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*RESEARCH ARTICLE*

# TOPICAL ANTISEPTICS IN EAR SURGERIES AND OTOTOXICITY EFFECT: REVIEW ARTICLE

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## *Abstract*

**Background:** There is a wide variation in practice in the use of surgical preparation solutions among otolaryngologists in ear surgery. Chlorhexidine gluconate, povidone-iodine and alcohol are common topical antiseptics solution. The literature for risk and mechanisms of the ototoxicity by Antiseptics solution if reaches the tympanic cavity and inner ear causing functional impairment and cellular damage to tissues is being reviewed and compared.

**Aim:** We present the current antiseptics solutions used during ear surgery and their risk of ototoxicity. Depending on the available clinical trials that have shown their clear effect on both animal models and human ears.

**Result:** The three widely used topical antiseptics preparations for ear surgeries and have been studied in literature are: Alcohol, Chlorhexidine gluconate and Povidone-iodine. Alcohol and chlorhexidine gluconate have a toxic effect on the vestibular and cochlear function proven by significant changes in Vestibular evoked myogenic potential (VEMP) and Auditory brainstem response (ABR). On the other hand, low concentration of Povidone-iodine (5%) does not have this adverse effect, However non-significant changes in the ABR was found to be related to a high concentration of Povidone-iodine (10%).

**Conclusion:** Chlorhexidine gluconate and alcohol have a clear ototoxic effect and are not safe in ear surgery especially with perforated tympanic membrane, whereas diluted low concentration povidone-iodine is safe and to date is the standard topical antiseptic solution to be used for ear surgeries.



## Introduction:-

Till date there is no current standards regarding which antiseptic solution should be used preoperatively to prevent surgical site infection in ear surgery(1). Povidone-iodine, Chlorhexidine and Alcohol are the commonly used in surgical preparation. Till date,there is a wide variation in practice in the use of surgical preparation solutions among otolaryngologists performing ear surgery. Lai Philipand colleagues 2011 did an electronic survey among members of the Canadian Society of Otolaryngology-Head and Neck Surgery. Under "do you perform tympanoplasty" in terms of the choice of preparation solation. The result was 96%used an antiseptic preparation solution at surgery,

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whereas 4% did not. 5% used a chlorhexidine-based preparation, 4% used an alcohol-based solution, 86%used aqueous povidone-iodineand 4% used others. 29% of the surgeon used a barrier method, 31% answered "always," 24% answered "sometimes" and 7%answered, "I don't know"(2).

The risk and mechanisms of the ototoxicity by Antiseptics solution if reaches the tympanic cavity and inner ear causing cellular damage to tissues and functional impairment are reviewed , and compared in our presented review.

The aim of this review is to high light the use of currentstandards and safe antiseptics solutions during ear surgery with their risk of ototoxicity. Depending on the available clinical trials that have shown their clear effect on both animal models and human ear

## Methods:-

A systematicEnglish articles search was performed looking at data base science pub-med. Since February2016 inboth, animal and human studiesin the relevant kay words. Including (Patient) human and animal going to ear surgery, (Intervention )use of antiseptic, (Compare) antiseptic type ether Chlorhexidine and Alcohol or povidone-iodine and (Outcome) ototoxicity effect. After filtration, we found out 15 studies that closely match our aim of review.

## Result:-

All in English. Two articles on both Chlorhexidine and Alcohol, only onProspective controlled article on antiseptic was found. Whileseven specific articles on Chlorhexidine, five specific articles on povidone-iodine were included.

**Mechanism of action:-**

**Povidone-iodine:-**

Iodide was first used in the treatment of wounds in (1839)(3). Iodine is complexed by iodide and polyvinylpyrrolidonevia a hydrogen bond between the two pyrroles.It has affinity to delivers the iodine directly to the bacterial cell membranes. Depending on the concentration of the povidone–iodine solution, the free iodine canact as bactericidal component. Iodine and iodophors have a wide range of activity against Gram-negative bacteria and Gram-positive, tubercle bacilli, fungi, protozoa and viruses. At the same time, having some activity against bacterial spores (4, 5).

