Review Article

Clinical application of skin antisepsis using aqueous olanexidine: a scoping review

Yutaro Shinzato,† Eiryu Sakihara,† Yuki Kishihara, Masahiro Kashiura, Hideto Yasuda, and Takashi Moriya

Department of Emergency and Critical Care Medicine, Jichi Medical University Saitama Medical Center, Saitama, Japan

Abstract

Surgical site infections (SSIs) and catheter-related bloodstream infections (CRBSIs) caused by bacteria from surfaces poorly disinfected with chlorhexidine gluconate (CHG) and povidone-iodine (PVP-I) are increasing. Olanexidine gluconate (OLG) was developed in 2015 in Japan to prevent SSI and CRBSI caused by bacteria resistant to CHG and PVP-I. This scoping review aimed to identify the knowledge gap between what is known and what is not known about the disinfection efficacy of OLG. We searched MEDLINE through PubMed, the Cochrane Central Register of Controlled Trials, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the International Clinical Trials Registry Platform search database, ClinicalTrials.gov, and the Web-based database of Japanese medical articles for works published to July 18, 2021. Manual reference searches were also carried out. A total of 131 studies were screened. Forty-seven studies were included in this review and classified into two major categories: studies on pharmacological effects and spectrum (n = 29) and studies on clinical and adverse effects (n = 18). Olanexidine gluconate showed bactericidal activity against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, in addition to common Gram-positive and Gram-negative bacteria. In clinical settings, although there is limited evidence on SSI prevention, 1.5% OLG might be more effective than 10% PVP-I and 1% CHG in preventing SSI. However, the clinical usefulness of OLG is unclear due to the limited number of clinical studies. Also, clinical research is limited to studies targeting SSI prevention, and there are no clinical studies on CRBSI. Further clinical studies are needed on SSI and CRBSI prevention.

Key words: Catheter-related bloodstream infection, olanexidine, scoping review, skin antiseptic solution, surgical site infection

INTRODUCTION

MICROORGANISMS ON THE skin surface can cause various infections in hospital settings. Among such infections, surgical site infection (SSI) and catheter-related bloodstream infection (CRBSI) lead to higher mortality rates, longer hospital stays, and higher medical costs.[1–4]

Various disinfectants have been developed to prevent SSIs and CRBSIs. Regarding the balance between disinfection efficacy and adverse events, the guidelines of the Centers for Disease Control and Prevention and the National Institute for Health and Clinical Excellence recommend the use of alcohol-containing chlorhexidine gluconate (CHG).[5,6] Chlorhexidine gluconate use is associated with a lower incidence of CRBSI, when compared to the use of povidone-iodine (PVP-I) or alcohol.[7] Thus, CHG is recommended for CRBSI prevention.[8–11]

However, the occurrence of SSI and CRBSI caused by bacteria on surfaces that are poorly sterilized with CHG or PVP-I has been increasing in recent years.[5,10–13] Specifically, *Staphylococcus aureus* and *Enterococcus* species are the most common causative bacteria of SSIs and CRBSIs.[14,15] Clinical studies have shown that PVP-I is ineffective in disinfecting surfaces with enterococci, which include vancomycin-resistant enterococci (VRE).[16,17] Furthermore, the studies have reported the inefficacy of CHG in disinfecting surfaces with methicillin-resistant *S. aureus* (MRSA) and VRE.[18,19]

To prevent SSIs and CRBSIs caused by bacteria resistant to CHG and PVP-I, olanexidine [1-(3,4-dichlorobenzyl)-5-

†These authors contributed equally to this work.

Corresponding: Hideto Yasuda, MD, PhD, Department of Emergency and Critical Care Medicine, Jichi Medical University Saitama Medical Center, 1-847 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama, 330-0834, Japan. E-mail: yasudahideto@me.com

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octylbiguanide] gluconate (OLG) was developed in Japan in 2015. In vitro, OLG has a broad-spectrum, disinfecting, and fast-acting activity against drug-resistant bacteria.[20–25]

A randomized controlled trial (RCT) comparing the activity of OLG and PVP-I showed that OLG is superior to PVI in the prevention of SSIs.[26] Although some of the disinfection effects of OLG have been clarified, some aspects of the clinical use of OLG need clarification: whether OLG is more effective than CHG for skin disinfection, which is recommended for CRBSI and SSI prevention; whether CHG is effective in preventing non-SSI infections; and whether OLG is more effective than other disinfectants against resistant bacteria in clinical settings.

Therefore, we undertook a scoping review to clarify what is currently known and what remains unclear about OLG's disinfectant activity. Specifically, we focused on two points: OLG's pharmacological effect, including its spectrum and associated adverse events; and its clinical effects, including prevention of SSI and CRBSI. The results were summarized separately for each of these points.

METHODS

THE PRESENT SCOPING review included all studies on OLG, regardless of their design. The studies included in vitro studies of animals and humans, case reports, observational studies, and RCTs. Conference abstracts with unavailable full texts were excluded, due to insufficient information for this review. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.[27] We searched MEDLINE through PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the International Clinical Trials Registry Platform (ICTRP) search database, ClinicalTrials.gov, and the Web-based database of Japanese medical articles (Ichu-shi) for articles published to July 18, 2021. Manual reference searches were also undertaken as appropriate. When searching MEDLINE/CENTRAL/CINAHL, we used the following search terms: "olanexidine", "OPB-2045" (OPB; the development code of olanexidine), "olanedine", and "olanexidine gluconate". When searching Ichu-shi, the search terms used in the MEDLINE/CENTRAL/CINAHL search were translated into Japanese. There was no language restriction. The extracted studies were screened independently by two reviewers (ES and YS) to determine their eligibility for inclusion. Disagreements were discussed and resolved between the two reviewers. If the disagreement could not be resolved, the decision was left to a third reviewer (HY).

RESULTS

A TOTAL OF 131 studies (25 from PubMed, 13 from CENTRAL, 80 from Ichu-shi, six from CINAHL, two from the manual reference search, and five from ICTRP/ClinicalTrials.gov) were screened (Fig. 1, Table S1). Twenty-nine studies were excluded during the first screening (duplicates, 11; unavailable full text, 18). In the second screening that entailed a review of full texts, 50 studies were excluded: four in which OLG was not mentioned and 46 conference abstracts (Table S2). Finally, 47 studies were included in the review.

Forty-seven studies were classified into two major categories based on their focus areas: studies on pharmacological effects and spectrum (n = 29) and studies on clinical and adverse effects (n = 18). The studies on pharmacological effects and spectrum were animal or in vitro studies. The studies on clinical and adverse effects were human studies (Table 1).

In many studies, CHG and PVP-I used were formulated without alcohol. In studies in which CHG and PVP-I with alcohol were used, supplementary explanations were provided.

Pharmacology

Structural formula

Olanexidine gluconate is a biguanide antiseptic solution that was developed by Otsuka Pharmaceutical Factory, Inc. in 2015. To reduce skin irritation without decreasing its antimicrobial effect, the medicinal ingredient olanexidine (1-(3,4-dichlorobenzyl)-5-octylbiguanide [OPB-2045]) is converted to gluconate, and the solubilizer polyoxyethylene (20) polyoxypropylene (20) glycol (POEPOPG) is added to complete OPB.[23] The chemical formula is 1-(3,4-dichlorobenzyl)-5-octylbiguanide mono-D-gluconate[28] (Fig. 2).

