controls whereas Betadine had 0%. [23]

NEW has been demonstrated to significantly improve wound reperfusion. Documented improvements in $TcPO_2$ are all measured within 1 cm of the ulcer and are sustained for at least 36 hours without additional exposure to superoxidized water. [24]

Mast cell degranulation initiates the early phase of allergic responses. Pre-treatment of mast cells with 25% and 50% NEW inhibited antigen-induced mast cell degranulation by 75–80%. [25]

9.

Review of Evidence: Comparative Efficacy

9.1 Comparison versus povidone-iodine

Nishimura M et al. Comparison of the hand disinfectant effects between super hypochlorous water and 7.5% povidone-iodine. *Paediatr Dental J*. 2004: 14(1); 1-4. [4]

This study included 30 subjects who were first educated on the correct methodology for hand sanitisation. The subjects that used NEW had a 0.48 log reduction in hand bacterial count (p=0.024), while those using povidone-iodine 7.5% had a 0.03 log reduction (not significant).

Kapur V and Mawaha A K. Evaluation of effect and comparison of superoxidised solution (Oxum) v/s povidone iodine (Betadine). *Ind J Surg.* 2011: 73(1); 48-53. [5]

Oxum is the tradename for Microdacyn in India.

Two hundred patients with a variety of wounds were treated with either NEW-saturated gauzes or povidone iodine-saturated gauzes. All patients received antibiotics. The mean follow-up of 21 days showed that the average reduction in Diabetic Foot Ulcer (DFU) wound size in the Oxum-treated group was 70% compared to 50% in the povidone iodine-treated group. Pus discharge in patients with abscesses was reduced earlier in the Oxum-treated group (100% vs. 90% at day 12 for Oxum vs. povidone-iodine) and there was an earlier appearance of granulation and epithelisation (100% versus 85% at day 18 for Oxum versus povidone-iodine). Oxum was safe and efficient as a wound care product and superior to povidone-iodine.

Dalla Paola L et al. Use of Dermacyn, new antiseptic agent, for the local treatment of diabetic foot ulcers. *J Wound Heal*. 2005: 2; 201. [6]

Two hundred and twenty consecutive patients with stage II/III infected diabetic foot ulcers (DFU) were treated with either Dermacyn dressings or povidone-iodine dressings. The mean follow-up time was 94.8 days. At the time of surgical closure, 75% of the Dermacyn group and 48% of the povidone-iodine group were microbiologically negative (p<0.005).

Pandey P K et al. Outcomes of superoxide solution dressings in surgical wounds: a randomized case control trial. *Int J Biol Med Res*. 2011: 2(4); 965-968. [7]

One hundred patients with a variety of wounds were randomised to treatment with either NEW-saturated dressings (Group A) or povidone-iodine saturated dressings (Group B). The incidence of infection in primarily sterile cases was 15% in group A and 36% in group B, respectively. The most common infecting organism isolated in the study was *Pseudomonas aeruginosa* followed by *Staphylococcus aureus* and *Klebsiella* spp. Decrease in surface area of wounds at the end of the 1st, 2nd, 3rd, and 4th weeks, which was statistically significant, was more in the NEW group compared to the povidone-iodine group (p=0.005, 0.002, <0.001, and 0.001, respectively). This study revealed less induration in wound margins when superoxidized solution was used. This finding appears to be consistent with the fact that this solution does not damage cellular elements or restrict microcirculation of wound. [23, 24] Thus, the solution ensures the wellbeing of surrounding healthy tissues. In addition, this study also revealed the early reduction in discharge from wounds dressed with NEW as compared to povidone-iodine solution. Granulation tissue formation was earlier in the NEW group as compared to the povidone-iodine group and also covered a greater wound surface area as compared to povidone-iodine.

Piaggessi A et al. A randomised controlled trial to examine the efficacy and safety of a new super-oxidized solution for the management of wide postsurgical lesions of the diabetic foot. *Int J Low Extrem Wounds*. 2010: 9(1); 10-15. [8]

Forty patients with >5 cm^2 postsurgical wounds secondary to infected DFU were randomised to either treatments with

Microcyn or povidone-iodine as adjuncts to systemic antibiotics and debridement as needed. Patients were followed for 6 months. Healing as measured by complete re-epithelisation at 6 months occurred in 90% of the Microcyn-treated group compared with 55% of the povidone-iodine-treated group (p<0.01). The Microcyn-treated group also experienced significantly shorter period of antibiotic treatment (10.1 weeks vs. 15.8 (p = 0.016) and interventions (4 vs. 11, p=0.022). The Microcyn-treated group also had fewer episodes of reinfection (p<0.01).