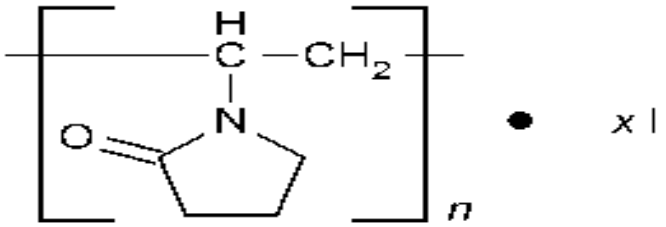


**Figure 1:-** Structure of povidone-iodine

The antiviral mechanism of action of iodine is not clear. However, lipid enveloped viruses are thought to be more sensitive than non-lipidenveloped viruses and parvoviruses (6).Manufacturer's data show that iodophors are bactericidal, virucidal, fungicidal and tuberculocidal but are not sporicidal at recommended use dilutions (7).

**Chlorhexidine:-**

In 1950s it was consider as an antiseptic agent in in Manchester UK by imperial chemical industries (8). Chlorhexidine is colorless and odorless. In addition, it is water insoluble and when formulated with acetic acid or gluconic become soluble. Chlorhexidine is bisbiguanide that consists of two chloroguanide chains linked by hexamethylene chain (9).

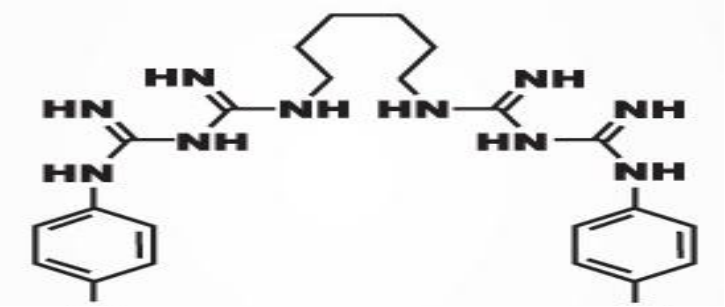

**Figure 2:-** Structure of chlorhexidine.

It disrupts the cytoplasmic membrane of bacteria at bacteriostatic concentrations and causing leakage of components of cytoplasm and bactericidal at higher concentrations via irreversible damaged the intracellular nucleic acids and adenosine triphosphate. The bactericidal effect increases with prolonged exposure for most bacteria. Chlorhexidine has an increased affinity for the cell wall of gram-positive organisms than for gram-negative bacteria. Also, has fungicidal, fungistatic, and some virus-killing properties. The antimicrobial activity of chlorhexidine is not affected by the body fluids such as blood (10).

**Alcohol:-**

Alcohols exhibit rapid broad-spectrum antimicrobial activity against vegetative bacteria (including mycobacteria), fungi and viruses but are not sporicidal. At the same time havingactivityagainstspore germination and sporulation(11), but reversibleeffect (12). Because of the lack of sporicidal activity, it not recommended for sterilization. Lower concentrations can be used as preservatives and to potentiate the activity of other biocides. Many alcohol products include low levels of other biocides (in particular chlorhexidine), which remain on the skin following evaporation of the alcohol, or excipients, which decrease the evaporation time of the alcohol (13).

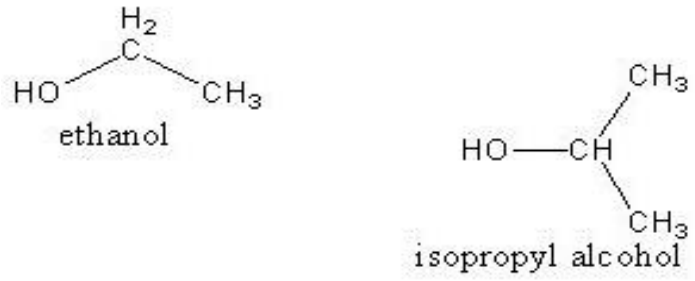


**Figure 3:-** Structure of ethanol alcohol and isopropyl alcohol.

Dependent on the concentrations of both the active agent and the test microorganism, ethyl alcohol is more potent against viruses (14).Isopropyl alcoholconsidered slightly more efficacious against bacteria (15).

