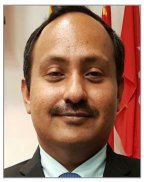
Studies on the efficacy of hypochlorous acidoxidizing solution in treating infected wounds



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This study investigates the effectiveness of hypochlorous acidoxidizing solution (AOS) in treating chronic wounds at the Wound Care Unit, Hospital Kuala Lumpur. The trial aims to assess healing speed, the reduction of infection rate, pain score, tissue improvement, and the control of inflammation. We chose six cases by simple random sampling and assessed them for 16 weeks. The cases include five cases of diabetic foot ulcer (DFU) and one case of abscess. The wounds were assessed for wound size and depth (in cm), visual analogue score (VAS), and wound bed preparation (WBP) score to evaluate the inflammation and the granulation tissue. We gave a score from 1 to 3 depending on the quantity of the exudation and from A to C depending on the quantity of granulation tissue. AOS shows a tremendous improvement in wound condition by augmenting wound healing, improvement in pain score, and reduction of infection. The small sample size of this study was its limitation; we need a larger sample to further assess the efficacy and full potential of AOS.

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The importance of wound irrigation and cleansing solutions is often ignored; Wound cleansing can help with wound bed preparation (WBP) by removing microorganisms and biological debris to create an environment beneficial to healing, as well as facilitating wound assessment via clear visualisation of the wound.

The ideal wound cleanser is non-toxic to viable tissue, cost-effective and stable. A sterile non-toxic isotonic solution such as normal saline is commonly used to irrigate wounds. Normal saline is not only cost-friendly but gentle enough to refrain from damaging healing tissues (Griffiths et al, 2001). Nonetheless, saline generally does not contain preservatives and is likely to allow bacterial growth once exposed to opportunistic microorganisms.

Commercial wound cleansers such as povidone-iodine (PI), hydrogen peroxide (H_2O_2), and sodium hypochlorite (NaClO) are able to remove or soften necrotic tissue and debris. The Agency for Health Care Policy and Research (AHCPR) guidelines discourage the use of commercial wound cleansers to clean open wounds because they do not effectively kill bacteria at concentrations safe enough for healing tissue (Lindfors 2004).

AOS (Nexodyn-APR Applied Pharma Research [APR] SA) is an acidoxidizing that can be used for debridement, irrigation, and moistening of acute and chronic wounds. AOS contains high-purity hypochlorous acid (HClO; >95% HClO of free chlorine species), which accounts for the creation of an ideal microenvironment to sustain the physiological healing process; pH of the solution is between 2.5 and 3.0 and high oxidation-reduction potential (ORP>1000mV) (AOS wound care solution [package insert], 2015). This combination contributes to its strong antimicrobial activity, reduction in inflammatory processes and physiological stimulation of tissue-repair processes.

AOS is intended for use under the supervision of health professionals for cleansing, irrigating, moistening and debriding to remove organic and inorganic debris from partial- or full-thickness acute and chronic dermal lesions, such as leg ulcers, stasis ulcers, diabetic foot ulcers (DFU), pressure ulcers (PU), postoperative wounds, grafted and donor sites and first- and second-degree burns. AOS can also be used for cleansing

and moistening minor cuts, minor burns, superficial abrasions and minor skin irritations. It is contraindicated in cases of hypersensitivity to any component of the product including hypochlorous acid, chlorine, and hypochlorite ion (AOS wound care solution [package insert], 2015).

AOS also works by mechanically removing bacteria and any biological residues when it is sprayed on the tissue. The AOS has direct antimicrobial action, owing to its oxidation-reduction properties. The pH of the solution, which is between 2.5–3.0, will impair bacterial growth (Liao et al, 2007) and induce matrix metallopeptidases (MMP) inhibition. The combination of these effects creates the condition for the physiological stimulation of tissue-repair processes.

A review by Nagoba et al (2015) shows that an acidic pH reduces the activity of proteases and inhibits the penetration of toxic ammonia produced by bacteria into healthy cells. In addition, low pH also improves tissue oxygenation and promotes epithelisation. In another assessment of cleansing solution by D'Atanasio et al (2015), AOS demonstrated a higher percentage of preservation of cell viability when compared with betaine plus polyhexanide and superoxidized solutions. This is essential because the preservation of cell viability will allow the reconstructive activity of wound repair in chronic wounds.

