Cardiovascular Catheterization Using New Antiseptic Agent Olanexidine Gluconate

CLINICAL STUDY

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Takahiro Matsumoto,[1,2] MD, Eiji Tamiya,[1] MD, Haruyo Yamashita,[1] MD, Tomosato Takabe,[1] MD, Akihito Nakajima,[3] MD, Shouichi Yamamoto,[1] MD, Shuko Nojiri,[4] PhD, Tatsuji Kanoh,[1] MD, Hiroyuki Daida,[2] MD

From the [1]Department of Cardiology, Koto Hospital, Tokyo, Japan, [2]Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan, [3]Department of Internal Medicine, Koto Hospital, Tokyo, Japan and [4]Medical Technology Innovation Center, Juntendo University, Tokyo, Japan.

Address for correspondence: Takahiro Matsumoto, MD, Department of Cardiology, Koto Hospital, 6-8-5, Ojima, Koto-ku, Tokyo, 136-0072, Japan. E-mail: matsuabc2020@outlook.jp

Summary

Olanexidine gluconate 1.5% (Olanedine®) is a colorless and transparent antiseptic agent introduced in 2015. In this study, we examined its usefulness and safety for cardiovascular catheterization and compared them to 10% povidone-iodine (PI). The study (Olanedine® and PI, respectively) was conducted on 1001 (1000) consecutively enrolled patients [649 (687) males; mean age: 72.1 ± 9.6 (70.9± 9.6) years] who underwent cardiovascular catheterization [diagnostic cardiac catheterization 624 (509) cases, percutaneous coronary intervention 288 (390) cases, and endovascular treatment 89 (101) cases]. Clinically, there were no significant differences in the backgrounds between the two groups. The amount of Olanedine® used per case was about 20mL. Blood tests were performed before and after catheterization. The presence or absence of discoloration on clothes containing cotton by Olanedine® was also examined. One mild rash which disappeared within one day occurred in each of the two groups. Some blood tests before and after cardiac catheterization showed significant differences, but they did not seem to be clinically relevant. The use of Olanedine® in hemodialysis patients (117 cases) was uneventful. Its use in 37 patients with contraindications for ethanol disinfection was also uneventful. While PI is extremely difficult to remove from white coats containing cotton, Olanedine® did not cause any discoloration on clothes. This is

the first report of cardiovascular catheterization using Olanedine®. The efficacy and safety of Olanedine® and PI seem to be equivalent. Olanedine® could be a new useful option as a disinfectant of cardiovascular catheterization.

Key words: Olanexidine gluconate, New antiseptic agent, Cardiovascular catheterization, Povidone iodine

Since September 2015, olanexidine gluconate (Olanedine®, Otsuka Pharmaceutical Factory, Tokushima, Japan) has been marketed as a 1.5% disinfectant solution, but there has been no report of its use in diagnostic and therapeutic cardiovascular catheterization.

Obara H, et al revealed the efficacy of Olanedine® (294 cases) on the reduction of superficial surgical site infection as well as the reduction of overall surgical site infection, without increasing toxicity, compared with aqueous povidone-iodine (PI), (293 cases) in clean-contaminated surgeries (esophagus, stomach, colon, liver, pancreas and so on).[1)]

PI is used as an antiseptic solution in diagnostic and therapeutic cardiovascular catheterization.[2)] However, PI takes a long time to wipe off after catheterization and dose not disappear when it adheres to the clothes. PI has been reported to be associated with

anaphylactic shock, and in some cases, its extensive use might lead to increased blood iodine level and thyroid dysfunction.[3-5] In addition, PI has been reported to cause burns when applied in large amounts.[6] Moreover, the iodine pigment has to be wiped off after surgery, but PI is difficult to remove from white coats.

Nakata, et al developed a new bactericidal biguanide compound, Olanedine® [1-(3,4-dichlorobenzyl)-5-octylbiganuide mono-D-gluconate] (Figure 1).[7] The efficacy of Olanedine® against methicillin-resistant Staphylococcus Aureus (MRSA) and vancomycin-resistant Enterococci (VRE) in both *in vitro* and *in vivo* animal models is higher than that of chlorhexidine gluconate (CHG) and PI, and Olanedine® has a broad spectrum of antibacterial activity against bacterial strains, including clinical isolates. The bacterial mechanism of Olanedine® differs from that of a similar biguanide compound, CHG.[8,9]

In this study, we examined the utility and safety of the use of colorless Olanedine® for diagnostic and therapeutic cardiovascular catheterization and compared them to PI.