9.2 <u>Comparison versus saline or placebo.</u>

Hadi S F et al. treating infected diabetic wounds with superoxidized water as anti-septic agent: a preliminary experience. *JCPSP*. 2007: 17(12); 740-743. [9]

One hundred patients with DFU wounds randomised to treatment with either daily NEW or saline soaked gauzes. All patients received IV antibiotic therapy and surgical debridement as necessary. Patients treated with NEW had a significantly shorter period of hospitalisation than saline-treated patients (1-7 days hospitalisation of 68% vs. 20%, p <0.05) and a higher proportion experienced a down-grading of their DFU (IV to I, 62% versus 15%, p<0.05).

Martinez-de Jesus F et al. Efficacy and safety of neutral pH superoxidised solution in severe diabetic foot infections. *Int Wound J*. 2007: doi:10.1111/j.1742-481X.2007.00363.x [10]

Forty-five patients with DFU were randomised to either treatment with standard care with or without NEW, which was applied as a foot soak followed by spray application. Standard care consisted of broad spectrum IV antibiotics, surgical debridement, and glycaemic control. Odour reduction was achieved in all NEW-treated patients compared to patients treated without NEW (100% versus 25%; p<0.01) and surrounding cellulitis diminished in 17 patients (80.9% versus 43.7%; p<0.001). Nineteen patients in the NEW group showed advancement to granulating tissue stage (90.4% versus 62.5%; p<0.05) with significantly less tissue toxicity (94% versus 31.2%; p<0.01).

Ichihara T et al. The efficacy of irrigation using electrolyzed strong acid solution during open heart surgery. *Jap J Thor Surg*. 2011: 57(12); 1110-1112. [11]

One hundred forty-one patients undergoing open heart surgery were treated with either warm saline lavage or warm NEW lavage directly before suturing the chest cavity. The lavage involved staunching of the blood flow after the completion of heart manipulation/removal of the cardioplegia system then irrigating the inside of the mediastinal space with approximately 1000 ml of warmed solution directly before suturing the chest cavity. After suturing the chest cavity and irrigating the subcutis with approximately 500 ml of solution, the subcutis wound was closed. Wound infection by MRSA (including skin surface and subcutis-only infection) resulted in 5 confirmed cases of mediastinitis in the saline lavage group, while no cases were confirmed in the NEW lavage group (p<0.05). One case of occurrence of wound infection/mediastinitis from other bacteria was confirmed in both the saline group and NEW group, while instances of death related to MRSA (including mediastinitis) were confirmed in 3 cases from saline lavage and 0 cases from NEW lavage.

Khan S M et al. Evaluation of pre-operative peritoneal lavage by super-oxidized solution in peritonitis. *Mid East J Int Med*. 2009: 2(3); 15-35. [12]

Eighty patients with peritonitis were assigned to either 1 hour gastric lavage with saline or NEW following surgery. Purulent discharge occurred in 20% of patients receiving NEW lavage versus 52.5% of patients receiving saline lavage (p<0.01). The incidence of burst abdomen among the NEW lavage patients was significantly less than those receiving saline lavage (27.5% versus 47.5%, p<0.05).

Garg P K et al. Evaluation of intraoperative peritoneal lavage with super-oxidized solution and normal saline in acute peritonitis. *Arch Int Surg*. 2013: 3(1); 43-48. [13]

One hundred patients with acute peritonitis were randomly assigned post-surgical treatment with either 1 hour NEW lavage or saline lavage. Surgical site infection occurred in 14% of NEW lavage patients vs. 40% of saline lavage patients (p=0.0034). Eight (16%) patients in the control group (saline lavage) compared to 2 (4%) patients in the study group (NEW lavage) died in the study.

Kubota A et al. Efficacy and safety of strong acid electrolyzed water for peritoneal lavage to prevent surgical site infection in patients with perforated appendicitis. *Surg Today*. 2015: 45; 876-879. [14]

Forty-four patients with perforated appendicitis were randomised to receive either NEW lavage or saline lavage. The incidence of surgical site infection (SSI) was significantly lower in NEW lavage group than in saline lavage group (0 and 20 %, respectively; p< 0.05).