Mechanism of action

There were four studies on bactericidal action[23,28–30] and one on the inhibitory action of inflammatory chemokines.[31]

Bactericidal action (in vitro/animal studies)

The mechanism underlying the bactericidal action of OLG differs between low and high concentrations, although the detailed mechanism has not been elucidated. At low concentrations (median effective dose [ED50], 8.4–25 μg/mL as the lower limit; no upper limit concentration), OLG has a higher affinity for bacterial surface proteins such as the lipoteichoic acid of Gram-positive bacteria and

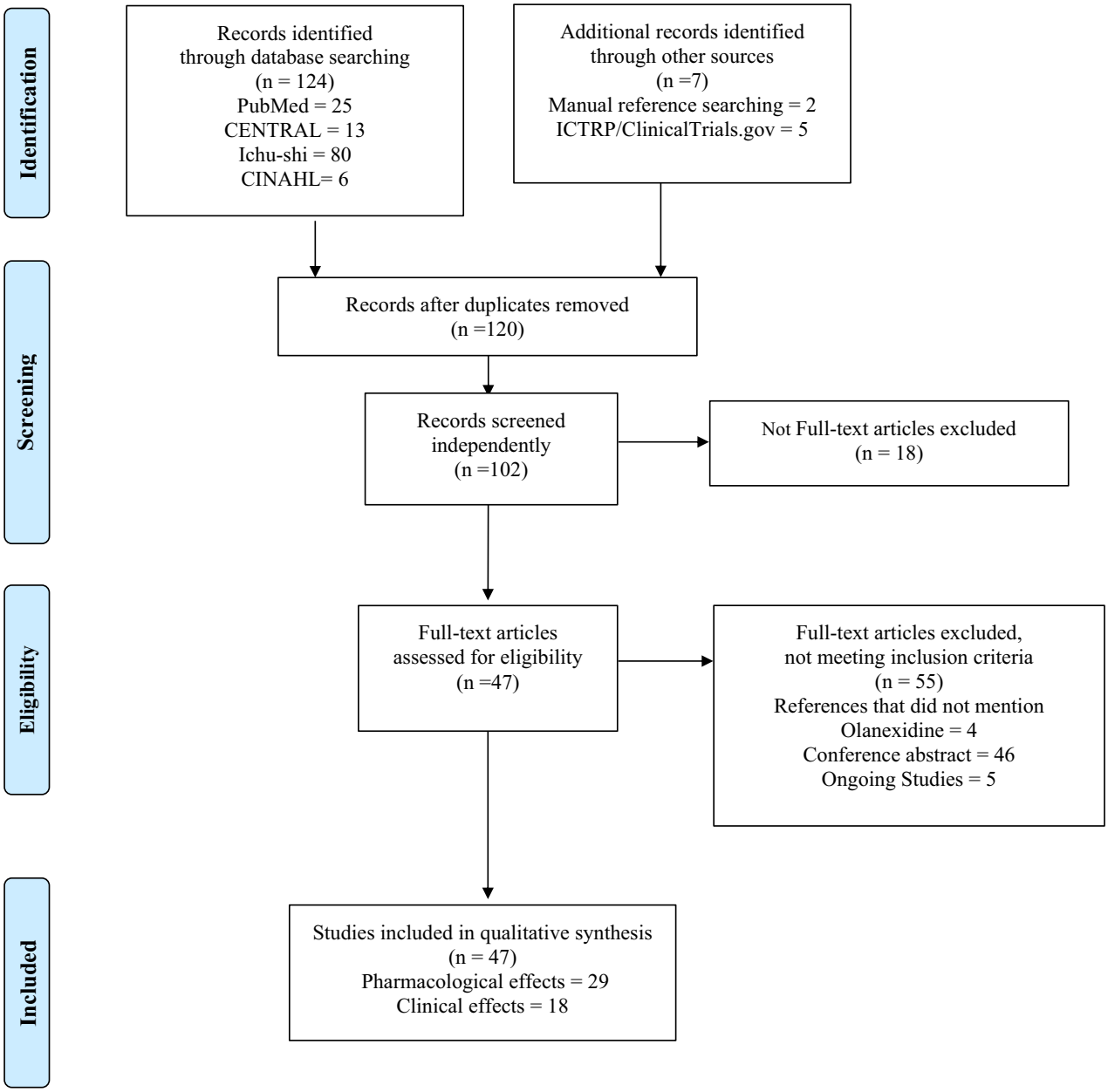

Fig 1. Flowchart of study screening and inclusion in the present scoping review of studies regarding the clinical application of skin antisepsis using olanexidine. CINAHL, Cumulative Index to Nursing and Allied Health Literature; ICTRP, International Clinical Trials Registry Platform.

lipopolysaccharide (LPS) of Gram-negative bacteria, compared to CHG with an ED50 of 27–610 μg/mL.[23] Similarly, for phospholipids such as lysyl-phosphatidylglycerol (L-PG) and phosphatidylethanolamine (PE), at a concentration higher than the minimal inhibitory concentration (0.63 μg/mL against Gram-positive bacteria and 4.0 μg/mL against Gram-negative bacteria), OLG had a stronger disruptive effect than CHG on membranes containing L-PG and PE.[23] These actions cause irreversible leakage of intracellular components, which leads to a bactericidal effect.[23] However, at high concentrations (>160 μg/mL), OLG showed a bactericidal effect by aggregating bacteria through a protein

Table 1. Summary of included studies that reported the clinical use of olanexidine gluconate (OLG)

No.	First author, year	Country	Design	Object	Intervention	Comparison	Outcomes	Main findings
Pharmacological effects								
1	Seyama et al. 2019[21]	Japan	In vitro	Microorganisms, containing clinical isolates	1.5% OLG	None	Viable bacterial count (CFU/mL) after 1.5% OLG administration using time-kill assay	• 1.5% OLG showed fast-acting fungicidal activity against all Gram-positive and Gram-negative bacteria tested, including multidrug-resistant strains, *Candida albicans*, *Microsporum canis*, and *Malassezia furfur*
2	Medical package insert[28]	Japan	In vitro animal study	Microorganisms, containing clinical isolates	1.5% OLG	None	MBC or $\log_{10}$ reduction	• Spectrum of 1.5% OLG against bacteria, viruses, and fungi is described based on the results of clinical trials undertaken by pharmaceutical companies
3	Imai et al. 2020[33]	Japan	In vitro	Norovirus (all 11 genotypes of GI, GII, and GIV)	OLG-HR (1.5%), 1.5% OLG, 0.5% OLG	EtOH, 0.1% benzalkonium chloride, 0.5% CHG	Log_{10} reduction	• Two types of disinfectants using OLG (hand sanitizer and surgical bandage), two types of ethanol solutions with different pH (approximately 3 and 7), and the base ingredient of OLG hand sanitizer were evaluated for their ability to kill 11 types of human noroviruses
4	Hagi et al. 2015[23]	Japan	In vitro	Microorganisms, containing clinical isolates	1.5% OLG	CHG (concentration unknown) PVP-I (concentration unknown)	MBC (μg/mL)	• MBC of OLG was low for both Gram-positive cocci and Gram-positive rods, including multidrug-resistant bacteria. The bactericidal spectrum of OLG was comparable to that of CHG and PVP-I • OLG probably binds to the cell membrane, disrupts membrane integrity, and its bacteriostatic and bactericidal effects are caused by irreversible leakage of intracellular components

Table 1. (Continued)

No.	First author, year	Country	Design	Object	Intervention	Comparison	Outcomes	Main findings
5	Inoue et al. 2015[25]	Japan	In vitro	Microorganisms, containing clinical isolates	1.5% OLG	None	MBC (μg/mL)	• Bactericidal efficacy of OLG against MRSA and VRE was compared with CHG and PVP-I using MBC as an indicator, and the bactericidal efficacy was equal or better
6	Nishioka et al. 2018[22]	Japan	In vitro animal study	Applied to the skin of the Yucatan micropig (culture collections)	1.5% OLG	0.5% CHG 10% PVP-I 1% CHG-AL	Log_{10} reduction at 30 s and 3 min	• OLG showed a fast-acting bactericidal activity that was similar to or stronger than that of CHG formulations up to a concentration of 1% and PVP-I with a short exposure time of 30 s, and substantivity until 12 h after rinsing, whereas the other antiseptics hardly showed any substantivity
7	Nakaminami et al. 2019[20]	Japan	In vitro	qacA/B-positive or negative MRSA	1.5% OLG	None	MBC50 (50% strain bactericidal) and MBC90 (90% strain bactericidal) (μg/mL)	• Fast-acting bactericidal activity of OLG against qacA/B-positive MRSA is higher than that of CHG
8	Nii et al. 2019[31]	Japan	In vitro	Human oral keratinocytes with the addition of LPS from *Porphyromonas gingivalis*	0.1% OLG	None	Degree of decrease in pro-inflammatory cytokines produced by human oral keratinocytes after application of 0.1% OLG	• Inflammatory cytokines, which cause chronic inflammatory reactions such as periodontitis, decreased after application of 0.1% OLG, suggesting that OLG could have anti-inflammatory effects
9	Imai et al. 2021[34]	Japan	In vitro	Influenza A (H1N1), human coronavirus OC43, feline infectious peritonitis virus, human herpesvirus, respiratory syncytial virus	OLG-HR (1.5%), 1.5% OLG, 0.5% OLG	EtOH, 0.1% benzalkonium chloride, 0.5% CHG)	Mean log_{10} reduction	• OLG-containing disinfectants are as effective as EtOH in disinfecting some viruses
10	Nakata et al. 2017[36]	Japan	In vitro animal study	Microorganisms from Male cynomolgus monkey's skin	1% OLG, 1.5% OLG, 2% OLG	0.5% CHG, 10% PVP-I and normal saline (as a negative control)	Bacterial count after 10 min and 6 h, and the log_{10} reduction after	• Bactericidal effects of OLG were comparable to those of commercial antiseptics such as CHG and PVP-I in non-

