

Treatment of Surgical Site Infection with Aqua Oxidation Water: Comparison with Povidone Iodine

Atsushi NANASHIMA, Hiroyuki YAMAGUCHI, Terumitsu SAWAI, Takashi TSUJI, Shinichi SHIBASAKI, Seiji MATSUO, Masaaki JIBIKI, Toru YASUTAKE, Tohru NAKAGOE, Hiroyoshi AYABE

The First Department of Surgery, Nagasaki University School of Medicine

Aqua oxidation water is a new disinfectant with a bactericidal activity based on high oxidation-reduction potential and acidity. We compared the effectiveness of aqua oxidation water and povidone iodine against the surgical site infection (SSI). The bacteriological effect against several organisms and the efficacy of both disinfectants were almost similar. However, the duration of treatment with aqua oxidation water was shorter than that with the povidone iodine in healed wounds ($p < 0.05$) and the number of patients treated with aqua oxidation water who reported pain was smaller than that with povidone iodine ($p < 0.05$). Our results indicated that aqua oxidation water useful and effective for the treatment of incurable SSI.

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Key Words: aqua oxidation water; povidone iodine; surgical site infection; disinfectants

Introduction

Surgical site infection (SSI) is a frequent complication of surgery (between 1.5 to 5.1% after clean surgery) and is related to various factors such as type of surgery, nutrition status, etc.¹ To date, the use of disinfectants, such as povidone iodine (PI), together with antibiotics, may prevent the development of SSI as well as allow a rapid healing.^{2,3} Clinical experience indicates, however, that SSI could occur in spite of stringent sterilization or administration of antibiotics.

A new disinfectant; the aqua oxidation water (AOW),² also termed oxidizing water,⁴ or superoxidized water⁵ has been developed recently and used extensively in Japan. The high oxidation-reduction potential and acid-

ity ($\text{pH} < 2.7$) of AOW provide the characteristic antimicrobial effects. Tanaka et al.⁵ showed that AOW has a wide-spectrum bactericidal *activity in vitro*. Most bacteria and fungi are eliminated within a short period after contact (unpublished data from Shionogi & Co., Ltd., Aburahi Laboratories, Shiga, Japan). Furthermore, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, which are common pathogens in hospital-acquired infections,^{6–8} are also eradicated by AOW *in vitro*.⁵ The bactericidal effect of AOW are comparable to that of 80% of ethanol, but more powerful than that of distilled water, 0.1% of chlorhexidine and 0.02% of povidone iodine.⁵ The aim of the present study was to compare the bacteriological and clinical effect of AOW and PI in patients with SSI. Furthermore, although the clinical use of AOW has not been officially approved in Japan so far, the present clinical study of the effectiveness and safety of AOW may provide the great benefits for patients who had the prolonged or incurable wound infection on the basis of the previous reports *in vitro*.⁵

Patients and Methods

Patient population

We examined the clinical effects of AOW in 46 patients admitted to the First Department of Surgery, Nagasaki University School of Medicine, between 1993 and 1997. SSI occurred in 112 of 1135 patients (9.9%) in the field of gastrointestinal and hepato-biliary-pancreas surgery during this period. The patients included 32 males and 14 females, ranging in age from 25 to 83 years (mean age; 54.6 years). Each patient had a contaminated subcutaneous infection at the site of surgical wounds. The control group consisted of 42 patients who were treated with PI only and included 27 males and 19 females, ranging in age from 19 to 86 years (mean age; 52.2 years). The present study was the historical study but not randomized or controlled

Address Correspondence: Atsushi NANASHIMA, M.D.

The First Department of Surgery, Nagasaki University School of Medicine 1-7-1 Sakamoto, Nagasaki 852-8501, JAPAN

TEL: +81-95-849-7304, FAX: +81-95-849-7306

E-mail: a-nanasm@alpha.med.nagasaki-u.ac.jp

trial. All operative procedures were gastrointestinal, colorectal and hepato-biliary-pancreas surgery and there were no significant differences between both groups. The clinical use of AOW was approved by the Humans Ethics Review Committee of our department and a signed consent form was obtained from each patient.