Bongiovanni C M. Effects of hypochlorous acid solutions on venous leg ulcers (VLU): experience with 1249 VLUs in 897 patients. *J Am Coll Clin Wound Spec.* 2016: 10.1016/j.jccw.2016.01.001 [31]

Initial treatment of all venous leg ulcers involved cleaning and debriding foreign matter, debris, and necrotic material via application of copious NEW, and under pressure if necessary. Where needed, this was accompanied by abrasion using sterile gauze soaked with NEW. In all cases requiring sharp debridement, this was performed in an appropriate surgical facility and within 10 days of presentation. Following initial treatment, all ulcers were dressed and/or loosely packed with sterile gauze soaked with NEW. An appropriately compressive, multi-layered, overlying bandage system, utilizing short-stretch or non-stretch materials was constructed such that the greatest compression was at the ankle level. Light abrasion utilizing sterile cotton gauze soaked with NEW, followed immediately by flushing the wound with more of the solution effectively destroyed the extant biofilm *in situ*. With several repetitions over several days, it also prevented biofilm from re-establishing. All 1249 venous leg ulcers reported in this data set were healed completely. The longest healing times were encountered by 10 patients for whom compression therapy was contraindicated: diabetic patients with severe arterial occlusive disease [ABI < 0.6]. Nonetheless, aggressive management with NEW resulted in complete wound closure within 180 days for this treatment refractory cohort. Perhaps the greatest advance in Venous Leg Ulcer (VLU) care is the addition of NEW to the treatment armamentarium.

Cho H-J et al. Improved outcomes after low-concentration hypochlorous acid nasal irrigation in pediatric chronic sinusitis. *Laryngoscope*. 2015: March; 1-5. [15]

Twenty-six paediatric patients with chronic rhinosinusitis were randomised to twice daily irrigation with either saline or NEW for 4 weeks. There was no significant difference between the two groups in terms of overall symptom resolution. However, saline irrigation has been shown to afford a significant improvement in nasal symptoms of sinusitis patient (27.66%, p<0.001) in a 2012 meta-analysis. [22] The radiologic scores for bilateral maxillary, ethmoid, frontal, and sphenoid sinuses were rated on the following scale: 0=normal, 1=mucosal thickening (>4 mm) without opacity or fluid level, 2=partial opacification or fluid level, or 3=total opacification. The group treated with NEW irrigation achieved a significantly greater improvement in X-ray score (p=0.023).

Sasai-Takedatso M et al. Reduction of *Staphylococcus aureus* in atopic skin lesions with acid electrolytic water - a new therapeutic strategy for atopic dermatitis. *Allergy*. 1997: 52; 1012-1016. [16]

Twenty-two paediatric patients with atopic dermatitis were enrolled in a randomised, double-blind, placebo-controlled trial of NEW vs. tap water sprayed on lesions twice daily for 1 week. Colony counts of *Staphylococcus aureus* on skin lesions in the NEW group, both 3 min after spraying (p<0.05) and 1 week after skin treatment *(*p<0.01*),* were significantly decreased compared with colony counts before treatment. There was no significant difference in the placebo group before and after treatment. Grading of skin scores was 0–2 in the ascending order of severity with respect to inflammation, lichenification, and cracking. These signs were assessed on four areas of the body (i.e. face, trunk, arms, and legs0 with the maximum possible score of 24. Scores for itching and sleep disturbance were graded 0—3 in the ascending order of severity. Therefore, the maximum possible total score was 30. Both the subjects'

guardians' evaluation and a referee physician's evaluation of treatment effect were significantly higher in the NEW group than in the placebo group (p<0.01).

Draelos Z D. Antipruritic hydrogel for the treatment of atopic dermatitis: An Open-Label Pilot Study. *Cutis*. 2012: 90; 97-102. [17]

Seventeen adult patients with mild to moderate atopic dermatitis were treated with NEW Hydrogel three times daily for 14 days. There were 3 efficacy end-points: investigator global assessment (IGA), investigator pruritis assessment (IPA), and participant itch assessment (PIA). All three endpoints showed a statistically significant improvement. The IGA rating of 2 (mild) or 3 (moderate) score improved 43% from a baseline score of 2.7 to a day 14 score of 1.53 (p<0.001) on a 5-point scale (0=clear; 4=severe). The severity of pruritus decreased in 88% (15/17) of participants from baseline to day 14 based on the IPA and 82% (14/17) of participants based on the PIA. Most participants (82% [14/17]) experienced relief from itching by day 3.