A wealth of evidence and real-world experience consistently shows that AOS reduces healing time, protects from the risk of infection, reduces clinical signs of local infection and wound-associated pain with a highly tolerable profile (Iacopi et al, 2018; Strohal et al, 2018; Ricci et al, 2016). Adding AOS to the standard of care for DFU results in faster healing time and protection from the risk of infection (Iacopi et al, 2018). AOS reduces clinical signs of local infection, wound-associated pain in leg ulcers (Strohal et al, 2018) and is well tolerated. No adverse events associated with the use of AOS were reported in any of the listed studies (Iacopi et al, 2018; Strohal et al, 2018; Ricci et al, 2016).

Objective

To evaluate the effectiveness of hypochlorous acid in treating wounds by assessing the healing speed, the reduction of infection rate, pain score, tissue improvement and the control of inflammation.

Methods

We selected six cases by simple random sampling and assessed at each visit for 16 weeks from August 2019 until January 2020. The patients enrolled in the study suffer from DFUs (five cases) and foot abscess (one case). During each visit, we sprayed the wound areas abundantly with AOS twice. The first time was to cleanse the wound and the second followed debridement. We allowed the AOS to dry before applying the dressing.

During each dressing change, the wounds were assessed for size and depth (cm) and visual analog scale (VAS) following the application. We used

Table 1. Staging system for wound bed preparation. Staging of the wound is done by combining the score of the wound bed appearance with that of the wound exudate, i.e., A1, B3, etc. Staging adapted from Falanga (2000)

Wound bed appearance score	Wound bed characteritics		
	Granulation tissue	Fibrinous tissue	Eschar
A	100%	–	–
B	50–100%	+	–
C	<50%	+	–
D	Any amount	+	+

Wound exudate score	Extent of control	Exudate amount	Dressing requirement
1	Fully	None/minimal	No absorptive dressings required. If clinically feasible, dressings could stay on for up to a week
2	Partially	Moderate amount	Dressing changes required every 2–3 days
3	Uncontrolled	Very exudative wound	Absorptive dressings changes required at least daily

Table 2. Summary of main results for the six cases

Case	Type of wound	WBP Score		Wound depth	Presence of infection		VAS		Wound surface (cm^2)	
		Initial	Final		Initial	Final	Initial	Final	Initial	Final
1	DFU	A2		1cm	No	No	2	0	3rd: 1.75	Both Healed
2	DFU	B2		<0.5cm	Yes	No	2	0	4th: 3.5	Healed
3	Abscess	B2	A1	<0.5cm	Yes		7	0	6.0	Lat: 0.25
4	DFU	B2	A2	<0.5cm		No	3	0	Lat: 33.75	Dor: 45.0
5	DFU	B2	B2	<0.5cm			2	0	Dor: 201.5	Med: Healed
6	DFU	B2	A2	<0.5cm	Yes	No	2	0	Med: 27.0	9.0

Case 1

- A 32-year-old Malay male with underlying type 2 diabetes mellitus
- The patient was referred for diabetic foot ulcer over the right foot, wound age: 1 month
- The wound healed after 42 days

Time	Day 1	Day 42
		
Wound size (cm^2)	3rd web space: 1.75cm^2 4th web space: 3.5cm^2	3rd web space: Healed 4th web space: Healed
WBP score	A2	
Wound depth (cm)	3rd web space: 0.5cm 4th web space: 1.0cm	3rd web space: Healed 4th web space: Healed
Infection	No	No
Visual analogue scale (VAS)	2	0
Comment		Discharge

the WBP score, which is a scoring model meant to evaluate the inflammation and the granulation tissue. We gave a score from 1 to 3, depending on the quantity of the exudation, and from A to C depending on the quantity of granulation tissue *(Table 1)*.

Patients fulfilling the inclusion criteria below were analysed to evaluate the addition of AOS to the therapeutic scheme in the treatment of chronic wounds:

- Subjects ≥30 years old
- Chronic ulcers ≥4 weeks old
- An unsatisfactory clinical improvement for at least the past month, despite standard treatment.

We performed this study following the principles of good clinical practice guidelines, in compliance with the Declaration of Helsinki and with approval from the hospital review board. We obtained informed consent and permission to use clinical images and case details for publication/research purposes.

