The Comparative Efficacy of Tea Tree Oil Body Wash versus Chlorhex-idine Body Wash to Prevent Colonization with *Methicillin-Resistant Staphylococcus Aureus* in a Pediatric Unit

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Abstract

Background: Methicillin-resistant Staphylococcus Aureus (MRSA) stands for methicillin-resistant Staphylococcus aureus, a type of bacteria that is resistant to several antibiotics. Non-intact skin, such as when there are abrasions or incisions, is often the site of an MRSA infection. MRSA has become endemic in hospitals over the past years. The current recommendation for MRSA decolonization is to use a daily chlorohexidine skin wash for five days. Tea Tree Oil (TTO) can also be considered for the eradication of MRSA on the skin. However, no study has evaluated the TTO potential for MRSA decolonization in hospitalized children.

Methods: In this single-center, comparative prospective, open-label clinical trial, the effect of TTO body wash on MRSA decolonization was compared to that of chlorhexidine body wash at Logh-man-e-Hakim Hospital (Tehran, Iran). Several samples were taken from the catheter sites of children for MRSA detection. Patients were assigned to receive either TTO or chlorhexidine. After five days of applying the solutions, resampling was conducted to assess the coloniza-tion of MRSA.

Results: Both TTO and chlorhexidine groups showed favorable results for MRSA decolonization. From 382 patients, 91 were MRSA-positive (about 23.82%), and of these 91 patients, 41 (45%) were female and 59 (55%) were male. The mean ± SD of the growth inhibition zone against MRSA was 19.20 ± 3.73 and 33.41 ± 9.53 for chlorhexidine and TTO, respectively.

Conclusion: TTO body wash proved to be more effective than chlorhexidine in MRSA decolonization in hospitalized children. Implementation of such decolonization can improve patients' outcomes and prevent MRSA transmission.

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Keywords: Tea Tree Oil; Hospital-Acquired Infection; Chlorhexidine; Methicillin-Resistant Staphylococcus aureus

Introduction

Staphylococcus aureus (S. aureus) is a Gram-positive and facultative anaerobe cocci that is one of the most important species in the genus Staphylococci. This bacterium may be present in the form of normal flora of the skin or nose. It is estimated that about 20% of people are long-term carriers of the bacteria. S. aureus forms a yellow colony due to the production of carotenoid golden pigments called staphyloxanthin. These pigments act as antioxidants; therefore, they keep the bacteria safe and play an important role in its pathogenesis. Methicil-lin-resistant S. aureus (MRSA) are strains of bacteria that are resistant to most antibiotics. MRSA is mostly present in hospitals and is called hospital-acquired MRSA (1–3).

Tea Tree Oil (TTO) originates from Melaleuca alternifolia, which is from the Myrtaceae family and is endemic to Australia. For 100 years, TTO has been used extensively as an an-ti-inflammatory and antiseptic agent, but in recent years it has started to attract worldwide attention. This oil contains numerous compounds, including terpene hydrocarbons, monoter-penes, sesquiterpenes, and alcohol. Terpinen-4-ol is the main antimicrobial

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component, but other components, such as a-terpineol, also have antimicrobial activities similar to those of terpinen-4-ol (4–6). TTO has a relative density of 0.885–0.906, is only sparingly soluble in water, and is miscible with nonpolar solvents (7). Six varieties, or chemotypes, of M. alternifo-lia have been described, each producing oil with a distinct chemical composition. These in-clude a terpinen-4-ol chemotype, a terpinolene chemotype, and four 1,8-cineole chemotypes. The terpinen-4-ol chemotype typically contains levels of terpinen-4-ol of between 30 and 40% and is the chemotype used in commercial TTO production (8).

Since 1990, several reports have confirmed the antimicrobial characteristics of TTO. It has been shown that TTO is effective against Gram-negative bacteria, Escherichia coli, Gram-positive bacteria, and Staphylococcus. In addition, several studies suggest that TTO is an effective antiseptic against acne-inducing bacteria (9).