9.3 Compared with Other Antimicrobials

Landsman A et al. An open-label, three-arm pilot study of the safety and efficacy of topical Microcyn Rx wound care versus oral levofloxacin versus combined therapy for mild diabetic foot infections. *J Am Podiatr Med Assoc*. 2011: 101(6); 484-496. [18]

Sixty-seven patients with mildly-infected DFU were randomised to 10 days therapy with either daily Microcyn treatment irrigation alone, daily saline irrigation plus levofloxacin, or daily Microcyn treatment irrigation plus oral levofloxacin. The intention-to-treat clinical success rate at day 10 was higher in the Microcyn-treated alone group (75.0%) than in the saline plus levofloxacin group (57.1%) or in the Microcyn treatment plus levofloxacin group (64.0%). The per-protocol test of cure for patients treated with Microcyn alone was 93.3% vs. 56.3% for saline plus levofloxacin (p=0.033).

Tirado-Sanchez A et al. Efficacy and tolerance of superoxidized solution in the treatment of mild to moderate inflammatory acne. A double-blinded, placebo controlled, parallel-group, randomized, clinical trial. *J Derm Treat.* 2009: 20; 289-292. [19]

A total of 89 patients with mild to moderate inflammatory acne were enrolled in this double blinded, clinical trial. Patients presented with 10–50 inflammatory lesions (papules and pustules) and an absence of nodulocystic lesions were randomised to treatment with either NEW, benzoyl peroxide (BP), or placebo twice daily for 12 weeks. Efficacy was evaluated by counting the changes in the numbers of facial inflammatory lesions. Response was graded as excellent (?75–100% reduction of lesions), good (?50–74% reduction), fair (?25–49% reduction), or poor (<25% reduction). Improvement was excellent in 9 patients (23%) using NEW, compared with 5 patients (21%) using BP (p=0.378); good in 21 patients (54%) using NEW, 12 patients (50%) using BP (p = 0.794), and 4 patients (18%) taking placebo (p=0.001); and fair in 6 patients (15%) using NEW, 5 patients (21%) using BP (p=0.415), and 12 patients (55%) taking placebo (p=0.014). No systemic side effects were observed.

Mizutani M Y et al. The effectiveness of hand-disinfection by a flow water system using electrolytic products of sodium chloride, compared with a conventional method using alcoholic solution in an intensive care unit. *Crit Care*. 1998: 2; 79-80. [20]

Forty members of the ICU staff without skin disease disinfected their hands by following three different methods for 15 seconds (one method per day): NEW, alcohol, water. NEW eliminated 93.2% of colony forming unit (CFU), which was equivalent to the amount eliminated by alcohol and significantly better than water (52% CFU elimination, p<0.05).

Nerandzic M M et al., Novel strategies for enhanced removal of persistent *Bacillus anthracis* surrogates and *Clostridium difficile* spores from skin. *Plos One*. 2013: 8(7); 1-9. [21]

Six volunteers were contaminated sequentially with 6 $\log_{10}$ *Clostridium difficile* and *Bacillus atrophaeus, Bacillus thuringiensis,* or *Bacillus subtilis* as the *B. anthracis* surrogate spores. Baseline hand disinfection levels and levels after hand disinfection were measured. The hand disinfection interventions were alcohol hand gel, 0.05% triclosan liquid soap, NEW soak, soap and water followed by NEW soak, 70% alcohol wipes, and NEW wipes.

Soap and water hand washing followed by NEW soak resulted in ~2 log reduction of *C. difficile* or *B. anthracis* surrogate spores, while alcohol hand gel resulted in <0.5 log reduction of spores. In comparison to soap and water, NEW soak enhanced reduction in spores by a further 0.5 to 1.2 log CFU (*p*?0.001).

Helme A J et al. Bactericidal efficacy of electrochemically activated solutions and of commercially available hypochlorite. *Brit J Biomedic Soc*. 2010: 67(3); 15-108. [30]

NEW was compared with an equivalent hypochlorite concentration of commercially available hypochlorite solution against 7 common microbial pathogens. Commercially available hypochlorite was 100% effective against all species at 0.111% NaOCl, while pH neutral NEW was 100% effective against all species at 0.006% NaOCl.

