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ORIGINAL RESEARCH

The Effectiveness of Polyhexanide in Treating Wound Infections Due to Methicillin-Resistant Staphylococcus Aureus: A Prospective Analysis

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Purpose: Polyhexanide is a safe and effective wound care antiseptic commonly used in clinics as wound rinsing solution and gel. However, the efficacy of Polyhexanide in treatment of wound infected with MRSA (*methicillin-resistant Staphylococcus aureus*) is unknown. The aim of this study is to assess the effectiveness of polyhexanide with povidone iodine in treating wound infected with MRSA.

Patients and Methods: A prospective analysis of 62 patients with wound infections, who were admitted to our department from 2016 to 2020, was conducted in order to assess the efficacy of different treatment approaches. The patients were divided into two groups: the experimental group and the control group. In the experimental group, 30 patients underwent treatment with a combination of diluted povidone iodine and polyhexanide immersion. Conversely, in the control group, 32 patients received treatment with diluted povidone iodine along with systemic antibiotic therapy. The time required for dressing changes, bacterial clearance rates, and the Bates-Jasen wound assessment tool (BWAT) scores were utilized as indicators to evaluate the effectiveness of the treatments.

Results: In our study, the findings indicated that the experimental group exhibited a lesser number of days for the bacteria culture to turn negative compared to the control group, with statistical significance ($p<0.05$). Furthermore, the decline in the BWAT score was significantly greater in the experimental group than in the control group ($p<0.05$). However, no significant differences were observed in terms of dressing times and wound coverage between the two groups ($p>0.05$).

Conclusion: Polyhexanide combined with povidone iodine can effectively remove MRSA infection in wounds and reduce antibiotic dosages.

Keywords: methicillin-resistant staphylococcus aureus, wound, polyhexanide

Introduction

Wound treatment is a common medical issue that can arise from various causes such as trauma, diabetic foot ulcers, and pressure sores. These injuries can be quite challenging to deal with, particularly when they become infected. In such cases, the treatment becomes even more complicated due to the presence of resilient bacteria. One of the main challenges in treating an infected wound is the presence of Methicillin-resistant Staphylococcus aureus (MRSA) and Carbapenem-resistant Enterobacteriaceae (CRE). These bacteria have developed resistance to commonly used antibiotics, making them difficult to eradicate. As a result, healthcare professionals face an uphill battle in effectively treating these types of infections.

Over the past few years, there has been a gradual rise in the prevalence of drug-resistant bacteria, primarily attributed to the improper and excessive usage of antibiotics, glucocorticoids, and Immunosuppressive agents. Consequently, this alarming trend has resulted in a substantial upsurge in morbidity, mortality, and a substantial escalation in healthcare

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expenses, thereby establishing MRSA as a significant global public health concern.[1,2] Moreover, the occurrence of trauma-induced skin and soft tissue damage as well as pressure ulcers significantly compromises the integrity of the skin, rendering individuals more susceptible to methicillin-resistant Staphylococcus aureus (MRSA) wound infections. The injury itself contributes to diminished blood supply in the affected skin and soft tissues, thereby adversely impacting the efficacy of antibiotic treatment. Simultaneously, the presence of infection exacerbates tissue necrosis, further impeding the therapeutic potential of antibiotics. Furthermore, the unfavorable state of the wound creates an ideal milieu for the formation of biofilms. These biofilms not only induce wound necrosis and heightened exudation but also exhibit resistance to antibiotics, ultimately culminating in a state of chronic inflammation that proves arduous to resolve.[3]

A recent study showed that presence of biofilm in chronic wound was 78.2%.[4] It is more difficult to therapy that biofilm formation in multidrug-resistant infection. Prontosan solution and gels are composed of Polyhexanide and betaine surfactant, which synergistically act to disrupt and eliminate biofilms. These biofilms demonstrate noteworthy antibacterial properties while exhibiting minimal cellular toxicity.[5] Study have demonstrated that, in comparison to normal saline, Polyhexanide exhibits superior efficacy in eradicating biofilms, mitigating inflammatory reactions, and expediting the process of wound healing.[6] Polyhexanide has been evidenced to effectively hinder bacterial activity, eradicate wound bacteria, and subsequently foster wound healing.[7–9]

Previous in-vitro research has exhibited the successful treatment of MRSA using Polyhexanide as a standalone agent or in conjunction with antibiotics.[10] Recently, He et al created AU-phmb nanoparticles that, when paired with photothermal therapy, may limit the development of bacterial biofilms and swiftly eliminate germs, facilitating the healing of Staphylococcus aureus infected wounds.[11] Nevertheless, the efficacy of Polyhexanide against MRSA in clinical therapeutic applications still lacks clarity.

