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The Effectiveness and Safety of 1% Silver Sulfadiazine (Flammazine) Cream in Preventing Infection in Potentially Contaminated Traumatic Wounds among Pediatric Patients 2 To <18 Years Old: An Open-Label, Single-Arm Phase 3 Clinical Trial

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Abstract

This is an open label, descriptive, single-arm study of patients, 2 to <18 years of age conducted at the out-patient department, Research Institute for Tropical Medicine (RITM), the primary objective of which is to evaluate the effectiveness and safety of silver sulfadiazine in preventing infection in potentially contaminated traumatic wounds among children 2 to <18 years of age.

All of the 50 subjects enrolled had contaminated wound upon enrolment, without oral antibiotics and other topical medications previously used. After seven days of Flammazine application, 100% had clinical successand after 14 days of application, 100% of the subjects likewise had persistent clinical success. At baseline, the most common criteria present was pain (96%) followed by erythema (94%). 58% had mild itching, and 56% had mild tissue edema. Overall, the SIRS (Severity of Infection Rating Scale) scores improved after 7 days (100%) and 100% of the subjects had SIRS score of 0 after 14 days.

The study has shown that 1% Silver Sulfadiazine appears to be an effective and safe alternative to antibiotics in the management of wound infections which are potentially contaminated among children 2 to <18 years of age.

Keywords: Silver; Efficacy; Safety; Healing; Wounds

Abbreviations

$AgNO_3$: Silver Nitrate; CRF: Case Report Forms; CDC: Centers for Disease Control and Prevention; FDA: Food and Drug Administration; LAR: Legally Acceptable Representatives; MRSA: Methicillin Resistant *Staphylococcus aureus*; MIC: Minimum Inhibitory Concentration; MS: Microsoft; RITM: Research Institute for Tropical Medicine; SIRS: Severity of Infection Rating Scale; SPSS: Statistical Package for the Social Sciences; SSD: Silver Sulfadiazine; VRE: Vancomycin Resistant Enterococci

Introduction

The use of silver in medicine dates back in ancient history. Its role would include water disinfection and storage, prevention of infection in wounds using silver foil and in facial reconstruction done in battlefield surgery by royal surgeons [1]. In the 1880's, German obstetrician Karl Crede used dilute solutions of silver nitrate and this reduced neonatal eye infections from 10.8% to under 2% [2].

Silver ions have been identified to have antimicrobial activity in as early as the 19th century and colloidal silver was accepted by the US Food and Drug Administration (FDA) as effective in the 1920's. With the introduction of penicillin in the 1940's, the use of silver dwindled and antibiotics became the standard treatment of bacterial infections.

In the 1960's, 0.5% silver was used again for the management of burn patients. In 1968, $AgNO_3$ was combined with a sulfonamide antibiotic to produce silver sulfadiazine (SSD) cream, a broader spectrum silver-based antibacterial for the management of burns. Because of increasing antibiotic resistance, wound dressings with varying levels of silver are being used to complement the use of antibiotics [3].

During the last two decades of the 20th century, silver-based textiles were developed for burn and wound dressings. Deitch examined the antimicrobial properties of silver-coated nylon and showed it to be effective against *P. aeruginosa, S. aureus and Candida albicans* [4].

In medicine, silver is used in the form of salts such as silver sulfadiazine (Flammazine, Silvadene), silver sustained release products such as silver-plated nylon (Silveron) and silver nanocrystalline (Artcoat) dressings. Silver nitrate is also being used as a cautery agent. On the other hand, silver proteins are used as antiseptic solutions for gynecological procedures, irrigation, suppositories and eye drops and for sterilization of procedures [5].

Evidences from several clinical studies support the efficacy and safety of silver sulfadiazine in treating burn wound. Silver sulfadiazine has been a standard topical antimicrobial treatment for burn wound both in adults and pediatric patients.