Yamada Y et al., Effect of superoxidized water on disinfection of the hands and environment. Jpn J Hosp Pharm. 1995: 21(6); 525-530. 36

The disinfection of superoxidized water, 0.2% benzalkonium chloride and 0.3% triclosan were compared on hands (14 subjects), floors and working tables. The mean reduction in bacteria on hands was 86.5%, 96.5% and 37.1% respectively. There was no significant difference superoxidized water and 0.2% benzalkonium chloride in alcohol. Superoxidized water for 5 minutes resulted in complete elimination of bacteria on parenteral bottles returned to the pharmacy from the general wards. Superoxidized water resulted in 100% kill of oxacillin-resistant S aureus on tables and floors.

10.

Summary of Safety Evidence

Microdacyn mimics the body's natural cellular defence system in that the Reactive Oxygen Species (ROS) mimic macrophage oxidative burst. [10] The extreme hypotonicity leads to osmotic shock and microbial rupture. [28]

The goal of antiseptic is to reduce potentially pathogenic microbial populations to safe levels. In the clinical environment, agents must not be hazardous or toxic to living tissue according to their particular application and in-use concentrations. A large scientific body of evidence now exists indicating the safety and non-toxicity of NEW. NEW does not target cell nuclei, produces only limited damage to cell membranes, and does not induce DNA oxidation or accelerated ageing. It is also worth noting that NEW presents no environmental hazard since it slowly reverts to salt water during the period of chemical relaxation and is effectively inactivated by organic matter when present in trace amounts. [28]

A single-dose and 28-day repeated dose oral toxicity study of NEW in rats found no evidence of adverse effects. In addition, mice given free access to NEW as drinking water for 8 weeks showed no toxic side effects. [32] Moreover, no toxicity was observed using in-use concentrations during acute oral toxicity tests (LD_{50}) upon application to mucous membranes, in accumulation irritation tests, or in sensitisation tests, indicating its biocompatibility. [33] In fact, the observed biocompatibility of NEW has often been determined at relatively high exposure levels, in comparison with the anticipated low levels that would be used in real clinical situations. The incubation of NEW with human cell lines *in vitro* has shown more mixed results where some studies had no effect, while others had significant cytotoxicity, although usually to a lesser degree than other commonly used biocides. However, *in vitro* cytotoxicity is not always indicative of toxicity when used *in vivo*, as observed previously. *In vitro* mutagenicity studies failed to find any evidence of NEW

induced genotoxicity, using either the Ames test or the genotoxicity micronucleus test, indicating its safe usage. [33, 34] Moreover, a recent wide-ranging toxicity study on a neutralised NEW found that it did not degrade nucleic acids or induce oxidative damage in dermal fibroblasts *in vitro*. [10] This study led the authors to conclude that NEW did not target cell nuclei, produced only limited damage to cell membranes and did not induce DNA oxidation or accelerated ageing. It is also worth noting that NEW presents no environmental hazard because it slowly reverts to salt water during the period of chemical relaxation, and is effectively inactivated by organic matter when present in trace amounts. [1]

Electromicyn technology is a pH neutral, hypotonic solution of highly oxidative species including hypochlorous acid, ozone, superoxide, and peroxide. It exerts powerful antibacterial, antiviral, antifungal, sporicidal, and antibiofilm activity based principally on a physicochemical mode of action, thereby avoiding the risk of resistance developing. Electromicyn is not only potently biocidal but also has significant wound healing properties, which is unique amongst other topical antiseptics. In clinical trials, Electromicyn demonstrated generally superior wound healing and antiseptic outcomes vs. commonly used alternatives that are currently included on the WHO EML. The acute and chronic safety of Electromicyn is well documented such that it has FDA approval for use around eyes and on mucosa. Furthermore, Electromicyn is offered at a lower cost than the alternative topical antiseptics listed in the WHO EML.

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11.

Comparative Cost

WHO pricing for 500 mL 10% povidone-iodine to Fiji in 2006 was 6.68 USD or 0.134 USD per 10 mL.

The proposed pricing of Electromicyn Wound Care Solution 500 mL (NEW supplied by Te Arai BioFarma Ltd) spray bottle to WHO is 5.52 USD or 0.11 USD per 10 mL

The proposed pricing for Electromicyn Hydrogel 250 g spray bottle is 6.00 USD or 0.24 USD per 10 mL.

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