Povidone iodine, a widely employed bactericide in clinical settings, possesses the capacity to eradicate both Gram-positive and Gram-negative bacteria.[12] Furthermore, its efficacy extends to multi-drug resistant bacteria, as evidenced by various research investigations.[13] Based on these studies, it has been postulated that the utilization of Polyhexanide in conjunction with Povidone iodine could potentially offer a promising therapeutic approach for the management of wound infections caused by Methicillin-resistant Staphylococcus aureus (MRSA).

In present study, We evaluated the efficacy of polyhexanide in combination with povidone iodine by comparing the therapeutic effects of polyhexanide and antibiotics in the treatment of wounds infected with MRSA.

Materials and Methods

Patients and Study Design

A prospective study was conducted with a cohort of 62 patients who were admitted to our department between February 2016 and February 2020, all of whom had MRSA wound infections. Inclusion criteria for the study consisted of: (1) presence of various degrees of soft tissue wound infection in the limb; (2) absence of any pre-existing skin diseases prior to trauma; (3) confirmation of MRSA infection through bacterial drug sensitivity testing, with axillary temperature not exceeding 37.2°C, and negative blood culture prior to treatment; and (4) absence of allergy to the experimental drug. Exclusion criteria included: (1) pregnancy or lactation, along with incomplete data; (2) presence of severe immune deficiency and cachexia in individuals with allergic constitutions; (3) growth of multiple pathogens in bacterial cultures; and (4) age below 15 years or above 85 years.

The patients were allocated into either the experimental or control group based on their personal preference, as illustrated in the flow chart. Prior to participating in the study, all patients provided their consent by signing a formal agreement. The research protocol adhered to the principles outlined in the Helsinki declaration and received approval from the ethics committee of the Scientific Research Projects under Medical Ethics Committee of Zhongnan Hospital of Wuhan University (2020060).

The polyhexanide, which is the main ingredients, acts as a potent inhibitor of bacterial biofilm formation and provides the best environment for wound healing.[7,14,15]

The MALDI–TOF MS mass spectrometry with a culture medium of 5% sheep blood and VITEK 2 Compact AST-GP67 CARDS (Meriere, France) was routinely used for MRSA identification and drug sensitivity.

Treatment of Patients

Upon the admission of patients to our department, a meticulous examination and evaluation of their wounds were expeditiously conducted. Subsequently, samples of wound secretions were acquired for the purpose of bacterial cultures and drug sensitivity tests. Simultaneously, blood cultures were also executed. As a pre-treatment measure, the Bates-Jensen Wound Assessment Tool (BWAT) scale[16] was employed to determine the wound score.

In the control group, patients were routinely subjected to wound debridement upon admission to ensure the effective removal of necrotic tissue and wound exudates. Dressings were subsequently changed daily, and the wounds were cleansed using a diluted solution of active iodine (0.1%) before being wrapped with gauze. In cases where the wound exhibited significant exudate, the dressing was replaced twice daily. To address potential bacterial infections, a broad spectrum antibiotic was administered intravenously prior to the receipt of final results from bacterial cultures. Following confirmation of the presence of MRSA through bacterial culture, an intravenous dose of Vancomycin was administered.

In the experimental group, wound debridement was conducted similarly to the control group. Subsequently, the wounds were cleansed using a diluted active iodine solution (0.1%) and then covered with gauze soaked in polyhexanide for a duration of 15 minutes. Following this, the wounds were rinsed with sterile normal saline. The wound surface was then coated with polyhexanide gel and wrapped with six to eight layers of sterile gauze. Dressings were changed once daily as part of the routine procedure. Simultaneously, wound secretions were collected daily for bacterial culture. It is worth noting that patients in the experimental group did not receive any antibiotic treatment.