In a single-blind study that was conducted on 124 patients, the effect of TTO gel was com-pared to benzoyl peroxide at 5%. Both medicines showed significant improvement in reduc-ing the number of inflamed and non-inflamed lesions. Although TTO had a slower onset of action, it was associated with fewer side effects (10).

In a randomized double-blind study in 2007, Enshaie et al. evaluated the impact of TTO gel (5%) in patients with mild to moderate acne and reported favorable outcomes. Other studies have clearly demonstrated a wide range of antibacterial, antifungal, antiviral, and antiproto-zoal properties for TTO (11).

It has been suggested that TTO compounds disrupt the structure and function of bacterial membranes and destroy the integrity of the membrane. In 2008, Looghlin et al. studied the bactericidal effects of TTO on human skin and showed that it has an antimicrobial effect on MRSA and coagulase-negative staphylococci, including S. epidermidis. In their study on the prevalence of MRSA and identification of the mec A gene through polymerase chain reaction (PCR), Rasoul Shokri et al. found that the prevalence of MRSA species with the multi-drug resistance gene has reached a significant level (12). In 2008, Karpanen et al. conducted a study to evaluate the impact of chlorhexidine alone in comparison with chlorhexidine plus TTO on S. epidermidis. Their findings suggested that the mixture of TTO and chlorhexidine had a synergistic effect and eliminated S. epidermidis more effectively compared to chlor-hexidine alone (13).

The commercial TTO industry was born after the medicinal properties of the oil were first re-ported by Penfold as part of a larger survey into Australian essential oils with economic po-tential. During that nascent stage (14,15).

Consequently, to optimize antimicrobial activity, a lower limit of 30% and no upper limit were set for terpinen-4-ol content. Conversely, an upper limit of 15% and no lower limit were set for 1,8-cineole, although the rationale for this may not have been entirely sound. For many years, cineole was erroneously considered a skin and mucous membrane irritant, fueling ef-forts to minimize its level in TTO. TTO is produced by steam distillation of the leaves and terminal branches of M. alternifolia. Once condensed, the clear to pale yellow oil is separated from the aqueous distillate. The yield of oil is typically 1–2% of the wet plant material weight. Alternative extraction methods, such as the use of microwave technology, have been considered, but none have been utilized on a commercial scale (16–21). Compared to chlor-hexidine solution, which is particularly effective against Gram-positive bacteria (at concentra-tions ≥ 1 μg/L) on coagulase-positive and coagulase-negative staphylococci colonized at the intravenous catheter site in children (22,23). Chlorhexidine is one of the most widely used antimicrobials within clinical practice for skin antisepsis and is currently recommended within the Evidence-Based Practice in Infection Control (EPIC) and Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines. However, its antimicrobial efficacy is significantly reduced by factors including pH and organic matter. Therefore, additional strat-egies for skin antisepsis or improvements to existing methods need to be considered (24).

Methods

The participants were neonates and children aged 0–12 who were hospitalized in the chil-dren's unit of Loghman-e-Hakim Hospital. The participants who had a peripheral catheter for at least 48 h were selected for sampling. Name, surname, age, gender, history of illness, and allergy information were obtained from each patient. A unique number was allocated to each patient and solution. The parents of each patient received a solution and its instructions for use; moisten a cotton wool pad and apply 2-3 cc of the solution to the catheter injection site to cover the area in contact with catheter, in the case of allergy, rinse thoroughly with clean water, do not apply to damaged, broken or irritated skin, avoid contact with the eyes, for ex-ternal use only store in a cool, dark place. After five days of using the solution dilution: CHX (20% in water), TTO (40.2% terpen-4-ol and 3.5% cineol) made by:admail 838, Croydon, U.K. CR9 4WZ , volume: 200 cc, and its usage instructions, which describe applying the solu-tion to the catheter site every six hours for five days. Non-invasive skin sampling was per-formed from the site of catheter insertion into the skin using a sterile swab (which was auto-claved for 1.5 h) (Figure 1) (25–26).