Silver sulfadiazine has also been used to treat wounds other than burns. A multicenter study was conducted in 446 patients to evaluate

the therapeutic benefits of silver sulfadiazine in various types of infected skin lesions such as abscess, post-surgical infection, circulatory wound, burns including chemical burns and other wound infection. This showed the favorable effects of silver sulfadiazine in wound healing. Even with studies demonstrating its efficacy in treating non-burn wounds [6,7], there is still a concern on the safety of using silver sulfadiazine especially among pediatric patients, even for short-term use. Furthermore, lack of local studies in this group confounds the concern not only to safety, but also to efficacy.

This study was conducted to evaluate the efficacy and safety of silver sulfadiazine in preventing infection in potentially contaminated traumatic wounds among children 2 to <18 years of age.

Materials and Methods

Objective of the study

The primary objective of the study is to determine the effect of silver sulfadiazine in preventing bacterial infection in potentially contaminated traumatic wounds, among Filipino pediatric patients aged 2 to <18 years by demonstrating the proportion of patients with persistent clinical success. Its secondary objective is to demonstrate the safety profile of silver sulfadiazine.

Study design

This is a pilot open-label, single-arm descriptive study conducted at the Research Institute for Tropical Medicine (RITM) from February to July 2016. Fifty patients, 2 to<18 years of age were enrolled, with the following inclusion criteria: those with potentially contaminated traumatic wound based on the 1999 CDC surgical wound classification; superficial wound which do not go beyond the dermis and duration of wound must be 1 day old (i.e. within 24 hours upon wound was obtained).

Exclusion criteria were the following: presence of skin diseases at or near the wound area; Immuno-suppressed state or other serious systemic disease, such as, but not limited to, diabetes, vascular disease, undernourishment; signs and/or symptoms of systemic infection such as fever, tachycardia, tachypnea, and hypotension; presence of skin infection/disorder not amenable to topical antibacterial treatment only; presence of secondarily-infected animal/human bite. All animal bites were excluded, infected or non-infected; presence of infected burn wound; presence of trauma wound that needs suturing; post-surgical wound; topical or systemic use of antimicrobials or other products which in the investigator's opinion could confound the evaluation of the effect of the study drug; known or suspected hypersensitivity to silver sulfadiazine or any of the excipients in the silver sulfadiazine 1% cream; participation in any other investigational drug study or use of (an) investigational drug(s) within the 30 days prior to randomization.

Methodology

Written informed consent from parents/legally acceptable representatives (LAR) and not from patients >12 years old were obtained. This study was approved by the Institutional and Ethical Review Board of the Research Institute for Tropical Medicine.

Starting on the first visit, parents/LAR or patients were instructed to clean the wound and apply silver sulfadiazine cream once daily for 14 days according to the wound care instruction. On the 7th day of treatment (Visit 2), patients returned for follow-up clinical evaluation. If wound was infected and needs oral antibiotic treatment, this was considered a "failure". Patients who were classified as having "persistent clinical success" and assessed to have no further need for topical treatment, were instructed to stop treatment with silver sulfadiazine. Patients returned for final evaluation on the 14th day of treatment (visit 3). Those who were classified as "clinical recurrence" were managed accordingly with oral antibiotics based on the clinical judgment of the physician.

This study used the parameters for Severity of Infection Rating Scale (SIRS) which are based on the physical appearance of the wound and symptoms felt by the patient, namely: exudates/pus, crusting, erythema, edema, tissue warmth, itching and pain. Patients were assessed on primary outcome; secondary outcome and severity of infection rating scale (SIRS) score.

Demographic and clinical information were written on Case Report Forms (CRF). Photographs on wounds were taken before application of 1% silver sulfadiazine and on the two succeeding visits (Day 7 and Day 14).

All data were encoded in an MS Access database or MS Excel.

Data analysis

Continuous variables were summarized with standard descriptive statistics and categorical variables with frequencies and percentages. Ninety-five percent confidence intervals were provided for descriptive statistics when necessary. All data were analyzed using (SPSS).