Methods

The procedures followed were in accordance with the “Declaration of Helsinki” and the ethical standards of the responsible committee on human experimentation of Koto

Hospital (2017-10). All patients had a good understanding of the study and signed written informed consents. We examined the safety and efficacy of Olanedine® by comparing with PI.

The baseline characteristics of the study subjects using Olanedine® and PI are presented in Table I. The study using Olanedine® (PI) was conducted on 1001 (1000) consecutive patients [649 (687) males and 352 (313) females; mean age: 72.1 ± 9.6 (70.9± 9.6) years] who underwent diagnostic and therapeutic cardiovascular catheterization in our hospital between March 2018 and September 2019 (December 2016 and February 2018); their underlying diseases were as follows; diabetes in 523 (552) cases, hypertension in 731 (761) cases, dyslipidemia in 655 (701) cases, and chronic renal failure (hemodialysis) in 117 (127) cases.

The procedures using Olanedine® (PI) consisted of diagnostic cardiac catheterization in 624 (509) cases, percutaneous coronary intervention in 288 (390) cases, and endovascular treatment in 89 (101) cases. The amount of Olanedine® was as follows; approximately 15 mL for the radial artery (694 cases), approximately 15 mL for the brachial artery (149 cases), and approximately 25 mL for the femoral artery (158 cases). Blood tests for white blood cell count, and C-reactive protein, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, and creatinine levels were carried

out before and after diagnostic and therapeutic catheterization. Furthermore, the presence and severity of the rash, redness, and swelling at the disinfected site were examined.

The results of blood tests conducted before and after the procedure were compared using the paired *t*-test, and the level of significant difference was set at $p < 0.05$. Data were shown as medians and interquartile ranges. In addition, we checked whether the patients had contraindications for ethanol solution as a disinfectant. Furthermore, if the patients wore clothes containing cotton, the presence or absence of pigmentation on their clothes by Olanedine® was observed. Analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Clinically, there were no significant differences in the backgrounds between the Olanedine® group and the PI group (Table I). Table II shows the results of the blood tests using Olanedine® and PI before and after cardiovascular catheterization. One mild rash which disappeared within one day occurred in each of the two groups. Some blood tests before and after cardiac catheterization showed significant differences, but they did not seem to be clinically relevant. ~~Some blood tests showed significant differences, but they did not seem to be clinically relevant. A mild rash (which was not accompanied by itching~~

~~and which disappeared within one day) by Olanedine® was observed in one patient (0.10%). Of the 1000 consecutive cases using PI, skin rash occurred in one case.~~

Two patients in both groups had a mild rush (Olanedine®; a-62-year old male without diabetes mellitus, PI; a-78-year old female without diabetes mellitus). Both groups did not develop MRSA infection. The usage of Olanedine® in hemodialysis patients was also uneventful. In addition, because Olanedine® originally contained no pigment, it need not be wiped off after catheterization and does not cause any discoloration on the clothes containing cotton. Furthermore, there were 37 individuals with contraindications for ethanol disinfection, but the usage of Olanedine® was uneventful in all the cases.

Discussion

While PI is widely used as a preoperative disinfectant, it has also been reported to cause anaphylactic shock, thyroid dysfunction, and burn injury.[3-6] Furthermore, numerous studies have shown that PI is not always better than other disinfectants. PI and benzalkonium chloride disinfectants become inactivated or diluted over time, but benzalkonium chloride maintained a threshold concentration, and its antibacterial effect was longer lasting than that of PI. Thus, benzalkonium chloride is considered to exert antiseptic effect that is more prolonged than that of PI.[10]