The findings were recorded, and after the completion of 91 children, as the figure 1, after catheter is removed the sample is taken non-invasively from the skin of the catheter site with a sterile awab, data analysis was performed. The sampling was conducted at three time points: before catheter insertion, after changing the catheter by the nurse, and after administering the intervention at the location every six hours for five days. In fact, the first and second sam-plings were performed to identify the pathogen, while the third sampling was done to inves-tigate the effect of intervention solutions.

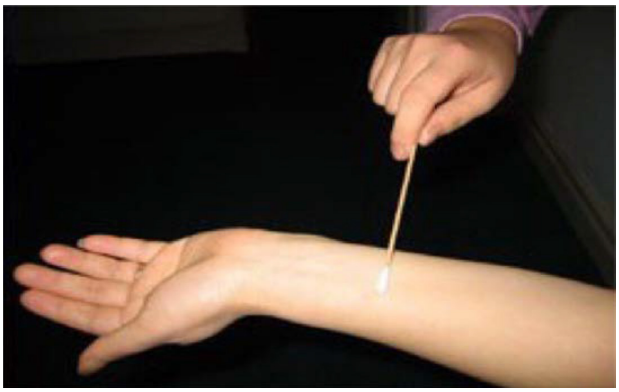

Figure 1

After describing the study, its objectives, and the sampling process, an informed consent form was obtained from the parents of the children,

Bacterial Culture, Tests, and Procedures

Brain-heart infusion (BHI) or Broth (Merck, Germany) medium is the appropriate culture me-dium for S. aureus and S. epidermidis. In order to prepare one liter of BHI culture medium, 37 g of BHI medium was dissolved in one liter of distilled water (27). The solution was then stirred and heated until a homogenized culture medium was achieved. Five ml of the solution was poured into each test tube, and samples were autoclaved at 121 °C for one hour. In cases where the BHI medium turned from transparent to opaque, the samples were judged to be infected with S. aureus or S. epidermidis. In order to differentiate S. aureus from S. epider-midis, a coagulase test was conducted using mannitol-salt agar. S. aureus forms yellow colo-nies with a purple-red halo in this medium.

After putting a drop of physiologic serum on the lam and adding the bacteria, a homogenous suspension was made. Then, a drop of hydrogen peroxide was added to the suspension. The formation of bubbles was indicative of a catalase enzyme in the bacteria.

After transferring the samples to the laboratory, the samples were incubated for 18–24 h at 37 °C. A four-stage culture of the bacteria was conducted to achieve a single colony on the man-nitol salt agar culture medium. The plates were stored for 18–24 h in a 37 °C incubator. Cata-lase and coagulase tests were performed on the plates with yellow medium. S. aureus changes the phenol red to phenol yellow due to the fermentation of mannitol in the medium and changes the pH. The positive results for both the catalase and coagulase tests are indicative of the presence of S. aureus on the plate. A total of 4–5 colonies of S. aureus were added to a test tube containing physiologic serum and compared to the McFarland 0.5 standard. If the standard of McFarland 0.5 solution was met, the microbial suspension was cultivated by ster-ile swabbing on a plate containing Mueller–Hinton agar (MHA). Using sterile forceps near the flame, a methicillin disc was put in the middle of the plate. The plate was incubated for 18–24 h at 37 °C. Plates that did not show a bacteria growth inhibition zone were indicative of MRSA presence. The MRSA-containing plates were isolated, and the other plates were re-moved. A microbial suspension was prepared for each plate and compared with McFarland's 0.5 standard. A microbial suspension was added to three 6 cm plates and three 10 cm plates using a sterile swab. Antibiotic disks, including vancomycin (VAN), chloramphenicol (CHLO), gentamicin (GEN), linezolid (LIN), rifampin (RIF), and teicoplanin (TPN), were placed on the three 10 cm plates. Neomycin and mupirocin discs were used as controls. The plates were kept in the incubator for 18–24 h at 37 °C. After removing the plates, the diame-ter of the growth inhibition zone was measured in millimeters. These steps were performed independently for 80 MRSA samples. The findings of the growth inhibition zone for the anti-biotics used in the disk-diffusion method were interpreted based on CLSL guidelines (2014).