Table 1. (Continued)

No.	First author, year	Country	Design	Object	Intervention	Comparison	Outcomes	Main findings
				Applied to normal skin without any treatment to simulate a standard pre-surgical application, and dirty skin with blood			application of the antiseptic The bactericidal effect of the antiseptic on blood-contaminated skin	blood-contaminated conditions • Effect of OLG was hardly affected by blood, unlike commercial antiseptics
11	Sakagami et al. 2000[29]	Japan	In vitro	MRSA	OLG (concentration unknown)	None	MIC and MBC of OLG	• OLG showed strong bactericidal activity against MRSA • Marked decrease in MRSA cell numbers was recognized as the OLG concentration was increased
Pharmacological effects								
12	Umehara et al. 2000[40]	Japan	In vitro	Dog liver microsomes	OLG (concentration unknown)	None	Measurement of metabolites of OLG	• Olanexidine is likely to be mediated by the CYP2D subfamily in dog liver microsomes
13	Umehara et al. 2000[41]	Japan	In vitro	Rat and dog liver microsomes	OLG (concentration unknown)	None	Measurement of metabolites of OLG	• Degraded products of OPB-2045 are produced by C-C bond cleavage after monohydroxylation, dihydroxylation, and ketol formation at the site of the octyl side chain with possible involvement of cytochrome P450 systems
14	Sakagami et al. 2000[30]	Japan	In vitro	*Pseudomonas aeruginosa*	OLG (concentration unknown)	None	MIC and MBC of OLG	• OLG was bactericidal by acting on the cell membrane and cell wall of *Pseudomonas aeruginosa* at MIC • Bactericidal effect of OLG was different at low and high concentrations
15	Nakazawa et al. 2018[24]	Japan	In vitro	*Staphylococcus aureus*	1.5% OLG	20% CHG	MIC	• OLG has bactericidal effect against MRSA with qacA/B gene
16	Fujio et al. 2000[42]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Reproductive and developmental adverse events	• No effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development
17	Kudo et al.1998[38]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Measurement of metabolites absorbed subcutaneously	• OLG remained in the skin and was poorly absorbed

Table 1. (Continued)

No.	First author, year	Country	Design	Object	Intervention	Comparison	Outcomes	Main findings
18	Kudo et al. 1998[43]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Measurement of metabolites absorbed subcutaneously	• OLG remained in the skin and was poorly absorbed
19	Kudo et al. 1998[44]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Measurement of metabolites absorbed subcutaneously	• OLG remained in the skin and was poorly absorbed
20	Kudo et al. 1998[39]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Measurement of metabolites absorbed subcutaneously	• OLG remained in the skin and was poorly absorbed
21	Kudo et al. 1998[45]	Japan	Animal study	Beagle dogs	OLG (concentration unknown) subcutaneous administration	None	Measurement of metabolites absorbed subcutaneously	• OLG remained in the skin and was poorly absorbed
Pharmacological effects								
22	Kudo et al. 1998[46]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Reproductive and developmental adverse events	• No effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development
23	Takenaka et al. 1998[47]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Reproductive and developmental adverse events	• No effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development
24	Takenaka et al. 1998[48]	Japan	Animal study	Rabbits	OLG (concentration unknown) subcutaneous administration	None	Reproductive and developmental adverse events	• No effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development
25	Takenaka et al. 1998[49]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Reproductive and developmental adverse events	• No effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development
26	Takenaka et al. 1998[50]	Japan	Animal study	Rats	OLG (concentration unknown) subcutaneous administration	None	Reproductive and developmental adverse events	• No effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development

Table 1. (Continued)

No.	First author, year	Country	Design	Object	Intervention	Comparison	Outcomes	Main findings
27	Hosoya et al. 2016[32]	Japan	Gray paper	None	None	None	None	• Brief description of the bactericidal action of OLG and the results of clinical trials
28	Oie 2019[69]	Japan	Gray paper	None	None	None	None	• OLG has the advantages of less dripping and nonflammability. However, OLG is expensive
29	Taketomi 2015[70]	Japan	Gray paper	None	None	None	None	• OLG product features were described
Clinical effects								
30	Harihara et al. 2015[52]	Japan	RCT	Adults	1.5% OLG	Placebo 0.5% CHG	Bacteria count after 10 min of application	• Rate of adverse events in 1.5% OLG, 0.5% CHG, and placebo • Rate of adverse events in 1.5% OLG and 10% PVP-I
31	Obatake et al. 2020[51]	Japan	Not mentioned	Children	OLG (concentration unknown)	None	Disinfection effect after 10 min of application	• Evaluation after 10 min of application of OLG to normal skin revealed good disinfection effect
32	Nagai et al. 2000[53]	Japan	RCT	Adults	OLG (0.02%, 0.05%, 0.1%, 0.2%)	CHG (0.05%, 0.5%)	Exponential reduction value of total viable bacteria before and after application	• OLG was found to be more effective than CHG in reducing skin bacteria after 30 s and 3 min of application to normal skin
33	Kobayashi et al. 2000[54]	Japan	Not mentioned	Adults	0.05% OLG	None	Wound infection prevention and disinfection effects	• Application of 0.05% OLG to wounded skin was found to be effective in preventing wound infection and disinfection
34	Matsumoto et al. 2018[58]	Japan	Retrospective study	Adults	OLG (concentration unknown)	None	SSI incidence rate at 30 days postoperatively	• OLG was effective in preventing surgical site infection
35	Harihara et al. 2020[57]	Japan	Retrospective study	Adults	1.5% OLG (applicator)	10% PVP-I 1% CHG	All SSI incidence rates Adverse events	• Incidence rate of SSI in gastrointestinal surgery was found to be lower in 1.5% OLG • Incidence rate of rash was found to be higher with OLG compared to PVP-I
36	Obara et al. 2020[26]	Japan	RCT	Adults	1.5% OLG	10% PVP-I	30-day postoperative SSI rate	• 30-day postoperative SSI rate in semiclean gastrointestinal surgery was found to be lower in 1.5% OLG than 10% PVP-I

Table 1. (Continued)