**Ototoxicity in animal studies:-**

Several animal studies have been performed to re-examine both histologic and electrophysiologic evidenceof potential ototoxicity of Topical Antiseptics in ear. Özkiriş and colleagues, he investigated the ototoxic effects of different concentrations (5%, 7.5% and 10%) of povidone-iodine solutions applied to the middle ear cavity of rats using distortion product otoacoustic emissions. The animals were tested before, 1 and 10 days after solutions administration to the middle ear. The resulting of distortion product otoacoustic emissions were evaluated at different kHz. Reductions in distortion product otoacoustic emissions gram amplitudes were noted at high frequencies that is statistically significant in the group that received 5% at first day but this effect return at 10th day on. The other hand, significant differences were recorded in groups that received 7.5% and 10% povidone-iodine at low and high frequencies according to the control group at day 1 and 10. Based on results of this study,high concentration povidone-iodine solutions should not beused for ear surgery(16).Yagiz at, used fixed concentrations ofpovidone iodine(0.1ml of 10%)and investigated in guinea pigs by measuring transiently evoked otoacoustic emissions 10 days and four weeks. No change in transiently evoked otoacoustic emissions after 10 days and after 4

weeks of the application in the saline (negative control) group.Responses had cochlear toxic effect and disappeared in all ears of the gentamicin (positive control). Recording before and after povidone-iodine injection it similar to those done in positive control group with Pathological edema in the external auditory canal(17).Ichibangase T and colleagues used two different concentration of Povidone-Iodine (5% and 10%) in different age groups of the guinea pigand the compound action potential was measured at 24h, 7 days, and 28 days after application. The results of this study show mild hearing loss at 24h and 7 days using 10% solution, but no hearing loss with 5% solution at 7 days with the Outcome of the ototoxicity it affected by age of the animals and more toxic in infant(18).Morizono T, Sikoro MA, studied the ototoxic effect of povidone-iodine solution in the chinchilla and one day after topical application of dilutions of 1% povidone-iodine solution, a 1:4 dilution showed a substantial ototoxic effect on compound action potentials, while a 1:10 dilution did not(19).Aursnes J,did animal experiments that investigated ototoxicity of iodine when introduced into the tympanic cavity in guinea pigs and sacrificed 2 weeks later as surface preparations in phase-contrast microscopy. The duration of exposure was 10, 30, or 60 min. It was found that slight damage had occurred in the basal parts of the organ of Corti of those ears exposed to iodine or iodophor in 70% alcohol for 60 or 30 min and damage to the vestibular receptors was observed in ears exposed to iodophor in 70% alcohol for 60 min. on the other hand,chlorhexidine caused extensive damage to the neuroepithelial receptors of the inner ear(20).