A microbial suspension in the physiologic serum was made from the MRSA-positive samples with a McFarland 0.5 standard. The microbial suspension was cultivated on the plates con-taining MHA. A 6 mm well was made in each plate using a sterile Pasteur pipette. Different dilutions (1%, 2%, and 4%) of TTO in propylene glycol were prepared in separate test tubes, and 50 µL of each dilution was added to each well. A total of 50 µL of propylene glycol was used as a negative control. All the above steps were performed for 20 positive MRSA speci-mens. An inoculation loop of bacteria was gathered from the yellow mannitol environment and was dissolved in glass vials containing 20% glycerol and 80% Mueller–Hinton Broth me-dium. The vials were kept in the incubator for 24 h and were then frozen at −20 °C.

Results

Sampling was performed on a total of 391 hospitalized children that met the study criteria. The samples of nine children were excluded due to plate contamination. From a total of 382 patients, 91 were MRSA-positive (23.8%), and of these, 41 (45%) were female and 59 (55%) were male.

Antibacterial Effects of Different Antibiotics on MRSA

The descriptive statistics of the mean growth inhibition zone against MRSA are presented in Table 1. The mean diameter of the growth inhibition zone was highest for MUP and lowest for TPN.

Table 1. Descriptive statistics for the mean diameter of the growth inhibition zone against MRSA (mm).

	Mean	SD	Lowest Value	Highest Value
Muprocin	30.26	11.066	0	45
Neomycin	17.83	5.991	0	28
Linezolide	29.3	5.779	0	48
Chloramphenicol	23.15	4.444	0	34
Vancomycin	15.74	2.973	0	21
Teicoplanin	14.76	3.892	0	22
Rifampin	29.25	11.037	0	44
Gentamicin	15.24	6.683	0	36
Tea Tree Oil 4%	21.25	3.712	14	28
Tea Tree Oil 2%	6.9	7.181	0	15
Tea Tree Oil 1%	1.55	3.79	0	11
Tea Tree Oil PG	0	0	0	0
Tea Tree Oil	33.41	9.537	11	65

The mean diameter of the growth inhibition zone against MRSA for the different antibiotics was evaluated using repeated measures analysis of variance (ANOVA) and is presented in Table 2. Given the fact that Mauchly's sphericity test with a df = 27, a chi-square = 258.946, and a p-value = 0.001 did not validate the sphericity hypothesis of the covariance matrix, the Huynh-Feldt test was used. The significance level for the Huynh-Feldt test was less than 0.05 (P=0.01), which indicated that there was a significant difference between the mean diameter of the growth inhibition zone against MRSA between eight antibiotics.

According to the Bonferroni test findings in Table 2, the mean diameter of the growth inhibi-tion zone against MRSA was higher for MUP, LIN, and RIF and had a significant difference with other antibiotics, while the mean diameter of the growth inhibition zone against MRSA was lowest for TPN and GEN, with a significant difference with the remaining antibiotics. In addition, the mean diameter of the growth inhibition zone against MRSA was 33.41 and 19.20 for TTO and chlorhexidine solutions, respectively.

Table 2. The results of the Bonferroni test for comparing the mean diameter of the growth inhibition zone against MRSA for eight antibiotics.