Aqua Oxidation Water

The AOW was prepared from 5% NaCl solution with tap water and produced by electrolysis for approximately 10 minutes using the Super Oxseed JES-010 α 1000[®] (Amano Co., Yokohama, Japan and Shionogi & Co., Aburahi Lab., Shiga, Japan). AOW had a very low pH, ranging from 2.3 to 2.7, and the oxidation-reduction potential was high ranging from 1000 to 1200 mV. AOW also contained 30 ppm of free chlorine and 50 ppm of superoxide as byproducts of the electrolysis process. AOW was stored in a shielded bottle at room temperature for a week. PI (Isodine solution, Meiji Seika Co., Tokyo, Japan) was diluted to 0.02% and was also stored in a shielded bottle at room temperature.

Experimental protocol

Freshly prepared AOW was used for purulent wounds (pus) including surgical wounds. All patients had been treated with drainage and dressing. Most patients were given systemic antimicrobial drugs but no significant difference between groups (96% and 93%) before the use of AOW and PI, but no antibiotic or other disinfectants were applied on the infected wounds during the use of AOW and PI. Treatment of the wounds was applied once daily.

Assessment of treatment

Following the use of AOW or PI, the degree of inflammation, the amount of purulent material, blood tests (leukocyte count and CRP), body temperature and bacterial culture were evaluated after treatment for one or two weeks and compared with pre-treatment values. The purulent materials were taken with SEEDSWAB[®] No. 3 (Eiken Kizai Co., Tokyo). The material was then plated on sheep blood agar, Digalski' modified agar or chocolate agar for aerobic culture, on Anaero Columbia agar for anaerobic culture, and on Sabourand agar for culture of fungus. Quantification of organisms was performed using the Spiral System[™] (Gunze Sangyo, Inc., Tokyo). The bacteria isolated from the samples were identified by using Vitek Gram-Positive, Gram-Negative, or fungus Identification card (Vitek Systems, Inc., Hazelwood, MO). In the present study, the criteria of

the bacteriological effectiveness was defined in case the initial organism $>10^6$ reduced or completely disappeared after the use of AOW or PI.

The clinical effectiveness of treatment was divided into four grades; very effective, effective, no change and worse. "Very effective" represented a complete healing of the infected wound that never showed pus formation, redness and swelling, while "effective" denoted a reduction of infection but complete healing was not established. Comparisons between PI and AOW were tested for statistical differences using the Student' *t*-test. For differences between ratios, we used the χ^2 test. A *p* value <0.05 was considered significant.

Results

All patients were in a stable condition during the study and none refused therapy. As shown in Table I, associated disorders were similar in patients treated with AOW and PI. Three patients had diabetes (2 in AOW group and 1 in PI group). The period of use of AOW varied from less than one week to more than 1 month. The incidence of patients in AOW group, who treated with disinfectants for more than 30 days, was significantly less than that in PI group ($p < 0.05$). Complications caused by AOW were rare. In contrast, the incidence of patients, who complained pain, treated with PI was significantly higher ($p < 0.05$). Pain by AOW was slight. Bleeding was insignificant and ceased within a few days of treatment with AOW. Discoloration of the surrounding tissues during or after the application of AOW did not occur.

The general response to inflammation before and after the use of AOW and PI was examined. Leukocytosis ($>9,000/\text{mm}^3$) was observed in 11 patients (24%) of AOW group and 22 patients (52%) of PI group before the application of the disinfectant but the count normalized in nine and 15 patients after treatment, respectively. CRP was >2.0 in 19 (41%) of AOW group and 32 (76%) of PI group, but normalized in 18 and 22 patients, respectively. A high body temperature ($>37^\circ\text{C}$) was observed in 34 of AOW group and 34 of PI group but returned to normal in 12 and 24 patients, respectively. During the course of treatment, the laboratory tests did not worsen in those with normal values at baseline (pre-treatment). There was no significant difference in the general response between AOW and PI.

Table II lists the organisms isolated from the infected wounds treated with AOW and PI, and shows the bacteriological effectiveness of AOW and PI, respectively. These included 118 bacterial species and 3 fungi.

Table 1. Comparison between the use of aqua oxidation water and povidone iodine for the treatment of surgical site infection.