The ototoxicity of the antiseptic combination chlorhexidine gluconate with cetrimide (savlon) is reviewed by Galle HG and colleagues on guinea pigs and observed the vestibular dysfunction in 15 clinical cases 12 dogs and 3 cats, in 8 animal ruptured tympanic membrane developed vestibular ototoxicity after applied this antiseptic combination(21).Further evidence,for the ototoxicity of chlorhexidine is demonstrated by Igarashi Y, Suzuki J, 0.05% or 2% chlorhexidine gluconate solutions were topically infused into the middle ear cavities of 12 test cats and observed the histologic change by both scanning and transmission electron microscope. Then 9 animals were decapitated 7 days after the third application, while the other three animals were sacrificed at 4 weeks. In the 2% chlorhexidine group, they found that hair cells in the organ of Corti had degenerated and had lost their hair bundles. In the animals sacrificed at 4 weeks, the injuries present seemed to have progressed. Even at a clinical concentration of 0.05%, chlorhexidine caused intracellular degeneration but with little surface damage(22).Aursnes J (1981) used two different solvents of chlorhexidine with different duration of exposure in guinea pigsand sacrificed at 2, 3, 4 or 10 weeks after exposure.The damage was extent to surface preparations of the organ of Corti in the Cochlea and the mucosal lining of the tympanic cavity was seen in almost all exposed ears with related to the concentration, the duration and to the time lapse after exposure(23). In addition, he did another study (1981) in guinea pigs with two different concentrations of chlorhexidine in two different solvents and the duration of exposure was varied. The result showed Vestibular neuroepithelial damage in most of the animals(24). Igarashi Y and Oka Y, found the chlorhexidine gluconate has an morphological ototoxic effect on the labyrinthine vestibule and observed in boththe crista ampullaris and the macula with characteristic pronounced edema or amorphous dilatation of the nerve chalices with few small deformed mitochondria and even when used in dilute clinical concentration afterintratympanic applicationsof2% and 0.05% chlorhexidine gluconate in the cats (25).Morizono and colleagues supported this issue as well(26).

On other study Morizono T et al,demonstrated the ototoxicity of topically applied ethanol in guinea pigs quantitatively on cochlear microphonesand the effect of ethanol with round window application on the endocochlear potential. Simultaneous recording of endocochlear Potential from the 1st and 3rd turn of the cochlea showed a more marked decline in the 1st turn. 70% ethanol caused an irreversible decline in endocochlear potential, while 35%ethanol caused a reversible(27).

Prospective controlled animal trial on all the antiseptics used in the ear surgery was conducted by perez et al in(2000) to assessed the function of the vestibular and cochlear parts of the 25 adult fat sand rat's inner ear after topical application of a different agent: chlorhexidine, povidone-iodine, and alcohol andbased on the recording of vestibular evoked potentials (VsEPs) and auditory brainstem response (ABR). Administration of saline (control) affected neither VsEPs nor ABR. However, with gentamicin (ototoxic control) no responses in both VsEPs and ABR as expected. Povidone-iodine 10% did not affect VsEP recordings and had only a small effect on ABR after application. In contrast, chlorhexidine 0.5% had a clear toxic effect on the vestibular and cochlear function and all waves disappeared in all sand rats. In addition, 70% ethyl alcoholcaused the waves to disappear not in all(28).

**Ototoxicity in humans studies:-**

Sade (1969)wasfirst to question that a dead ear occasionally could result in a myringoplasty following the use of preparation solution during surgery (29). After that Ballantyne, recorded two patients with sudden sensorineural loss immediately after operation, whereas third patient developed a high-tone loss when seen 3 weeks postoperatively(30).

Again, why a simple procedure such as myringoplasty should result in a sensorineural hearing loss, by this question Bicknell's at 1971 start his study. He tried to find the possible etiology.In addition, performed a large study on series of 97 patients who had undergone myringoplasty. 0.05% chlorhexidine in 70% alcoholwas used for perioperative antiseptic sterilization. Following that he recorded 14 patients developed severe SNHL in their operated ear within the first 6 months of the operation and 13 patients having a profound sensorineural hearing loss. An awareness amongst otologist was created following his article. Moreover,until date it serves as a landmark article on this subject(31).

## Conclusion:-

Chlorhexidine has documented ototoxic effect and considered not safe in ear surgery especially with perforated tympanic membrane as concluded by Philip lai and colleaguesin their literature review (32). In addition, alcohol also have clear ototoxic effects as discussed in various literature. Whereas diluted low concentration povidone-iodine is safe and to date is the standard topical antiseptic solution to be used for ear surgeries. A barrier method should also be considered during ear surgery if there is a concern. We recommend long-term multicenter clinical trialsshould be performed to evaluate the safe use of antiseptics during surgery.

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