No.	First author, year	Country	Design	Object	Intervention	Comparison	Outcomes	Main findings
37	Shiyanagi et al. 2019[56]	Japan	Retrospective study	Children	1.5% OLG (applicator)	10% PVP-I	All SSI incidence rates	• Incidence rate of SSI in clean surgery was found to be low for 1.5% OLG and 10% PVP-I
38	Yamamoto et al. 2020[55]	Japan	RCT	Adults	Single application OLG applicator (concentration unknown)	Double applications OLG applicator (concentration unknown)	30-day postoperative incisional SSI rate	• No difference in the incidence of SSI at 30 days postoperatively between single and double applications of OLG
39	Sugai, 1999[65]	Japan	Not mentioned	Adults	OLG (0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%)	Placebo	Adverse events	• Adverse events resulting from the application of OLG to healthy adults
Pharmacological effects								
40	Sugai, 1999[66]	Japan	Not mentioned	Adults	OLG (0.1%, 0.5%)	None	Adverse events	• Adverse events resulting from the application of OLG to healthy adults
41	Sugai, 1999[67]	Japan	Not mentioned	Adults	0.1% OLG 0.5% OLG	None	Adverse events	• Adverse events resulting from the application of OLG to healthy adults
42	Sugai, 1999[68]	Japan	Not mentioned	Adults	OLG (0.005%, 0.01%, 0.03%, 0.05%, 0.1%)	Placebo	Adverse events	• Adverse events resulting from the application of OLG to healthy adults
43	Obara et al. 2020[26]	Japan	RCT	Adults	1.5% OLG	Placebo 0.5% CHG	Adverse events	• Rate of adverse events in 1.5% OLG and 10% PVP-I
44	Shiyanagi et al. 2019[56]	Japan	Retrospective study	Adults	1.5% OLG	10% PVP-I	Adverse events	• Rate of adverse events in 1.5% OLG and 10% PVP-I
45	Matsuoka et al. 2019[60]	Japan	Retrospective study	Adults	1.5% OLG	PVP-I (concentration unknown)	Adverse events	• Incidence rate of chemical burn was found to be lower with 1.5% OLG compared to 10% PVP-I
46	Iijima et al. 2020[59]	Japan	Case report	34 y.o. woman	OLG (concentration unknown)	None	Adverse events	• Erythma and pruritus appeared on day 10 after OLG application
47	Nagai et al. 2018[61]	Japan	Case report	65 y.o. man 64 y.o. woman	OLG (concentration unknown)	None	Adverse events	• Erythma appeared after day 6 of OLG application

Abbreviations: CFU, colony forming unit; CHG, chlorhexidine gluconate; CHG-AL, clorhexidine gluconate alcohol; EtOH, ethanol; LPS, lipopolysaccharide; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; OLG-HR, OLG/ethanol hand rub; PVP-I, povidone-iodine; RCT, randomized controlled trial; SSI, surgical site; VRE, vancomycin-resistant enterococci.

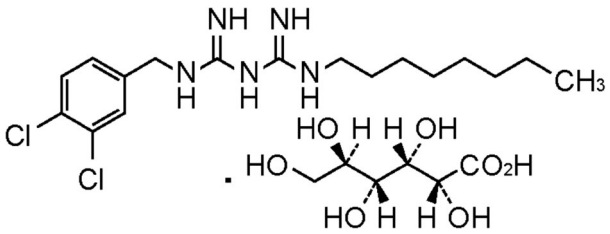

Fig 2. Chemical structure of olanexidine.

denaturation effect[23,28] (with olanexidine at a concentration of 15 000 μg/mL), which means that it has both low and high concentration effects.

Inhibitory action of inflammatory chemokines (in vitro)

In addition to the bactericidal effects of OLG, it is reported that OLG has an inhibitory action on inflammatory chemokines. Nii et al. administered the LPS of *Porphyromonas gingivalis* to immortalized human oral keratinocytes, which are regarded as oral epithelial cells, and tested whether the inflammatory cytokines produced by human oral keratinocytes decreased after 0.1% OLG application. The levels of inflammatory cytokines such as interleukin-8, chemokine (C-C motif) ligand 20, and growth-regulated oncogene protein-α, which cause chronic inflammatory reactions such as periodontitis, decreased after 0.1% OLG application. This suggests that OLG could inhibit the inflammatory response.[31]

Spectrum (in vitro)

Nine studies validated the spectrum: seven for bacteria and fungi[20–25,28] and four for viruses.[28,32–34] Several studies[20,23,25,28] used the minimum bactericidal concentration (MBC) at which bacterial growth did not occur as an indicator of the bactericidal effect of skin disinfectants.

Bacteria Seyama et al. undertook a study[21] to examine the bactericidal effect of 1.5% OLG on Gram-positive cocci, including MRSA and VRE, Gram-negative bacteria (*Burkholderia cepacia* and *Pseudomonas aeruginosa*), and fungi. The number of most Gram-positive cocci, including MRSA and VRE, reduced within 15 s after 1.5% OLG application (Table 2).

For MRSA, two studies showed that 1.5% OLG was more effective for disinfection than 0.5% CHG and 10% PVP-I (Table 3).[22,25] In addition, two studies[20,24] compared whether the MBC of OLG, CHG, and PVP-I changed in the presence or absence of *qacA/B*, which encodes a disinfectant efflux pump thought to be responsible for methicillin resistance. The researchers reported that only the MBC of OLG remained unchanged in the presence or absence of *qacA/B* (Table 3).

However, 1.5% OLG was more effective in disinfection against VRE than 0.5% CHG and 10% PVP-I.[22,25] Inoue et al.[25] also compared the MBC of OLG, CHG, and PVP-I against MRSA and VRE: the MBC of OLG against MRSA and VRE was equal to or lower than that of CHG or PVP-I (Table 3).

Regarding the bactericidal effect on resistant bacteria other than MRSA and VRE, such as methicillin-resistant *Staphylococcus epidermidis*, extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*, and multidrug-resistant *P. aeruginosa*, 1.5% OLG killed these bacteria within 15 s after 1.5% OLG application[21] (Table 3). However, *B. cepacia* was not eliminated more than 30 min after 1.5% OLG application,[21,23] and the bactericidal effect of 1.5% OLG on *B. cepacia* was comparable to those of CHG and PVP-I (concentrations unknown) reported in a previous study.[12] Furthermore, 1.5% OLG had a poor bactericidal effect on Mycobacterium, consistent with the previously reported bactericidal effect of CHG (concentration unknown).[21,35]

Fungi Surfaces contaminated with *Candida albicans* and *Malassezia furfur* were disinfected within 30 s after 1.5% OLG application, whereas those contaminated with *Microsporum canis* and *Trichophyton rubrum* were disinfected within 3 and 10 min, respectively, after 1.5% OLG application.[21] However, *Aspergillus brasiliensis* was not eliminated even after 10 min of 1.5% OLG application[21] (Table 2).

Viruses Influenza A virus, which has an envelope, was inactivated by 1.5% OPB for more than 1 min after application. However, feline calicivirus, which does not have an envelope, was not inactivated even 10 min after application.[28]

In addition, Imai et al.[33] reported on the efficacy of OLG hand rub against 11 genotypes of noroviruses, in which ethanol was added to OLG (concentration unknown) for hand disinfection. The OLG hand rub had the highest antiviral effect, when compared to other agents (ethanol [pH 7], ethanol-A [pH 3], and OLG), suggesting its potential for use as a hand sanitizer (Table 2). Imai et al.[34] also reported on the potential usage of OLG formulations as environmental disinfectants for the control of infections by enveloped viruses (influenza A [H1N1], human coronavirus, feline infectious peritonitis virus, human herpesvirus, and respiratory syncytial virus).