Antibiotic (i)	Antibiotic (j)	Mean Difference	SE	Significance Level	Confidence Interval for Difference in Means	
					Lower Limit	Upper Limit
Mupirocin	Neomycin	12.438 *	1.398	0.001	7.917	16.958
Mupirocin	Linezilide	0.962	1.282	1	−3.184	5.109
Muprocin	Chloramphenicol	7.113 *	1.252	0.001	3.065	11.16
Muprocin	Vancomycin	14.525 *	1.231	0.001	10.545	18.505
Muprocin	Teicoplanin	15.50 *	1.247	0.001	11.468	19.532
Muprocin	Rifampin	1.013	1.439	1	−3.642	5.667
Muprocin	Gentamycin	15.025 *	1.565	0.001	6.964	20.086
Neomycin	Linezolide	−11.475 *	0.972	0.001	−14.618	−8.332
Neomycin	Chloramphenicol	−5.325 *	0.863	0.001	−8.117	−2.533
Neomycin	Vancomycin	2.088	0.726	0.145	−0.260	4.435
Neomycin	Teicoplanin	−3.063 *	0.751	0.003	0.633	5.492
Neomycin	Rifampin	−11.425 *	1.342	0.001	−15.763	−7.087
Neomycin	Gentamycin	2.587 *	0.784	0.04	0.54	5.121
Linezolide	Chloramphenicol	6.150 *	0.604	0.001	4.196	8.104
Linezolide	Vancomycin	11.563 *	0.568	0.001	11.725	15.4
Linezolide	Teicoplanin	14.538 *	0.687	0.001	12.317	16.758
Linezolide	Rifampin	0.05	1.183	1	−3.775	3.875
Linezolide	Gentamicin	14.063 *	1.036	0.001	10.713	17.412
Chloramphenicol	Vancomycin	7.412 *	0.467	0.001	5.903	8.922
Chloramphenicol	Teicoplanin	8.388 *	0.558	0.001	6.582	10.193
Chloramphenicol	Rifampin	−6.10 *	1.187	0.001	−9.937	−2.263
Chloramphenicol	Gentamicin	7.912*	0.904	0.001	4.99	10.835
Vancomycin	Teicoplanin	0.975	0.431	0.737	−0.417	2.367
Vancomycin	Rifampin	−13.513 *	1.182	0.001	−17.334	−9.691
Vancomycin	Gentamicin	0.5	0.793	1	−2.065	3.065
Teicoplanin	Rifampin	−14.488 *	1.241	0.001	−18.499	−10.476
Teicoplanin	Gentamicin	−0.457	0.774	1	−2.987	2.028
Rifampin	Gentamicin	14.13 *	1.313	0.001	9.767	18.258

Antibacterial Effect of TTO and Chlorhexidine Solutions against MRSA

The interpretation of the mean diameter of the growth inhibition zones and the comparison of the antimicrobial activity of these two solutions are as follows: The mean diameter of the growth inhibition zone against MRSA was higher for TTO (33.41 ± 9.53) and lower for chlorhexidine (19.20 ± 3.73). There was a statistically significant difference in the mean di-ameter of the growth inhibition zones against MRSA between TTO and chlorhexidine (0.001) (28).

Antibacterial Effect of Different Dilutions of TTO on MRSA

The mean diameter of the growth inhibition zone against MRSA was highest for a 4% dilu-tion and lowest for a 1% dilution. The mean ± SD of the growth inhibition zone against MRSA was zero for PG; therefore, PG was removed from the test. there was a significant difference between the mean diameters of the growth inhibition zone against MRSA between different dilutions of TTO (P=0.001).

For comparing the antibacterial effects of different dilutions of TTO on MRSA, a repeated measurement test was used. The findings are presented in Table 3 below.

Table 3. The Bonferroni test results for the mean diameter of the growth inhibition against MRSA for different dilutions of TTO (mm).

Concentration (i)	Concentration (j)	Averages Difference(i–j)	Standard Error	*p*-Value	Certain Distance for Averages Difference	
					Low-Limit	High-Limit
1%	2%	14.350 *	1.475	0.001	10.478	18.222
1%	3%	19.70 *	0.924	0.001	17.275	22.125
2%	3%	5.350 *	1.405	0.001	1.661	9.093

Assessment of the Antibacterial Effect of MUP, LIN, RIF, and TTO on MRSA

The mean diameter of the growth inhibition zone against MRSA is shown in Table 1. The findings suggest that TTO had the highest antibacterial effect against MRSA.