Octenidine dihydrochloride 0.1% has the strongest antimicrobial activity against Staphylococcus aureus biofilms grown on vascular grafts; its antiseptic effect is superior to that of chlorhexidine combined with either PI or octenidine dihydrochloride.[11] Furthermore, preoperative hand washing is important in the prevention of surgical site infection. Originally, CHG and PI have been used for preoperative hand disinfection. There are also waterless hand rub products for the operating room staff. Studies have shown that waterless hand rub and CHG have a stronger antiseptic effect than that of PI.[12] The prevalence of surgical site infection is higher in gastrointestinal surgery than in other surgical procedures. According to the guidelines, CHG and PI have been found effective in reducing the rate of surgical site infection, but the optimal method of disinfection has not been established. In addition, previous studies have shown that the use of PI as a disinfectant in neonates and mothers before and after childbirth could cause hypothyroidism due to the iodine load; if hypothyroidism develops, it might not be diagnosed immediately, which might later cause a psychomotor developmental delay and learning disabilities.[13]

Furthermore, intravascular catheter-related infections are life-threatening, but their incidence can be reduced by improving skin disinfection. A previous study also showed that chlorhexidine alcohol for skin disinfection was more useful than PI alcohol against

catheter-related infections.[14)]

Meanwhile, Olanedine® is a new disinfectant developed in Japan, and it has anti-microbial activity against a wide range of gram-positive and gram-negative bacteria.[15)] In addition, PI attached to white coat containing cotton is extremely difficult to remove, but injectable phloroglucinol has been reported to be more effective than bleach or water in removing the stain.[16)] Moreover, Olanedine® is a disinfectant, which can be stored at room temperature, and is less cumbersome to use as only 15-25 mL of the solution needs to be poured from a 200-mL container into a sterilized beaker. The efficacy and safety of Olanedine® and PI seem to be equivalent. In our study, Olanedine® can be used as an extremely safe and useful disinfectant. Olanedine® showed more potent bactericidal activity against MRSA and VRE both *in vitro* and *in vivo* compared to PI and CHG.[8)] As the side effects of Olanedine®, Nagai, et al reported the first two cases of allergic contact dermatitis caused by Olanedine®.[17)] However, they appears to be clinically acceptable. The reason why the side effects of the PI group in our study were less was thought to be that the antiseptic field of the cardiovascular catheterization was narrow.

Conclusions

This is the first report of cardiovascular catheterization using Olanedine®. The efficacy and safety of Olanedine® and PI seem to be equivalent. Unlike PI, Olanedine® need not be wiped off after surgery and does not cause any discoloration on clothes. Olanedine® can also be used without any issues in patients with contraindications for ethanol disinfection.

Therefore, Olanedine® could be a new option among antiseptics for diagnostic and therapeutic cardiovascular catheterization.

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Disclosure

Conflicts of interest: None declared.

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Figure legends

Table I. Data are presented as number of patients (%), or as the mean ± standard deviation.

TableII. Data are presented as medians (interquartile range). WBC, white blood cell count; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, glutamyl transpeptidase; CRE, creatinine.