Results

The trial showed an overall massive improvement in the wound conditions. There was a significant reduction in size (71.9%) and pain score reduction (VAS 0) in all 6 patients and no infection in all 4 patients with previousy infected wounds at the end of the study *(Table 2, Figure 1)*. WBP noted improvement with increased granulation tissue

Case 2

- A 91-year-old Indian male with underlying type 2 diabetes mellitus
- The patient was referred for diabetic foot ulcer of the left foot, wound age: 1 month
- The wound healed after 112 days

Time	Day 1	Day 42
		
Wound size (cm^2)	$6.0cm^2$	Healed
WBP score	B2	
Infection	Yes	No
Visual analogue scale (VAS)	2	0
Comment	2	Discharge

production and reduction in fibrin and unhealthy tissue. There were 2 patients were discharged during the trial period with a healed wound.

Case 1

A 32-year-old Malay male with underlying type 2 diabetes mellitus was referred for diabetic foot ulcer over the right foot. The wound age was 1 month and it healed after 42 days *(Case 1)*.

Case 2

A 91-year-old Indian male with underlying type 2 diabetes mellitus was referred for DFU of the left foot. The wound age was 1 month and the healed after 112 days *(Case 2)*.

Case 3

A 57-year-old Chinese male with underlying hypertension and hepatitis C was referred for right

Case 3

- A 57-year-old Chinese male with underlying hypertension and hepatitis C
- The patient was referred for right foot abscess , wound age: 2 months
- The wound healed after 36 days

Time	Day 1	Day 38	Comment
			
Wound size (cm^2)	Lateral: $33.75cm^2$ Dorsal: $201.5cm^2$ Medial: $27.0cm^2$	Lateral: $0.25cm^2$ Dorsal: $45.0cm^2$ Medial: Healed	Lateral: 99.7% improvement Dorsal: 77.6% improvement Medial: Healed in 22 days
WBP score	B2	A1	
Infection	Yes	No	No more sign of infection
Visual analogue scale (VAS)	7	0	The pain score dropped to 0 almost immediately

Case 4

- A 52-year-old Malay male with underlying type 2 diabetes mellitus and hypertension
- Patient was referred for diabetic foot ulcer of the left foot, wound age: 7
- Wound showed good healing rate at 104 days

Time	Day 1	Day 104
		
Wound size (cm^2)	$60.0cm^2$	$9.0cm^2$
WBP score	B2	A2
Infection	No	No
Visual analogue scale (VAS)	3	0

Case 5

- A 67-year-old Indian male with underlying type 2 diabetes mellitus and hypertension
- The patient was referred for diabetic foot ulcer of the left foot, wound age: 5 month
- The wound was healing well at 94 days

Time	Day 1	Day 112
		
Wound size (cm^2)	$66.5cm^2$	$40.0cm^2$
WBP score	B2	B2
Infection	No	No
Visual analogue scale (VAS)	2	0

foot abscess. The wound age was 2 months and the healed after 36 days *(Case 3)*.

Case 4

A 52-year-old Malay male with underlying type 2 diabetes mellitus and hypertension referred for diabetic foot ulcer of the left foot. The wound age was 7 months and the showed a good healing rate at 104 days *(Case 4)*.

Case 5

A 67-year-old Indian male with underlying type 2 diabetes mellitus and hypertension was referred for diabetic foot ulcer of the left foot. The wound

Case 6

- A 46-year-old Malay male with underlying type 2 diabetes mellitus and hypertension
- The patient was referred for diabetic foot ulcer of the right foot, wound age: 8 month
- The wound healing was good

Time	Day 1	Day 112
		
Wound size (cm^2)	$60.0cm^2$	$45.0cm^2$
WBP score	B2	A2
Infection	No	No
Visual analogue scale (VAS)	2	0

age was 5 months and the was healing well at 94 days *(Case 5)*.

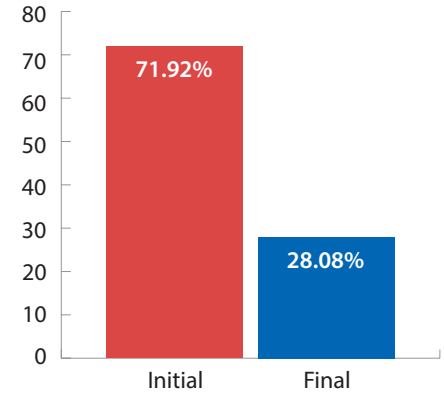
Case 6

A 46-year-old Malay male with underlying type 2 diabetes mellitus and hypertension was referred for diabetic foot ulcer of the right foot. The wound age was 8 months and the wound healing was good at 110 days *(Case 6)*.