Results

The study involved 50 subjects, 60% are male and 20% are female. All subjects were Filipinos (Table 1) with a median age of 5.9 years old. Silver sulfadiazine was applied according to the wound care instruction.

All subjects had potentially contaminated wound upon enrolment. None received prior oral antibiotics nor any topical medication.

100% of the subjects had clinical success seven days after the initial application of Flammazine. All subjects likewise had persistent clinical success after 14 days of application (Table 2).

The Severity of Infection Rating Scale (SIRS), with a scale of 0 (absent) to 3 (severe), was used. The possible maximum score was 21. The following parameters were evaluated: exudates/pus, crusting, erythema, edema, tissue warmth, itching and pain.

Baseline SIRS scores were taken on visit 1 (day 1 of application) and succeeding ones were taken on visit 2 (day 7 of application) and visit 3 (day 14 of application). On visit 1, the most common criteria were pain (96%) followed by erythema (94%), 58% had mild itching, and 56% had mild tissue edema. The most common SIRs criteria on visit 2 were mild itching (98%) followed by erythema (26%) and pain (14%). Overall, the SIRS scores improved on visit 2 and all subjects had SIRS score of 0 (absence of signs and symptoms) on visit 3.

With regards to the assessment on the use of Flammazine by parents, all subjects reported a score of 10 on all acceptability criteria. These would include ease of application/usage, absence of undesirable sensation like pain on application, absence of staining of skin and clothes, and acceptability of scent.

No adverse reaction or serious adverse event were reported.

Characteristics	N=50
Sex, n (%)	
Male	30 (60%)
Female	20 (40%)
Age (years), mean (SD)	5.9 years

Table 1: Demographics and baseline characteristics.

Post-treatment Outcome	N=50
Clinical success after 7 days	50 (100%)
Persistent clinical success after 14 days	50 (100%)
Clinical recurrence	0 (0%)
Unable to determine	0 (0%)

Table 2: Post treatment outcome.

Discussion

Mechanism of action of silver and silver sulfadiazine

Elemental iron cannot kill bacteria but when silver atoms are positively charged (Ag+), they become bactericidal. Silver compounds contain positive silver ions bound to negatively charged ions or molecules. When exposed to aqueous environments such as wound exudate, some of the silver ions become detached from the compound [8]. The detached silver ions bind to bacterial cell membranes, causing disruption of the bacterial cell wall and cell leakage. Silver ions transported into the cell disrupt cell function by binding to proteins and interfering with energy production, enzyme function and cell replication. These processes cause cellular death of the bacteria [9-11].

In a study on the mechanisms of action of silver sulfadiazine action on burn wound, sulfadiazine did not act as an antibacterial agent in low concentrations, but combination with silver produces a synergistic effect. The slow and steady reactions of silver sulfadiazine with sodium-chloride containing body fluids such as serum and exudate permit slow and sustained delivery of silver ions into the wound area [12,13].

Silver ions are active against a broad range of microorganisms: bacteria, fungi and viruses, including many antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant Enterococci (VRE) [13].

Efficacy results of this study

This study is so far, the first to be conducted locally.

This study used the parameters for Severity of Infection Rating Scale (SIRS) which are based on the physical appearance of the wound and symptoms felt by the patient, namely: exudates/pus, crusting, erythema, edema, tissue warmth, itching and pain. Overall, the SIRS scores improved on Visit 2 and all subjects had SIRS score of 0 (absence of signs and symptoms) on Visit 3.

Topical antiseptics, such as silver, differ from antibiotics: they have multiple sites of antimicrobial action on target cells and therefore a low risk of bacterial resistance. As a result, antiseptics have the potential to play an important part in controlling bioburden in wounds while limiting exposure to antibiotics and reducing the risk of development of further antibiotic resistance.

Safety

Only a small proportion of silver presented to a wound site in a dressing is involved in antimicrobial action. Most of the rest remains within the dressing or binds to proteins in the wound or wound debris [14,15].