In the study, all patients presenting with wound infections were administered supportive therapy, involving rest and nutritional support. Once the bacterial culture yielded negative results, the wounds were reassessed using the BWAT scale. Notably, the absence of secretions and the presence of fresh granulation tissue guided the subsequent treatment approach, which included suturing, split thick skin transplantation, or flap procedures, contingent upon the specific conditions of the wound.

Post-Therapy Assessments

To assess the efficacy of different treatments, various metrics were measured, including the number of dressing changes and the duration it took for the culture test to convert to a negative result. Additionally, the wounds were evaluated using the Bates-Jensen Wound Assessment Tool prior to the application of polyhexanide and subsequent to the achievement of a negative culture test outcome. The disparity in scores between the two groups was then analyzed and compared.

Statistical Analysis

The statistical software SPSS 26.0 was utilized to conduct all the statistical analyses in this study. The measurement data and counting data were represented as mean plus standard deviation, respectively. The variables of gender, injury position, wound exposure, and wound repair methods were compared using the chi-square test. The rank sum test was employed to examine complications. Age was analyzed using the Independent-Samples *t* test. Subsequently, it was found that the data pertaining to the days of bacteria culture turning to negative, number of dressing changes, and BWAT scores were not normally distributed after testing. Therefore, the rank-sum test was applied. In order to establish statistical significance, a P value of less than 0.05 was considered.

Results

Upon admission, a total of 30 patients were enrolled in the experimental group (Figure 1), exhibiting a mean age of 54.0 ±10.2 years. Conversely, the control group comprised 32 patients, with a mean age of 51.7±11.7 years (Table 1). The male to female patient ratio in the experimental group was 21:9, while the control group displayed a ratio of 25:7. In terms of wound area, the experimental group exhibited a range of 7.3 cm^2 to 47.9 cm^2, with an average of 22.4 cm^2. In comparison, the control group displayed a range of 7 cm^2 to 47.2 cm^2, with an average of 20.3 cm^2. Notably, there were no significant differences observed in wound areas between the two groups.

In the experimental group, wound formation occurred in 14 cases due to open fractures, 8 cases due to trauma, 6 cases due to bedsores, and 2 cases due to infection (Figure 2A-G). Similarly, in the control group, wound formation resulted from fractures in 12 cases, trauma in 12 cases, bedsores in 6 cases, and infection in 2 cases (Figure 3A-F). Statistical

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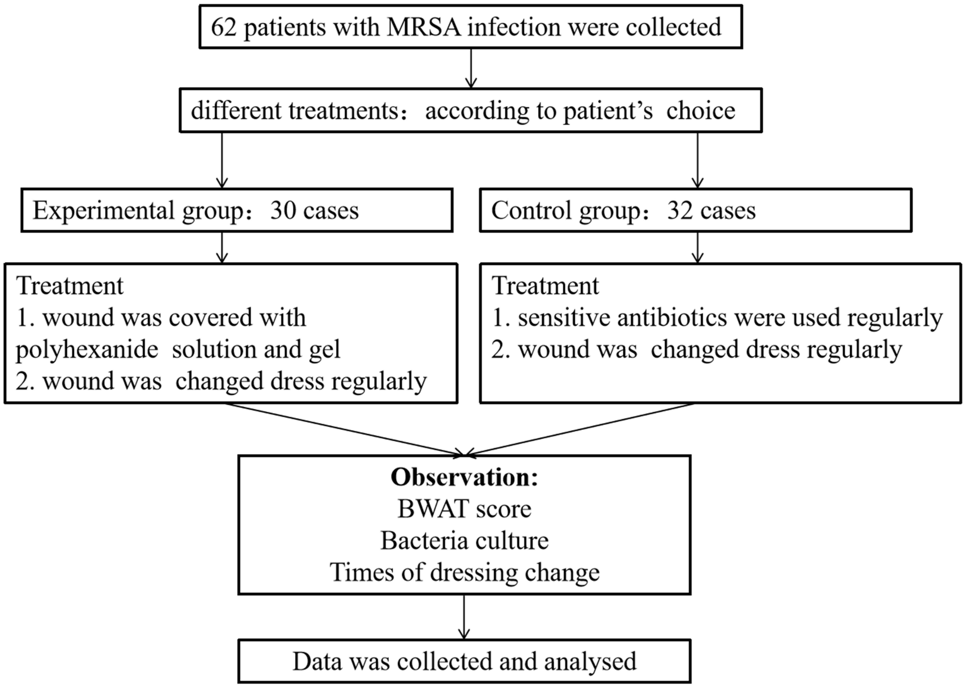