Immediate and sustained bactericidal action (in vitro/animal studies)

Four studies were identified: three on the time-to-onset of bactericidal action[20–22] and two on the duration of bactericidal action.[22,36]

Table 2. Antimicrobial spectrum of olanexidine gluconate (OLG)

First author, year	Microorganism	Method	Time and indicator	Result
Effective				
Bacteria				
Seyama et al. 2019[21]	Gram-positive bacterium *Enterococcus faecalis* Vancomycin-resistant enterococci *Staphylococcus aureus* Methicillin-resistant *Staphylococcus aureus* *Staphylococcus epidermidis* Methicillin-resistant *Staphylococcus epidermidis*	Evaluation of bactericidal effect by time kill assay (<10, detection limit)	Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, and 1 min after 1.5% OLG administration	15 s: <10 30 s: <10 1 min: <10 1 min: <10 15 s: <10 30 s: <10 1 min: <10
	Gram-negative bacterium *Acinetobacter baumannii* *Enterobacter cloacae* Extended spectrum β-lactamase producing *Klebsiella pneumoniae* *Escherichia coli* *Pseudomonas aeruginosa* Multidrug-resistant *Pseudomonas aeruginosa* *Serratia marcescens* *Bacteroides fragilis*	Evaluation of bactericidal effect by time kill assay (<10, detection limit)	Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, 1 min after 1.5% OLG administration	15 s: <10 30 s: <10 1 min: <10
Fungi				
Seyama et al. 2019[21]	*Candida albicans* *Malassezia furfur* *Trichophyton rubrum* *Microsporum canis*	Evaluation of bactericidal effect by time kill assay (<10, detection limit)	Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, and 1 min after 1.5% OLG administration	30 s: <10 10 min: <10 10 min: <10 3 min: <10 10 min: <10
Virus				
Medical package insert[28]	Influenza A	No detailed description	No detailed description	Inactivation in 1 min or more
Imai et al. 2021[34]	Influenza A (H1N1)	Suspension test (comparison agents: OLG-HR [1.5%], 1.5% OLG, 0.5% OLG, EtOH, 0.1% benzalkonium chloride, 0.5% CHG)	Mean $\log_{10}$ reduction ± 95% CI at 15 s, 30 s, 1 min	1.5% OLG, OLG-HR, and EtOH completely inactivated at all time
Imai et al. 2020[33]	Norovirus (all 11 genotypes of GI, GII, and GIV)	Assay $\log_{10}$ RNA copies by RT-qPCR (comparison agents: OLG-HR, EtOH [pH 7], EtOH-A [pH 3], OLG, base with OLG removed from OLG-HR)	Log_{10} reduction at 30 s, 1 min	30 s: $\log_{10}$ reduction of OLG-HR is the highest 1 min: $\log_{10}$ reduction of OLG-HR is the highest

Table 2. (Continued)

First author, year	Microorganism	Method	Time and indicator	Result
Imai et al. 2021[34]	Human coronavirus OC43	Suspension test (comparison agents: OLG-HR [1.5%], 1.5% OLG, 0.5% OLG, EtOH, 0.1% benzalkonium chloride, 0.5% CHG)	Mean $\log_{10}$ reduction ± 95% CI at 15 s, 30 s, and 1 min	Viral titers after exposure to 0.5% OLG, 1.5% OLG, OLG-HR, and EtOH for 15 s were under the quantification limits
	Feline infectious peritonitis virus			1.5% OLG, OLG-HR, and EtOH completely inactivated at all time
	Human herpesvirus			Viral titers were under the quantification limits at all time
	Respiratory syncytial virus			
Not effective				
Bacterium				
Seyama et al. 2019[21]	*Burkholderia cepacia*	Evaluation of bactericidal effect by time kill assay (<10, detection limit)	Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, and 1 min after 1.5% OLG administration	At all time points: not killed
Seyama et al. 2019[21]	Mycobacterium *Mycobacterium kansasii* *Mycobacterium intracellulare* *Mycobacterium fortuitum* *Mycobacterium chelonae* *Mycobacterium abscessus* *Mycobacterium avium*	Evaluation of bactericidal effect by time kill assay (<10, detection limit)	Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, 1 min, 60 min after 1.5% OLG administration	At all time points: not killed
Fungi				
Seyama et al. 2019[21]	*Aspergillus brasiliensis*	Evaluation of bactericidal effect by time kill assay (<10, detection limit)	Viable bacterial count (CFU/mL) at 0 s, 15 s, 30 s, and 10 min after 1.5% OLG administration	At all time points: not killed
Medical package insert[28]		No detailed description	MBC (%) at 30 min	30 min: not killed
Medical package insert[28]	*Microsporum canis*	No detailed description	MBC (%) at 30 min	30 min: not killed
Virus				
Medical package insert[28]	*Feline calicivirus*	No detailed description	Log_{10} reduction (only mentioned at 10 min)	10 min: not killed

Note: All studies are in vitro and animal studies.
Abbreviations: CFU, colony forming unit; CHG, chlorhexidine gluconate; CI, confidence interval; EtOH, ethanol; MBC, minimum bactericidal concentration; OLG-HR, olanexidine gluconate/ethanol hand rub; RT-qPCR, reverse transcription–quantitative polymerase chain reaction.

Table 3. Comparison of the bactericidal effects of olanexidine gluconate (OLG), chlorhexidine gluconate (CHG), and povidone-iodine (PVP-I)

First author, year	Microorganism	Object	Time and indicator	Concentration of OLG	Comparison (concentration)	Result
Gram-positive bacterium						
Hagi et al. 2015[23]	Methicillin-susceptible *Staphylococcus aureus*	Clinical isolates (30 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of PVP-I was the lowest (OLG, >3,480; PVP-I, 1,560) 1 min: MBC of PVP-I was the lowest (OLG, >1,740; PVP-I, 781) 3 min: MBC of CHG was the lowest (OLG, 869; CHG, 156)
Inoue et al. 2015[25]	Methicillin-resistant *Staphylococcus aureus*	Culture collections (1 strain)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was equal to that of PVP-I and lower than that of CHG 1 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG 3 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG
		Clinical isolates (30 strains)				30 s: MBC of PVP-I was the lowest (OLG, >3,475; PVP-I, 1,563) 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest
		Applied to the skin of mice (culture collections)	Log of the number of survived bacteria at 30 s, 3 min, and 10 min	1.5%	0.5% CHG 10% PVP-I	30 s: Log of the number of survived bacteria of 1.5% OLG was the lowest 3 min: Log of the number of survived bacteria of 1.5% OLG was equal to that of 10% PVP-I and lower than that of 0.5% CHG 10 min: Log of the number of survived bacteria of 1.5% OLG was equal to that of 10% PVP-I and lower than that of 0.5% CHG
Nishioka et al. 2018[22]		Applied to the skin of the Yucatan micropig (culture collections)	Log_{10} reduction at 30 s and 3 min	1.5%	0.5% CHG 10% PVP-I 1% CHG-AL	30 s: log_{10} reduction of 1.5% OLG was equal to that of 1% CHG-AL and higher than those of 0.5% CHG and 10% PVP-I 3 min: log_{10} reduction of 1.5% OLG was equal to that of 1% CHG-AL and higher than those of 0.5% CHG and 10% PVP-I

Table 3. (Continued)

First author, year	Microorganism	Object	Time and indicator	Concentration of OLG	Comparison (concentration)	Result
Nakaminami et al. 2019[20]		Clinical isolates (19 *qacA/B*-positive strains and 10 qacA/B-negative strains)	MBC50 (50% strain bactericidal) and MBC90 (90% strain bactericidal) (μg/mL) at 2 min, 5 min and 30 min	Unknown	CHG (unknown) PVP-I (unknown)	2 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG 5 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG 30 min: MBC of OLG was equal to that of PVP-I and lower than that of CHG MBC of OLG was the same with or without *qacA/B*
Hagi et al. 2015[23]	Coagulase-negative *Staphylococcus*	Clinical isolates (20 strains)	MBC (μg/mL) at 30 s, 1 min, and 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest
Nishioka et al. 2018[22]	*Staphylococcus epidermidis*	Applied to the skin of the Yucatan micropig (culture collections)	Log_{10} reduction at 30 s and 3 min	1.5%	0.5% CHG 10% PVP-I 1% CHG-AL	30 s: log_{10} reduction of 1.5% OLG was equal to those of 1% CHG-AL and 10% PVP-I. Log_{10} reduction of 1.5% OLG was higher than that of 0.5% CHG 3 min: log_{10} reduction of 1.5% OLG was equal to those of 1% CHG-AL and 10% PVP-I. Log_{10} reduction of 1.5% OLG was higher than that of 0.5% CHG
Hagi et al. 2015[23]	*Enterococcus* spp.	Culture collections (34 strains)	MBC (μg/mL) at 30 s, 1 min, and 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest
Hagi et al. 2015[23]	*Enterococcus faecalis*	Clinical isolates (30 strains)	MBC (μg/mL) at 30 s, 1 min, and 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest
Inoue et al. 2015[25]		Clinical isolates (30 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OL G was the lowest 3 min: MBC of OLG was the lowest
Inoue et al. 2015[25]	*Vancomycin-resistant*	Culture collections (1 strain)	MBC (μg/mL) at 30 s, 1 min, and 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest

Table 3. (Continued)

First author, year	Microorganism	Object	Time and indicator	Concentration of OLG	Comparison (concentration)	Result
	Enterococcus faecalis	Applied to the skin of mice (culture collections)	Log of the number of survived bacteria at 30 s, 3 min, and 10 min	1.5%	0.5% CHG 10% PVP-I	30 s: Log of the number of survived bacteria of 1.5% OLG was the lowest 3 min: Log of the number of survived bacteria of 1.5% OLG was the lowest 10 min: Log of the number of survived bacteria of 1.5% OLG was the lowest
Nishioka et al. 2018[22]		Applied to the skin of the Yucatan micropig (culture collections)	Log_{10} reduction at 30 s and 3 min	1.5%	0.5% CHG 10% PVP-I 1% CHG-AL	30 s: log_{10} reduction of 1.5% OLG was equal to that of 1% CHG-AL. Log_{10} reduction of 1.5% OLG was higher than those of 0.5% CHG and 10% PVP-I 3 min: log_{10} reduction of 1.5% OLG was equal to those of 1% CHG-AL and 0.5% CHG. Log_{10} reduction of 1.5% OLG was higher than that of 10%PVP-I
Hagi et al. 2015[23]	Gram-positive bacilli	Culture collections (9 strains)	MBC (μg/mL) at 30 s, 1 min, and 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of PVP-I was the lowest (OLG, 1,740; PVP-I, 781) 1 min: MBC of PVP-I was the lowest (OLG, 1,740; PVP-I, 781) 3 min: MBC of OLG was the lowest
Gram-negative bacterium						
Hagi et al. 2015[23]	Gram-negative strains except *Burkholderia cepatcia*	Culture collections (34 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest
	Burkholderia cepacia	Culture collections (2 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of PVP-I was the lowest (OLG, >6,950; PVP-I, 391) 1 min: MBC of PVP-I was the lowest (OLG, >6,950; PVP-I, 391) 3 min: MBC of PVP-I was the lowest (OLG, 434; PVP-I, 195)
	Escherichia coli	Clinical isolates (20 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest

Table 3. (Continued)

First author, year	Microorganism	Object	Time and indicator	Concentration of OLG	Comparison (concentration)	Result
	Klebsiella pneumoniae	Clinical isolates (20 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest
	Pseudomonas aeruginosa	Clinical isolates (20 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of PVP-I was the lowest (OLG, 869; PVP-I, 781) 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest MBC
	Serratia marcescens	Clinical isolates (20 strains)	MBC (μg/mL) at 30 s, 1 min, 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of PVP-I was the lowest (OLG, 3,480; PVP-I, 391) 1 min: MBC of PVP-I was the lowest (OLG, 434; PVP-I, 391) 3 min: MBC of OLG was the lowest
Hagi et al. 2015[23]	*Acinetobacter baumannii*	Clinical isolates (20 strains)	MBC (μg/mL) at 30 s, 1 min, and 3 min	Unknown	CHG (unknown) PVP-I (unknown)	30 s: MBC of OLG was the lowest 1 min: MBC of OLG was the lowest 3 min: MBC of OLG was the lowest
Nishioka et al. 2018[22]		Applied to the skin of the Yucatan micropig (culture collections)	Log_{10} reduction at 30 s and 3 min	1.5%	0.5% CHG 10% PVP-I 1% CHG-AL	30 s: log_{10} reductions of all skin antiseptics were equivalent 3 min: log_{10} reductions of all skin antiseptics were equivalent

Note: All studies are in vitro and animal studies.
Abbreviations: CFU, colony forming unit; MBC, minimum bactericidal concentration.

Immediate efficacy (in vitro/animal studies)

As mentioned in the section on spectrum, 1.5% OLG showed a disinfectant effect on a wide range of bacteria within 30 s (Tables 2 and 3). Furthermore, Nishioka et al.[22] compared the bacterial counts of MRSA, *S. epidermidis*, VRE, *Acinetobacter baumannii*, *Corynebacterium minutissimum*, and *Cutibacterium acnes*, which were problematic in SSI, while comparing 1.5% OLG with 0.5% CHG and 10% PVP-I. Compared to 10% PVP-I and 0.5% CHG, 1.5% OPB showed an equivalent or greater reduction in bacterial counts 30 s after application.

Substantivity (animal studies)

Nishioka et al.[22] discussed the amount of disinfectant left in the stratum corneum after 4, 8, and 12 h of rinsing immediately after application. The concentration of 1.5% OLG left was 2.8–4.2 times higher in the stratum corneum than that of 1.5% CHG at all incubation times. This indicated that the rate of washout for 1.5% OLG was lower than that for 1.5% CHG. The proportion of bacteria after 12 h of 1.5% OLG application was lower than that after 4 and 8 h, indicating that the bactericidal action time was approximately 12 h. Regarding the long action time of OLG, the reduced effectiveness of disinfectants was generally attributed to sweating and contamination with blood.[37] Nakata et al.[36] evaluated the effectiveness of reducing bacteria after 10 min and 6 h of application of 0.5% CHG, 10% PVP-I, and 1.5% OLG on blood-contaminated monkey skin. The decrease in bacterial count after 1.5% OLG application was higher than that after the application of 0.5% CHG or 10% PVP-I, indicating that the decrease in bactericidal action with blood contamination was smallest after 1.5% OLG application, compared to 0.5% CHG and 10% PVP-I.[36]

Pharmacokinetics (animal studies)

Thirteen studies on pharmacokinetics were identified: three on dermal absorption,[22,38,39] eight on metabolism and excretion,[38,40–46] and five on biogenesis.[42,47–50]

Concerning dermal absorption, Kudo et al. reported two studies: one in which the radioactivity at the injection site was measured at 1, 8, and 24 h after dermal administration of biguanide ^{14}C-labeled OLG (concentration unknown) in rats[38] and another in which the dermal absorption of 0.1% OLG after the application was measured in intact and damaged rat skin.[39] Olanexidine gluconate remained in the skin and was poorly absorbed in both studies. Regarding reproduction and development, Fujio et al. and Takenaka et al.[42,47–50] carried out animal experiments on rats and rabbits. Parental animals treated subcutaneously with 0.04%–0.0004% OLG showed no effect of the drug application on the estrus cycle of female rats, fertilization rate, nursery condition of mothers after birth, and all cycles up to fetal development.

Clinical setting

Considering that the balance between the benefits and disadvantages is important for clinical adaptation, we provide a description of the efficacy and safety.

Efficacy

Normal skin

Three studies were undertaken on normal skin.[51–53] Two of the studies were RCTs. Two studies included adults, and one study included children. One study compared 1.5% OLG, 0.5% CHG, and placebo.[51] One study compared OLG with CHG; the concentration of OLG ranged from 0.02% to 0.2%, and that of CHG ranged from 0.05% to 0.5%.[53] One study determined the efficacy of OLG (concentration unknown) without a comparator[51] (Table 4).

In an RCT that assessed the efficacy of 1.5% OLG on normal skin,[52] OLG showed a significant reduction in bacterial counts after 10 min of application on both the abdomen and groin, compared to placebo. Furthermore, 1.5% OLG was not inferior to 0.5% CHG. Obatake et al.[51] collected samples from the skin (groin and umbilicus) both before and after disinfection with OLG (concentration unknown) and compared the presence or absence of bacteria. It was reported that OLG had a good bactericidal effect on both the groin and umbilical areas; however, specific data were unavailable. In a comparison of the number of viable bacteria before and after disinfection with various concentrations of OLG and CHG,[53] both after 30 s and 3 min of disinfectant application, the exponential reduction in total viable bacterial counts was higher in the OLG groups than in the CHG groups at all concentrations.

Wounded skin

One study[54] evaluated wounded skin. The study population consisted of 50 adult inpatients who underwent clean or semiclean surgical procedures (Table 4). The researchers applied 0.05% OLG to surgically sutured wounds on postoperative days 3, 7, and 14. No antiseptics were used for comparison. The efficacy rate determined by infection prevention and disinfection efficacy was 59.6% (95% confidence interval, 44.4–73.6). The efficacy was adjudged comprehensively based on progress after application and was not described in detail.