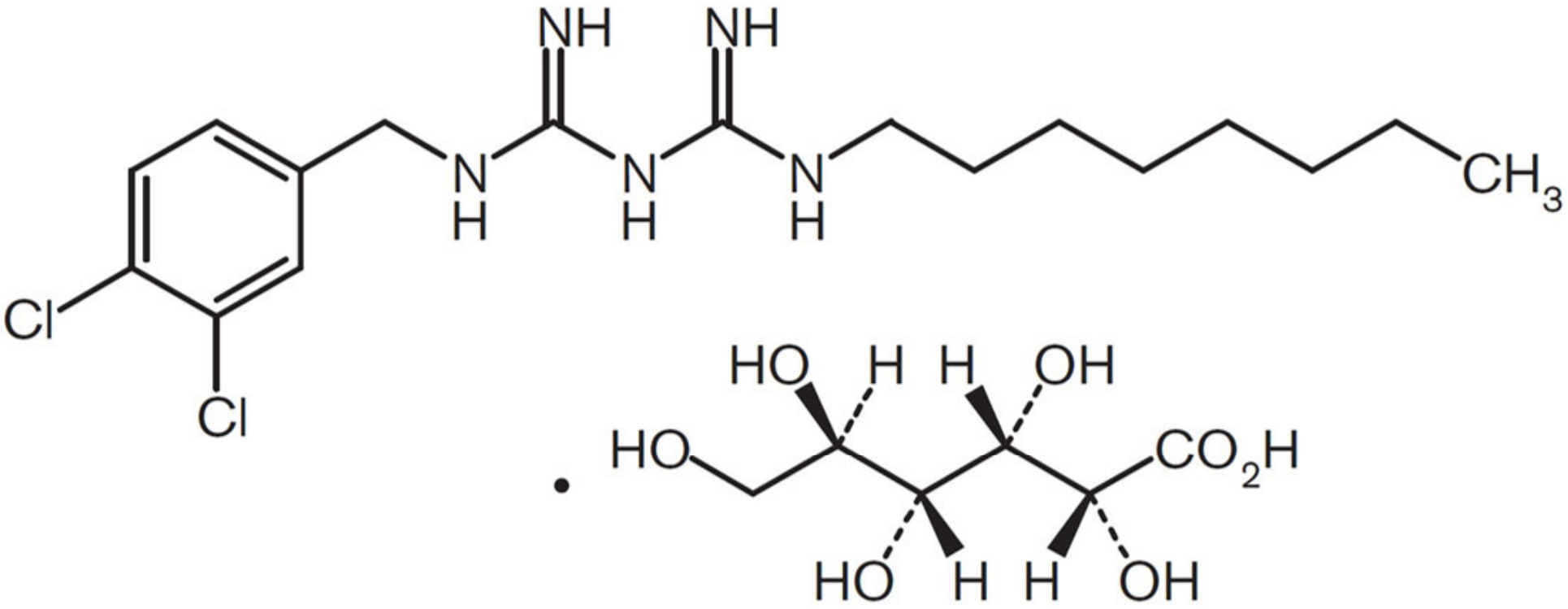
Figure 1. Chemical structure of olanexidine gluconate.

Table I.
Patient Characteristics

	Olanexidine (n = 1001)	Povidone-iodine (n = 1000)	p-value
Age, years	72.1 ± 9.6	70.9 ± 9.6	0.0016
Male	649 (64.8)	687 (68.7)	0.068
Hypertention	731 (73.0)	761 (76.1)	0.057
Diabetes mellitus	523 (52.2)	552 (55.2)	0.189
Dyslipidemia	655 (65.4)	701 (70.1)	0.0083
Hemodialysis	117 (11.7)	127 (12.7)	0.064
Procedures			
Diagnotic cardiac catheterization	624 (62.3)	509 (50.9)	
Percutaneous coronary intervention	288 (28.8)	390 (39.0)	<0.0001
Endovascular treatment	89 (8.9)	101 (10.1)	
Insertion site			
Radial artery	694 (69.3)	709 (70.9)	
Brachial artery	149 (14.9)	193 (19.3)	0.028
Femoral artery	158 (15.8)	98 (9.8)	

Table Ⅱ.
Result of the blood tests before and after cardiac cathetetrization

	Before	After	p-value
Olanexidine			
WBC ($\times 10^3 \mu L$)	6.21 (5.09-7.53)	6.40 (5.20-7.84)	0.011
CRP (mg/dL)	0.14 (0.06-0.41)	0.18 (0.07-0.64)	0.0005
AST (IU/L)	24 (17-42)	22 (16-38)	0.0005
ALT (IU/L)	21 (17-26)	20 (16-26)	0.283
γ-GTP (IU/L)	17 (12-25)	16 (11-24)	0.111
CRE (mg/dL)	0.89 (0.73-1.13)	0.87 (0.71-1.11)	0.113
Povidone-iodine			
WBC ($\times 10^3 \mu L$)	6.22 (5.23-7.44)	6.42 (5.27-7.84)	0.031
CRP (mg/dL)	0.15 (0.07-0.52)	0.20 (0.08-0.75)	0.005
AST (IU/L)	22 (18-28)	22 (18-28)	0.633
ALT (IU/L)	18 (13-27)	17 (12-26)	0.139
γ-GTP (IU/L)	27 (18-49)	27 (17-48)	0.705
CRE (mg/dL)	0.86 (0.68-1.13)	0.82 (0.67-1.14)	0.054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