Figure 1 Flowchart.

analysis showed no significant differences in age, gender, wound type, wound area, and other patient data between the two groups (P > 0.05).

In the experimental group, an average of 7.7±2.2 dressing changes were conducted from admission to negative bacterial culture. Conversely, the control group underwent 8.6±1.2 dressing changes. The dressing change frequency in the experimental group did not demonstrate any significant difference compared to the control group, as shown in Table 2.

In the experimental group, the average duration for the bacterial culture of wounds to transition to a negative state was determined to be 7.7±1.8 days, whereas in the control group, this duration was observed to be 8.7±1.6 days. It is

Table 1 Patients' Demographic and Clinical Data. Values are Expressed as Means ± SD

Items	Experiment Group	Control Group	t/x value	P value
Gender			0.543	0.465
Male	21	25		
Female	9	7		
Age	54.0±10.2	51.7±11.7	0.84	0.404
Injury position			0.436	0.881
Upper limbs	4	7		
Lower limbs	20	19		
Trunk	6	6		
Wound areas	23.1±13.1	20.3±10.1	0.928	0.357
BWAT score at admission	44.6±1.8	44.1±1.7	−0.766	0.444

(*Continued*)

Table 1 (Continued).

Items	Experiment Group	Control Group	t/x value	P value
Complications			0.367	0.714
Brain trauma	3	4		
Fracture	14	12		
Pneumonia	2	2		
Paraplegia	4	2		
Diabetes	6	7		
Hypertension	4	6		
Wound exposure			0.433	0.936
Bone exposure	5	7		
Tendon exposure	6	6		

worth noting that the time taken for bacterial elimination was considerably reduced in the experimental group as compared to the control group, with statistical significance observed ($p<0.05$) (see Table 2).

The evaluation of wound treatment effectiveness can be conducted by measuring the difference in scores obtained from the Bacterial Wound Assessment Tool (BWAT). This score is calculated by subtracting the initial score obtained at admission from the score obtained after bacterial presence becomes negative. The experimental group exhibited

Figure 2 Presentation Pictures of typical cases of experimental group.One patient developed an infectious wound with MRSA on the right leg (**A-C**). (**A**), wound infection with MRSA before debridement. (**B**) After treated with Prontosan®-soaked gauze 8 days, the wound infection has been cleared and the granulation was growing well. (**C**) wound was covered by skin graft. Other patient was suffered by wound infection with MRSA and soft tissue necrosis (**D-G**). (**D** and **E**) wound infection with MRSA and treated with Prontosan®-soaked gauze. (**F**) 3 days after treated by Prontosan, wound infection improved significantly. (**G**) wound was sutured after treated by Prontosan 9 day.