	AOW (%)	Povidone Iodine (%)
<i>n</i>	46	42
<i>Duration of Therapy (days)</i>		
0-7	14 (30)	6 (14)
7-14	25 (54)	12 (29)
>14	5 (11)	15 (36)
>30	2 (5)	9 (21)
<i>Associated Disorders for operation:</i>		
malignancy	29 (63)	35 (83)
IBD*	7 (15)	3 (7)
others	10 (21)	4 (10)
<i>Complications:</i>		
none	42 (91)	32 (76)
pain	3 (7)	10 (24)
bleeding	1 (2)	0 (0)

*: IBD; inflammatory bowel disease, prednisolone was used for all patients

Table 2. The bacteriological effects of aqua oxidation water and povidone iodine.

Initial Organism (>10 ⁶)	Disappeared		Reduced		Persisted		Total	
	AOW	PI	AOW	PI	AOW	PI	AOW	PI
<i>1. Actinomyces</i>	1	0	0	0	0	0	1	0
related organisms								
<i>2. Gram-positive cocci</i>								
MRSA	3	2	2	0	2	2	7	4
Other <i>staphylococci</i>	4	2	0	0	0	1	4	3
Streptococci	7	6	0	1	2	1	9	8
Others	2	5	0	3	2	3	3	11
<i>3. Gram-negative bacteria:</i>								
<i>P. aeruginosa</i>	3	6	3	1	4	3	10	10
<i>E. coli</i>	2	2	3	1	2	0	7	3
<i>B. fragilis</i>	3	1	1	0	1	1	5	2
<i>E. cloacae</i>	4	1	0	1	0	0	4	2
<i>Prevotella spp.</i>	3	1	0	1	0	0	3	2
<i>Klebsiella spp.</i>	2	4	0	0	0	2	2	6
Others	2	4	1	1	2	2	5	7
<i>4. Fungi:</i>								
<i>C. albicans</i>	1	0	0	0	0	2	1	2

AOW: aqua oxidation water, PI: povidone iodine

Treatment with AOW resulted in a complete eradication of 37 organisms (61%) from the wound site, and a reduction in the number of 10 organisms (16%). However, 15 organisms (23%) persisted (>10⁶) after treatment. Thus, AOW was effective against 47 different organisms (77%). In wounds infected with gram-negative and-positive bacteria, 71% of MRSA and 60% of *P. aeruginosa* were eliminated or reduced by AOW. These results were similar to those obtained with PI.

The clinical effectiveness of AOW treatment is summarized in Table III. AOW was very effective or effective in 35 cases (76%). AOW treatment did not worsen infection of any wound. The clinical effectiveness of AOW was equal to that of PI (76%). We also compared the mean duration of wound healing in cases responding "very effectively" to AOW or PI. The mean duration in AOW was 8.4±2.6 days and was significantly shorter than that of PI (15.5±11.0 days, p<0.05).

Table 3. Evaluation of clinical effectiveness by aqua oxidation water and povidone iodine.

Region	AOW (n=46)				PI (n=42)				P
	VE	E	U	W	VE	E	U	W	
Subcutaneous	11	7	2	0	6	3	4	0	NS
Drainage tube	4	2	4	0	9	3	2	0	NS
Abdominal cavity	5	6	5	0	4	7	4	0	NS

AOW: aqua oxidation water, PI: povidone iodine. VE; very effective, E; effective,

U; no change, W; worse

Discussion

Povidone iodine¹ is frequently used for the treatment of surgical wounds. While povidone iodine enhances healing in a large proportion of infected wounds, its use is costly, and it may cause irritation, abnormalities in blood chemistry, hyperthyroidism and soft tissue necrosis.² Furthermore, several bacteria strains are resistant to chlorhexidine and povidone iodine.^{9, 10} On the other hand, AOW is now used extensively in several hospitals across Japan for the treatment of infected pressure sores of bedridden patients, and the therapeutic effects have been noted.¹¹ Cost-effectiveness, as AOW is cheaper than other disinfectants. The cost of povidone iodine (Isodine, Meiji Seika) is about US\$ 10 per bottle (250ml) in Japan and, in our hospital, the total cost of povidone iodine was approximately US\$ 75,000 in 1995. Furthermore, the cost of purified water or maintenance of sterilizer is necessary for refining povidone iodine. In comparison, the retail price of Super Oxseed, the

device used to prepare AOW, is approximately US \$ 2,000 to 20,000. However, no expensive consumables, e.g., chemicals or filters, are used in the process of electrolysis and AOW is prepared using only salt and tap water. The availability of a low cost disinfectant is necessary to prevent hospital-acquired infections.¹² The device used to prepare AOW is easy to operate and allows the preparation of large volumes within a short period of time. Thus, the device is ideal for small institutions.