A broad range of bacteria have now been tested for their susceptibilities to TTO, Staphylo-cocus Aureus, and Methicillin Resistant Staphylococus Aureus (MRSA). The published sus-ceptibility data are summarized in Table 4. While most bacteria are susceptible to TTO at concentrations of 1.0% or less, MICs in excess of 2% have been reported for organisms such as commensal skin staphylococci (29,30).

Table 4. Susceptibility data for bacteria tested against M. alternifolia oil.

Bacterial Species	% (vol/vol) MIC	% (vol/vol) MBC	References
S. aureus	0.5–1.25	1–2	(30–32)
MRSA	0.04–0.35	0.5	(33–36)

Table 5. Descriptive statistics for comparing the growth inhibition zone against MRSA between TTO and chlorhexidine

	number	Mean	SD	Lowest Value	Highest value	t	degree	p-value
Chlorohexidine	57	19.20	3.73	11	30	12.867-	79	0.001
TTO	52	33.41	9.53	11	65			

Discussion

TTO was chosen for preparing a topical solution for MRSA-infected hospitalized children based on the following points: the highest mean diameter of the growth inhibition zone (33.41 mm); the natural nature of TTO; the absence of bacterial resistance among the samples tested with TTO; having the highest diameter of the growth inhibition zone among all the findings (65 mm); and the higher likelihood of developing bacterial resistance to rifampin. Based on the findings, between antibiotics, MUP and TPN had the highest and lowest antibiotic activ-ity against MRSA, respectively. The antibacterial effect was highest for TTO and lowest for chlorhexidine. In addition, the antibacterial effect of TTO against MRSA was highest for the 4% dilution and lowest for the 1% dilution (31–33).

Hospitalized patients are at greater risk for MRSA colonization, which can increase both the hospitalization period and costs. In 2004, in a randomized and controlled study, Dryden et al., (34) compared different TTO preparations with standard topical agents for MRSA decol-onization. Based on their findings, the efficacy of TTO was higher than chlorhexidine or sil-ver sulfadiazine

in MRSA decolonization from the skin lesions. This is in line with the present study. We found that the efficacy of TTO was significantly higher than that of chlorhexidine in MRSA decolonization from the skin. In 2007, Flaxman et al., (35) conducted a study to evaluate the effectiveness of TTO in eradicating MRSA. Their findings showed that TTO had a similar efficacy to mupirocin in MRSA decolonization from different sites of the body after 14 days of treatment. Similarly, in their study in 2008, McMahon et al., (36) concluded that TTO is an effective agent for MRSA decolonization at low concentrations.

Although in the study by McConeghy et al., (37), the use of TTO has been associated with causing allergic dermatitis and gynecomastia, no significant adverse events were noted during the present study. The safety of TTO has not been investigated in other studies in children. In addition, this is the first study to evaluate the efficacy of TTO on hospitalized children.

In contrast to our findings, Edmondson et al., (38) claimed in 2011 that TTO was ineffective in decolonizing MRSA from the wounds of 12 participants. However, this study is limited by the fact that it was an uncontrolled study. In another study in 2013, Blackwood et al. com-pared the efficacy of TTO with Johnson's Baby Softwash in the prevention of MRSA colo-nization in adults and reported that there was no significant difference between these prepa-rations (39,40). However, one of the limitations of their study was that the proportion of male and female adult participants was not balanced. The present study was conducted on children who were hospitalized for more than six days. The number of boys and girls was well bal-anced in our study. Further, since we conducted the study in a specific sector of a hospital, the environmental difference was not a confounding factor in our study, and all the partici-pants had relatively similar conditions.

Hospital staff are exposed to a higher risk for MRSA infection and can act as a mediator to transmit MRSA outside the hospital. Therefore, TTO can be utilized as an antiseptic in dif-ferent sectors of the hospital. We believe that using TTO as a disinfectant can reduce the hos-pitalization period and its related costs (41–43).

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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