Table 4. Effect of olanexidine gluconate (OLG) on normal skin and wounded skin

First author, year	Design	Object	Intervention	Comparison	Efficacy
Effect of OLG on normal skin					
Harihara et al. 2015[52]	RCT	Adults; region: abdomen, groin	1.5% OLG 237 cases	Placebo 119 cases 0.5% CHG 236 cases	Item: bacteria count after 10 min of application Result: (OLG vs. placebo) 1.5% OLG < placebo (OLG vs. CHG) 1.5% OLG is noninferior to 0.5% CHG
Obatake et al. 2020[51]	Not mentioned	Children; region: umbilicus, groin	OLG (concentration unknown), 20 cases	None	Item: disinfection effect after 10 min of application Result: good bactericidal effect
Nagai et al. 2000[53]	RCT	Adults; region: back	OLG (concentration: 0.02%, 0.05%, 0.1%, and 0.2%) Total 30 cases	CHG (concentration: 0.05% and 0.5%) Total 30 cases	Item: exponential reduction value of total viable bacteria before and after application Result: 30 s after application CHG (0.05%, 0.5%) < OLG (0.05%, 0.1%, 0.2%) 3 min after application CHG (0.05%) < OLG (0.1%, 0.2%)
Effect of OLG on wounded skin					
Kobayashi et al. 2000[54]	Not mentioned	Adults; sutured skin wound after surgical operation	0.05% OLG 50 cases Application period: immediately after suture and postoperative days 3, 7, and 14	None	Item: wound infection prevention and disinfection effects Result: 59.6%

Note: All studies are in vivo and human studies.
Abbreviation: RCT, randomized controlled trial.

Prevention of SSI

Five studies evaluated the effect on SSI prevention.[26,55–58] Two studies were RCTs, and three were retrospective observational studies. One study included children, and the remaining four studies included adults. One study compared OLG, PVP-I, and CHG,[57] two studies compared OLG to PVP-I,[26,56] and one study had no comparator.[58] One study

compared a single application of OLG to two applications of OLG[55] (Table 5).

A retrospective study[58] examined the effect of OLG (concentration unknown) on the prevention of SSI in 100 patients undergoing gastrointestinal surgery, breast malignancy surgery, and inguinal hernia repair. This study reported only one case (1%) of SSI within 30 days postoperatively in the OLG group. However, 84% of all patients in the study had a low-risk National Nosocomial Infections Surveillance SSI risk index.

Obara et al.[26] undertook an RCT with a large sample size comparing 1.5% OLG with 10% PVP-I for disinfection during adult gastrointestinal surgery. A total of 587 patients were included; 294 and 293 patients in the 1.5% OLG and 10% PVI groups, respectively. The 30-day postoperative SSI rate was significantly lower in the 1.5% OLG group (7% in the 1.5% OLG group vs. 13% in the 10% PVP-I group; adjusted risk ratio, 0.48; 90% confidence interval, 0.03–0.74; $p = 0.002$). Similarly, in another retrospective study of adult gastrointestinal surgery patients,[57] the overall SSI incidence rate was significantly lower in the 1.5% OLG group (7.2% in the 1.5% OLG group vs. 10.0% in the 10% PVP-I group). This study[57] did not describe the detailed statistical methods and results. A retrospective study of clean

Table 5. Effect of olanexidine gluconate (OLG) in the prevention of surgical site infection

First author, year	Design	Object	Intervention	Comparsion	Efficacy
Matsumoto et al. 2018[58]	Retrospective study	Adults; surgical type: gastrointestinal surgery breast malignancy inguinal hernia repair	OLG (concentration unknown), 100 cases	None	Item: SSI incidence rate at 30 days postoperatively Result: 1% (1 case/100 cases)
OLG vs. PVP-I, OLG vs. CHG					
Harihara et al. 2020[57]	Retrospective study	Adults; surgical type: gastrointestinal surgery	1.5% OLG (applicator), 2,077 cases	10% PVP-I, 1,556 cases 1% CHG, 1,514 cases	Item: All SSI incidence rate Result: 1.5% OLG < 1% CHG < 10% PVP-I
Obara et al. 2020[26]	RCT	Adults; surgical type: semiclean gastrointestinal surgery	1.5% OLG, 299 cases	10% PVP-I, 298 cases	Item: 30-day postoperative SSI rate Result: 1.5% OLG < 10% PVP-I
Shiyanagi et al. 2019[56]	Retrospective study	Children; surgical type: clean surgery (inguinal hernia, umbilical hernia, undescended testis, scrotal ema)	1.5% OLG (applicator), 164 cases	10% PVP-I, 130 cases	Item: all SSI incidence rate Result: no occurrence of either OLG or PVP-I
Single application vs. double applications					
Yamamoto et al. 2020[55]	RCT	Adults; surgical type: gastrointestinal surgery	Single application OLG applicator (concentration unknown), 198 cases	Double applications OLG applicator (concentration unknown), 202 cases	Item: 30-day postoperative incisional SSI rate Result: no significant difference

Note: All studies are in vivo and human studies.
Abbreviations: CHG, chlorhexidine gluconate; PVP-I, povidone-iodine; RCT, randomized controlled trial; SSI, surgical site infection.

pediatric surgeries[56] found no difference between the 1.5% OLG group and the 10% PVP-I group because no postoperative SSI occurred in either group.

Regarding the comparison between 1.5% OLG and 1% CHG, a retrospective study of adult gastrointestinal surgery patients[57] revealed that the overall SSI incidence rate was significantly lower in the 1.5% OLG group (7.2% in the 1.5% OLG group vs. 9.8% in the 1% CHG group). However, this study[57] did not describe detailed statistical methods or results.

One RCT[55] compared single and double application of OLG (concentration unknown) for disinfection during laparoscopic or robotic standby gastrointestinal surgery in adults. The incident rate of all SSIs within 30 days after surgery was not significantly different between the two groups, and single application was noninferior to double application (3.1% in the single application group vs. 2.0% in the double application group, $p = 0.537$).

Prevention of CRBSA

No relevant studies were identified.

Safety

The overall incidence of adverse events in OLG was very low, ranging from 2% to 5.8%.[26,52,56,57,59–61] Erythema, dermatitis, and pruritus each accounted for approximately 1.0%–1.9% of adverse events.[26,52,59,61] The time of appearance of skin rash was approximately 3–17 days (median, 7 days) after application[60] (Table 6). The severity of the disease ranged from mild to moderate, with some cases of spontaneous resolution and resolution after oral antihistamine or topical corticosteroid use.[26,52,56,57,59–61]

In an RCT[26] comparing 1.5% OLG and 10% PVP-I in adult gastrointestinal surgery, there was no significant difference in the rate of all adverse events between the two groups (2% in the 1.5% OLG group vs. 2% in the 10% PVP-I group, $p = 1.00$). Although the results of the detailed statistical analysis were not described, another RCT[52] also showed similar results (overall adverse event rate: 5.8% [3/52 cases] in the 1.5% OLG group vs. 7.4% [4/54 cases] in the 10% PVP-I group). In contrast, a retrospective study[60] comparing the incidence of postoperative dermatitis between OLG (concentration unknown) and PVP-I (concentration unknown) revealed that OLG yielded a significantly higher incidence (3.7% in the OLG group vs. 0.7% in the PVP-I group, $p < 0.0001$).

Only one study, a phase III trial,[52] compared OLG with CHG in terms of adverse event rates. The subjects were adults with healthy skin (abdomen and groin), and there was no difference in the rates of skin eruption between 1.5% OLG and 0.5% CHG (1.3% [3/237 cases] in the 1.5% OLG group vs. 0.8% [2/236 cases] in the 0.5% CHG group). However, the results of detailed statistical analysis were not described in this study.[52]

Ongoing clinical studies

Five ongoing clinical studies were identified. All are being undertaken in Japan, and three are related to SSI prevention. One study was related to disinfection at the time of blood culture collection, and one study was related to CRBSI (Table S3).