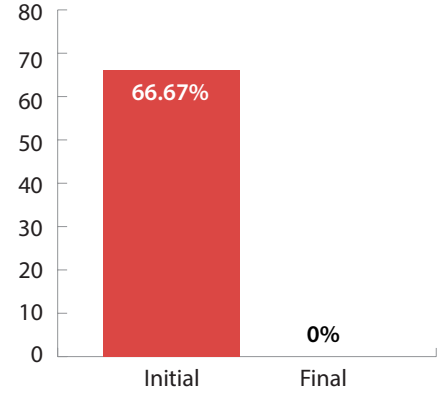
Discussion

- Overall reduction of the average wound size

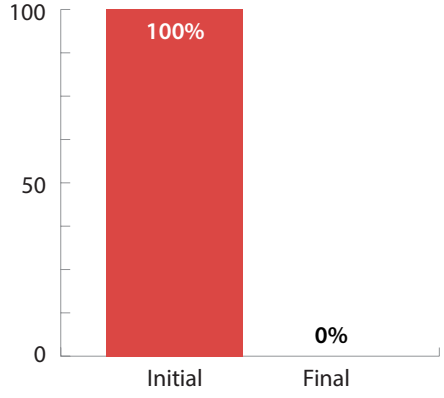
Reduction in average wound size



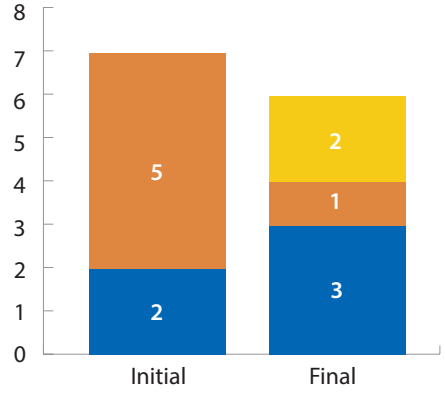
Infection Rate (%)



Visual Analogue Scale pain assessment



Wound bed preparation (WBP)



of 71.92%
- 44.44% healing rate (4 out of 9 wounds) (1 patient has 3 wounds and another patient has 2 wounds)
- Out of a total of 6 patients at T0, 4 patients have infected wounds
- At the end of the study, the infection rate dropped from 66.67% to 0%
- 100% success rate
- A decrease of 100% in pain score after the study demonstrates efficacy in pain management
- Wound bed preparation (WBP) noted improvement with increase granulation tissue production and reduction in fibrin and unhealthy tissue.

The results of this study show the usefulness of HClO in healing and improving the wound condition. There is a clinically relevant reduction of the wound area, improvement in WBP scores, and reduction in infection rate. Wound-associated pain was also significantly less. The ideal wound microenvironment that HClO creates is key for the significant healing process. Studying a population who were refractory to standard management showed that integrating Nexodyn™ AOS into standard care helps modulate local microenvironmental responses that inhibit physiological healing processes while also helping to reduce bacterial load (Ricci, 2016).

An *in vitro* study has shown how Nexodyn™ AOS induces a morphological change in the extracellular matrix of the biofilm structure, thereby making bacteria more accessible to cleansing (D'Atanasio et al, 2015). A study of 25 outpatients with non-infected and non-ischemic lesions demonstrated that Nexodyn™ AOS was superior to saline as wound cleanser, as it significantly reduces infection rate, requires fewer debridement procedures and heals faster with no adverse event recorded (Lorenza et al, 2015).

Another 30-patient pilot study, with locally infected or critically colonised lower-leg ulcers, shows AOS supported wound healing of locally infected ulcers, with no adverse events reported and high levels of comfort at application (Strohal et al, 2018). The modulation of the wound microenvironment, as well as the contribution to the control of local infection, has been shown by measuring wound-size reduction and complete healing, local infection scores, presence of bioburden on the wound surface, wound-bed pH and wound-associated pain. The small sample size of this study is its limitation; a larger sample is needed to further assess the efficacy and full potential of AOS. WAS

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