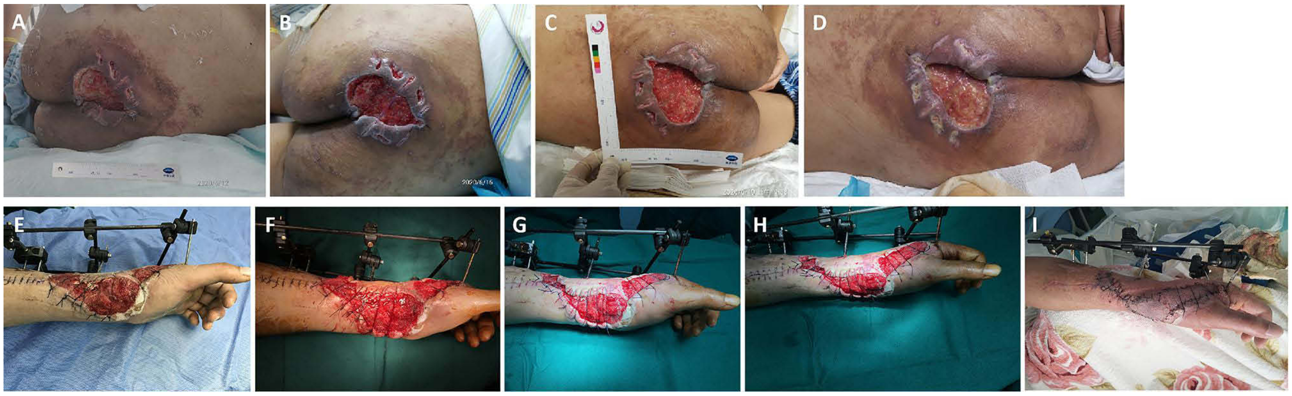

Figure 3 Presentation Pictures of typical cases of control group. A patient was admitted with a sacral caudal pressure sore infected by MRSA (**A-D**). (**A**) A round wound was placed at the sacrocaudal end, which infected by MRSA. (**B**) Secretions were still visible on the wound 4 days after treatment. (**C**) After 7 days of treatment, the granulation tissue of the wound increased significantly and there was still a little secretion. (**D**) After 12 days treatment, There was still a little necrotic tissue and secretions on the wound. A patient was suffered skin and soft tissue defect with MRSA infection at left arm (**E-I**). (**E**) There are necrotic tissue and secretions in the wound. Fig F, Wound necrosis and secretions were cleared by debridement. (**G**) After 5 days of treatment, wound infection was relieved and secretions decreased. (**H**) After 10 days of treatment, secretions were significantly decreased and granulation grew well. (**I**) After 14 day of treatment, wound were covered by skin graft.

a noteworthy improvement in wound condition, as evidenced by a decrease of 16.7±2.3 points in the BWAT score from the time of admission to when bacteria turned negative. In comparison, the control group experienced a decrease of 12.2 ±1.8 points. Notably, the BWAT score of the experimental group demonstrated a statistically significant decrease compared to the control group ($p<0.05$) (Table 2).

Following the transition of bacterial culture to negative, prompt wound closure was achieved through either skin or flap transplantation. Within the experimental group, a total of six patients presenting with extensive wounds were subjected to flaps and skin grafts, whereas the control group consisted of five cases. Remarkably, all patients displayed successful wound healing, with no recorded instances of postoperative infection recurrence.

Discussions

The present study substantiated that the combination of Polyhexanide and PVP-I exhibited synergistic effects in managing MRSA wound infection in the absence of antibiotics, ultimately leading to the successful eradication of MRSA. Additionally, these techniques facilitated the growth of granulation tissue and expedited the healing process of wounds, while circumventing the adverse effects commonly associated with antibiotic usage.

MRSA Infection in Surgical Wounds

MRSA has emerged as a significant pathogen associated with nosocomial infections. Surgical patients, in particular, are at a higher risk due to compromised skin barriers and the presence of necrotic material at the site of injury. These patients

Table 2 The Results of the Two Groups Were Compared

Items	Experiment Group	Control Group	t/x value	P value
Days of bacteria culture turning to negative	7.7±1.8	8.6±1.2	−2.21	0.034
Number of dressing change	7.7±2.2	8.7±1.6	−1.77	0.07
BWAT score	−16.7±2.3	−12.2±1.8	−8.908	0.000
Wound repair			0.305	0.839
Skin transplantation	16	15		
Flap transplantation	10	12		
Skin+flap	4	5		

often have prolonged hospital stays and receive multiple antibiotic treatments, which can lead to dysbacteriosis. Consequently, they are more susceptible to MRSA wound infections, which pose challenges in terms of treatment and tissue repair. The standard approach for treating MRSA infections involves the use of sensitive antibiotics like vancomycin and linezolid. Additionally, studies have demonstrated that combining vancomycin with rifampicin or sulfamethoxazole yields a more effective bactericidal effect compared to vancomycin alone.[17] However, the prolonged use of antibiotics is associated with significant side effects and high costs. Hence, there is a pressing need to explore novel and effective antimicrobial strategies for the prevention and treatment of MRSA wound infections.[18]