DISCUSSION

IN THE PRESENT scoping review, we searched and summarized the evidence from existing studies on OLG. The retrieved published works were classified into 29 in vitro studies or animal studies and 18 clinical studies. In addition to common Gram-positive and Gram-negative bacteria, OLG showed bactericidal activity against MRSA and VRE. In clinical settings, although there is limited evidence on SSI prevention, 1.5% OLG might be more effective than 10% PVP-I and 1% CHG. However, its usefulness under other conditions is unclear.

In vitro studies have shown that the antimicrobial spectrum of OLG is broad and seems to be effective against resistant bacteria. However, its clinical usefulness remains unclear. Olanexidine gluconate showed a broad-spectrum bactericidal effect on both Gram-positive and Gram-negative bacteria[21] (Table 1), and the bactericidal effects on resistant bacteria such as MRSA and VRE were characteristic[21] (Table 2). In emergency and intensive care, infections such as CRBSI and SSI caused by resistant bacteria (such as MRSA and VRE) are becoming a problem.[16–19] In addition, existing antiseptics such as PVP-I and CHG are considered ineffective against these resistant bacteria.[16–19] Therefore, OLG could be a useful disinfectant in emergency and intensive care settings. However, clinical studies on OLG are limited, and its clinical usefulness remains unclear.

In clinical settings, the usefulness of OLG is limited to its potential effect on SSI prevention. Moreover, the superiority of OLG over standard skin antiseptics such as chlorhexidine alcohol (CHG-AL) is unclear. All studies on the usefulness of OLG in clinical settings are related to SSI. An RCT[26] comparing 1.5% OLG with 10% PVP-I revealed that the overall SSI incidence rate was significantly lower in the OLG group. However, the comparator antiseptic used in this study was an aqueous formulation of PVP-I, which is a nonalcohol-based antiseptic and is already not

Table 6. Safety of olanexidine gluconate (OLG)

First author, year	Design	Object	Intervention	Comparsion	Adverse event
Sugai, 1999[65]	Not mentioned	Adults; region: forearm, back	OLG concentration: 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, and 0.5% Total 24 cases	Placebo 24 cases	Urticaria/light urticaria/ phototoxic reaction: safety
Sugai, 1999[66]	Not mentioned	Adults; region: back	0.1% OLG 9 cases 0.5% OLG 9 cases	None	Association unknown: transient elevation of white blood cells 1 case Serum/urine OLG unchanged Concentration: below the lower limit of detection
Sugai, 1999[67]	Not mentioned	Adults; region: forearm	0.1% OLG 6 cases 0.5% OLG 6 cases Application times: twice a day for 5 days	None	Local and systemic subjective/objective symptoms: none Serum/urine OLG unchanged concentration: below the lower limit of detection
Sugai, 1999[68]	Not mentioned	Adults; region: skin with artificially inflicted incisions	OLG concentration: 0.005%, 0.01%, 0.03%, 0.05%, and 0.1% Total 25 cases	Placebo 25 cases	Light Urticaria/ phototoxic/contact sensitization/contact phototoxic/contact urticaria reaction: safety
Harihara et al. 2015[52]	RCT	Adults; region: abdomen, groin	1.5% OLG 237 cases	Placebo 119 cases 0.5% CHG 236 cases	OLG erythema: 3 cases (1.3%) Placebo erythema: 1 case (0.8%) CHG erythema: 2 cases (0.8%)
Harihara et al. 2015[52]	RCT	Adults; surgical type: gastrointestinal surgery	1.5% OLG 52 cases	10% PVP-I 54 cases	OLG All: 3 cases (5.8%) erythema:1 case (1.9%) dermatitis:1 case (1.9%) pruritus:1 case (1.9%) PVP-I All: 4 cases (7.4%) erythema: 4 cases (7.4%)
Obara et al. 2020[26]	RCT	Adults; surgical type: semiclean gastrointestinal surgery	1.5% OLG 299 cases	10% PVP-I 298 cases	OLG All: 5 cases (2%) erythema:4 cases (1%) dermatitis:4 cases (1%) pruritus:2 cases (1%) PVP-I All: 5 cases (2%)

Table 6. (Continued)

First author, year	Design	Object	Intervention	Comparsion	Adverse event
					erythema: 1 case (<1%) dermatitis:2 cases (1%) pruritus:2 cases (17%)
Shiyanagi et al. 2019[56]	Retrospective study	Children Surgical type: Clean surgery (inguinal hernia, umbilical hernia, undescended testis, scrotal edema)	1.5% OLG (applicator) 164 cases	10% PVP-I 130 cases	Chemical burn incidence rate: OLG 0% vs. PVP-I 5% ($p < 0.05$)
Matsuoka et al. 2019[60]	Retrospective study	Surgical type: not mentioned	OLG (concentration unknown) 626 cases	PVP-I (concentration unknown) 567 cases	Rash incidence rate: OLG 3.7% vs. PVP-I 0.7% ($p < 0.0001$) Onset: days 3–17 (median, day 7)
Harihara, 2020[57]	Retrospective study	Adults Surgical type: Gastrointestinal surgery	1.5% OLG (applicator) 2,077 cases	10% PVP-I 1,556 cases 1% CHG 1,514 cases	OLG delayed onset dermatitis: a few cases/2,077 cases PVP-I and CHG: not mentioned
Iijima et al. 2020[59]	Case report	34 y.o. woman Surgical type: cesarean section	OLG (concentration unknown)	None	Type: erythma, pruritus Onset: Day 10
Nagai et al. 2018[61]	Case report	65 y.o. man Surgical type: thoracoscopic lobectomy 64 y.o. woman; surgical type: thoracoscopic lobectomy	OLG (concentration unknown)	None	Type: erythma, pruritus Onset: day 10 Type: erythma Onset: day 6

Note: All studies are in vivo and human studies.
Abbreviations: CHG, chlorhexidine gluconate; PVP-I, povidone-iodine; RCT, randomized controlled trial.

recommended for use as a skin antiseptic in many countries.[62] A study comparing 1.5% OLG with 1% CHG[57] also revealed that the overall SSI incidence rate was significantly lower in the OLG group. However, the interpretation of the results is limited by the fact that this was a retrospective study, and the results of detailed statistical analyses were not described. Therefore, the clinical usefulness of OLG against CHG-AL is still unclear. In the future, more studies comparing OLG with standard skin disinfectants and more studies on OLG for infection prevention are needed.

We reviewed studies on the in vitro pharmacological effects, antimicrobial spectrum, pharmacokinetics, and in vivo efficacy and safety on normal skin, wounded skin, and infection prevention. In the clinical setting, there were only studies related to the prevention of SSI with OLG,[26,56–58] and we did not identify any other studies on the prevention of infection, including CRBSI. Catheter-

related bloodstream infection is associated with high morbidity and mortality in critically ill patients[1,3,4,63]; therefore, high-quality clinical studies focusing on CRBSI prevention are needed in the future. A large randomized controlled study comparing 1.5% OLG and 1% CHG-alcohol for the prevention of CRBSI during central venous catheter insertion is currently ongoing in Japan.[64]

This review does have some limitations. The studies reviewed were all undertaken in Japan and, due to the novelty of the drug, the number of studies was limited.

CONCLUSION

OLANEXIDINE GLUCONATE IS a novel disinfectant with a broad spectrum and bactericidal effect against organisms, including MRSA and VRE, that are resistant to existing disinfectants such as PVP-I and CHG. Olanexidine gluconate might be more effective than PVI and CHG for SSI prevention. However, the clinical usefulness of OLG is unclear due to the limited number of clinical studies. In addition, clinical research is limited to studies targeting SSI prevention, and there is no clinical study on CRBSI. Therefore, further clinical studies are needed not only on the prevention of SSI but also on the prevention of CRBSI.

DISCLOSURE

APPROVAL OF THE research protocol: N/A.
Informed consent: N/A.
Registry and registration no. of the study/trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Search strategy on the applications of olanexidine.

Table S2. List of excluded studies.

Table S3. Ongoing studies on olanexidine.