Even if absorbed systemically, silver is excreted mainly via the biliary route in feces. Some is also excreted in urine. Silver is not absorbed into the central or peripheral nervous systems. Very little is systemically absorbed.

Silver is not an eye or skin irritant or skin sensitizer, human carcinogen or mutagen. Silver sulfadiazine is Philippine FDA-approved for treatment of infected burn wounds, prevention of infection of burn wounds, and treatment of infected skin lesions.

Limitation of the Study

There are pharmacological parameters identified to predict antimicrobial efficacy in the treatment of infection. The assignment of minimum inhibitory concentration (MIC) values and breakpoints is necessary in determining the susceptibility of organisms to systemic and topical agents and the incidence of microbial resistance. MIC50 and MIC90 values are used in the evaluation of the susceptibility of bacteria to antibiotics but not to silver-containing products. There are no standard MIC values assigned for silver containing products and in general, MIC values for silver containing products in clinical studies would reflect the values that were arrived at after comparison with the control. Most of these studies have produced different MIC data for $AgNO_3$. Because of the lack of standard MIC values and breakpoints, the SIRS criteria were used to determine efficacy of SSD [3].

While this study provided good results on the effectiveness and safety of 1% silver sulfadiazine among children 2 to <18 years old, this study involved a small number of 50 subjects. As this is a pilot study, it may be worth pursuing another study that will be participated by a bigger number of subjects.

Conclusion

The study has shown that 1% silver sulfadiazine appears be an effective and safe alternative to antibiotics in the management of wound infections which are potentially contaminated among children 2 to <18 years of age.

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References

1. Barillo DJ, Marx DE (2014) Silver in medicine: A brief history BC 335 to present. Burns 40: S3-S8.
2. Lansdown AB (2006) Silver in health care: Antimicrobial effects and safety in use. Curr Prob Dermatol 33: 17-34.
3. Chopra I (2007) The increasing use of silverbased products as antimicrobial agents: A useful development or a cause for concern? J Antimicrob Chemother 59: 587590.
4. Deitch EA, Marino AA, Gillespie TE, Albright JA (1983) Silver nylon: A new antimicrobial agent. Antimicrob Agents Chemother 23: 356-359.
5. Grier N (1983) Silver and compounds In: Block SS Disinfection, sterilization and preservation. (3rd edn) Phiadelphia: Lippincot Williams & Wilkins, USA. pp: 375-89.
6. De Boer P, Collinson PO (1981) The use of silver sulfadiazine occlusive dressings for finger-tip injuries. J Bone Joint Surg Br 63: 545-547.
7. Buckley SC, Scott S, Das K (2000) Late review of the use of silver sulfadiazine dressings for the treatment of fingertip injuries. Injury 31: 301-304.
8. Hermans MH (2007) Silver-containing dressings and the need for evidence. Adv Skin Wound Care 20: 166-173.
9. Lansdown AB (2002) Silver I: Its antibacterial properties and mechanism of action. J Wound Care 11: 125-130.
10. Fox CL, Modak SM (1974) Mechanisms of silver sulfadiazine action on burn wound infections. Antimicrob Agents Chemother 5: 582-588.
11. Lansdown AB (2004) A review of the use of silver in wound care: Facts and fallacies. Br J Nurs 13: S6-S19.
12. Lansdown AB, Williams A (2004) How safe is silver in wound care? J Wound Care 13: 131-136.
13. Lansdown AB (2010) A pharmacological and toxicological profile of silver as an antimicrobial agent in medical devices. Adv Pharm Sci Article ID 910686.
14. Wilkinson LJ, White RJ, Chipman JK (2011) Silver and nanoparticles of silver in wound dressings: A review of efficacy and safety. J Wound Care 20: 543-549.
15. Marx DE, Barillo DJ (2014) Silver in medicine: The basic science. Burns 40: S9-S18.