The LD₅₀ of AOW in rats exceeds 50 ml/kg (unpublished laboratory data, Shionogi Co.). There are, however, certain disadvantages with the use of AOW. These include an immediate loss of activity after the solution contacts organic substances in the wound, e.g., blood, lymph, etc. Therefore, it is necessary to wash the wound several times using large quantities of AOW after removal of such material.

To our knowledge, the clinical application of AOW as a disinfectant has not been officially approved nevertheless the effectiveness of AOW *in vitro* was clearly clarified. In fact, however, AOW may be clinically used for disinfections at many hospitals in Japan nowadays. By the previous study *in vitro*⁵, we believe that AOW should be very useful for the treatment of infected wounds. We also carefully checked any changes of wounds and general symptoms after use of AOW in each patient. Furthermore, AOW was applied only in the localized wounds on the surface of the body but not in the intra-abdominal space for the safety of patients.

With respect to the clinical effectiveness, "very effective" (complete healing) was observed in 20 cases (44%) and "effective" treatment in 15 cases (33%) in the present study. The degree of clinical effectiveness was similar to that of PI. Furthermore, incurable infected fistulae which were initially treated with PI healed dramatically after a few days of washing with AOW in three cases. We also noted enhancement of granulation tissue formation associated with the healing process following the use of AOW. Although various kind of systemic antibiotics were already given in most patients prior to use of AOW or PI, these are incurable in some of local SSI. In such conditions, the local treatment by washing using disinfectants may be more effective.

We believe that the healing effects of AOW are more powerful than other common disinfectants because of the specific features of AOW such as high oxidation-reduction potential and acidity. The present study was performed with no significant differences of the clinically healing effects between AOW and PI treated patients. An example of such effect was the shorter duration of AOW therapy compared with PI. Furthermore, the mean duration of wound healing in "very effective"

cases treated with AOW was shorter than that with PI.

We also evaluated the clinical effectiveness of AOW according to the affected region, which included the gastrointestinal tract, colorectal, and hepato-biliary-pancreatic regions. However, no differences were observed among these groups.

Our results showed a wide range of bacteria detected in the SSI. Although the bactericidal effect of AOW is superior to that of PI *in vitro*,⁵ AOW was biologically effective against most of these organisms in a manner similar to PI, including 71% of MRSA and 60% of cases with *P. aeruginosa*. MRSA and *P. aeruginosa* often show tolerance to antibiotics⁹ and, therefore, the biological or clinical effect of local treatment using disinfectants, e.g., AOW, may become important for wounds infected by such organisms. We stress that the biological effectiveness against such bacteria clinically very significant, because these bacteria cause chronic wound infections in hospitals.^{6-8, 12}

The side effects, including wound or mucosal irritation are trivial compared with other common disinfectants. In animal experiments, the safety of AOW when applied over the skin, eye, oral, esophageal and gastric mucosa (unpublished reports by Kitazato laboratory between 1990 and 1992, Tokyo, Japan) and peritoneum¹³ has been confirmed. The side effects of AOW were minimal in this study. Two patients developed irritation due to high acidity during washing but no major complication was observed and tended to be less than PI. Discoloration of the skin was not observed and in only one patient, bleeding occurred for a few days, but it improved with time and continuous washing. These results indicate that tissue irritation or damage is negligible in patients treated with AOW. Therefore, tissue reaction to AOW seems to be rare. However, the effect of the solution on exposed vessels in the wound and other side effects are unknown at present. In this regard, Yamamoto et al.¹³ examined the effects of AOW in a rat model of peritonitis and confirmed the safety of AOW and the lack of organ injury. By our results, the clinical safety of AOW for surgical wounds was clarified.

In conclusion, the results of this study indicate that AOW shows the bacteriological effectiveness against several common bacteria, similar to povidone iodine. Furthermore, AOW is clinically useful and safe as a disinfectant for external use for the treatment of SSI. We expect a wide use of AOW particularly in hospitals because of its effectiveness, low cost, safety and ease of preparation.

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