In recent times, there has been a surge in research on novel antibiotic therapies for the treatment of MRSA infection. This research encompasses various areas of investigation, such as exploring the competitive and coevolutionary dynamics between biological pathogens,[19] investigating the controlled decolonisation/colonisation of pathogenic bacteria, examining the efficacy of phage and lysosome antibacterial activity,[20] as well as exploring the potential of antimicrobial photodynamic therapy and colloidal silver irrigation.[21,22] Additionally, the use of biomaterials has emerged as a promising non-antibiotic alternative.[23] A recent study by He et al has demonstrated that HE MXenes display an enhanced ability to stimulate enzyme activity when exposed to near infrared light irradiation in a specific range. This heightened enzymatic activity enables the efficient eradication of MRSA biofilm-associated ailments and the effective elimination of bacteria, thereby exerting control over infections.[24] The extensive research conducted on multi-drug resistant bacteria has opened up new possibilities for the prevention and treatment of bacterial infections, as well as advancements in personalized medicine.

Mechanism and Benefits of Polyhexanide

At present, clinicians predominantly opt for a combination of established antibiotics as the primary approach to tackle MRSA infections. Nevertheless, numerous comprehensive guidelines pertaining to the administration of antibiotics and the healthcare environment exist, suggesting a multitude of factors that warrant careful evaluation prior to the prescription of antibiotics. Notably, individuals afflicted with MRSA, particularly those grappling with diabetes or HIV,[25] necessitate meticulous assessment due to the added complexities these diseases introduce to MRSA treatment owing to variations in pharmacokinetic parameters.

Polyhexanide has been identified as a highly effective antiseptic for clinical wound care in various studies. These studies have revealed that polyhexanide can effectively impede bacterial activity in both mixed and single biofilms formed on hydrophilic and hydrophobic abiotic surfaces.[26] Furthermore, Ciprandi et al conducted a retrospective analysis of children's medical records and found that polyhexanide was not only safe but also beneficial in promoting a favorable wound healing environment for the treatment of burns in children.[27] Frank Günther's research demonstrated the ability of Polyhexanide to effectively inhibit bacterial biofilms of MRSA.[28] An animal study also showcased the remarkable ability of PHMB to eliminate 99.64% of bacteria from MRSA-infected wounds within a span of six days.[29] In yet another study conducted by Thomas Wild, the successful disinfection of MRSA infection using polyhexanide was confirmed.[30] These findings collectively affirm the efficacy of polyhexanide in the prevention and treatment of MRSA infection. However, a randomized controlled trial (RCT) has demonstrated that a single course of polyhexanide may not completely eradicate MRSA infection.[31] In the present study, the results indicate that the combination of polyhexanide and PVP-I exhibits synergistic effects in the treatment of MRSA, thus effectively inhibiting its growth.

Limitations

This study is subject to several limitations. Firstly, the data was obtained from hospital medical records as well as the recollection of medical personnel, which introduces the possibility of certain deviations. Secondly, the small number of cases included in the study limits the generalizability of the findings and renders them preliminary in nature. To thoroughly assess the efficacy of polyhexanide in treating MRSA wound infections, it is imperative to conduct larger-scale prospective, randomized controlled clinical trials.

To conclude, the findings of this study revealed that the utilization of polyhexanide in conjunction with PVP-I demonstrated a significant reduction in bacterial clearance time, thereby offering a potentially viable substitute for intravenous antibiotic administration. These results suggest that, based on the insights gained from prior clinical investigations, this non-antibiotic approach could serve as an effective alternative method for managing MRSA wound infections.

Data Available Statement

All data of this study were available in results and made available by the corresponding author.

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Disclosure

The authors report no conflicts of interest with respect to the topic of this study.

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