COMPARATIVE STUDY FOR THE EFFICACY OF SOFINOX CREAM AGAINST *STAPHYLOCOCCUS AUREUS* WITH FUCIDIN CREAM, T-BACT OINTMENT AND SCREENING FOR RESISTANT MUTANTS

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ABSTRACT: Objective: To determine the Minimum Inhibition Concentration of Sofinox cream, Fucidin cream, T Bact ointment against *Staphylococcus aureus* and to screen for the development of resistant mutants and Whole Genome Sequencing(WGS) of the strains used and the strains showing raised MIC following serial passages. **Material and Methods:** An in vitro study was conducted to determine the Minimum Inhibition Concentration of Sofinox cream, Fucidin cream, T Bact ointment against seven strains *Staphylococcus aureus* (ATCC 25923, ATCC 43300, ATCC 700699, 2 clinical isolates of methicillin-sensitive *S. aureus* (MSSA) and 2 methicillin-resistant *S. aureus* (MRSA). We also screened the same strains for the development of resistant mutants of *Staphylococcus aureus* by sub MIC exposure to Sofinox cream, Fucidin cream and T Bact ointment up to 70 serial passage and their WGS. **Results:** The MIC values of the three topical antibiotics ranged between 16 µg to 64 µg for all the strains of Staphylococcal strains tested. The MIC value did not change for three strains of *Staphylococcus aureus*. An one-fold rise in MIC value occurred for four strains of the *Staphylococcus aureus* strains for Sofinox cream after 70 passages at sub MIC concentration. WGS analysis of the strains with Sofinox cream treatment, it was noted that 150 number significant genetic variations to MSSA (ATCC 25923) and 84 number for MRSA (ATCC 700699) and no significant changes with other strains. For two of the strains, the MIC value remained the same. Three strains showed a one-fold rise, and two strains showed a four-fold rise in MIC value for Fucidin cream after 70 passages at sub MIC concentration. Through the WGS analysis of the strains, it was noted that 185 significant genetic variations to one of the clinical isolates of MSSA followed by 102 to MRSA standard strain ATCC700699, the strains showing a one-fold rise in MIC showed 95, 85 and 76 number of genetic variations respectively. All the strains of *Staphylococcus aureus* showed a rise in MIC for T Bact, which ranged from one to four-fold rise. WGS analysis of the strains with T Bact ointment treatment, it was noted the variations ranging from 85 to 158 with a one-fold rise to a four-fold rise in MIC value. **Conclusions:** In the present study, it was observed that Sofinox cream had low resistance potential in vitro compared to Fucidin cream, whereas T bact ointment had more resistance potential when exposed to sub MIC concentration of the cream/ointment. Even the WGS analysis showed variations correlating with MIC values. Hence there is a less likely chance of development of resistant mutants with the topical use of Sofinox cream even up to 8 weeks.

KEYWORDS Minimum Inhibitory Concentration, Sofinox cream, Fucidin cream, T-Bact ointment, resistant mutants

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Introduction

The skin presents the first line of defence against a wide range of bacterial invaders. When the integrity of the skin is compromised accidentally or intentionally, its natural defences weaken, and a role for antibacterial agents emerges.[1] *Staphylococcus aureus* is the most prevalent pathogens involved in skin and soft tissue infections.[1] Therapeutic option for skin and soft tissue infections include incision and drainage in combination with antimicrobial therapy, which may be oral, topical or parenteral.[2]

The topical route of application offers several advantages over systemic administration, including the avoidance of systemic toxicity and side effects, the decreased induction of bacterial resistance, and the high concentration of antibacterial agent at the site of infection.[1]

The commonly used topical antimicrobials include Mupirocin, Neomycin, Bacitracin, Polymyxin, Erythromycin, Gentamycin, and Silver Sulfadiazine.[3] These topical agents offer an important option in the treatment of mild infections. They are valuable in wound prevention, localized infections, treatment of primary and secondary pyodermas and burns.[3]

However, resistance to topical antibacterial is a growing concern. Bacterial resistance can occur through many mechanisms. The mechanism depends on the site and mode of action of the antibiotic. Resistance can be categorized as intrinsic or acquired. Exposure to antibiotics provides the necessary selective pressure for the rise and spread of resistant pathogens. Infections caused by antibiotic-resistant microorganisms fail to respond to the standard medical treatments, resulting in prolonged illness, higher health care expenditures and a great risk of death. As antibiotic resistance continues to emerge,[3,4] alternative agents need to be sought for topical therapy. The whole-genome sequencing (WGS), combined with phenotypical methods, greatly enhance our understanding of the genetic basis of antimicrobial resistance, with the potential for identifying new antimicrobial drug targets, helps to provide information to predict antimicrobial resistance of the organism [5]. Farrell et al. found in their study the amino acid changes at specific locations with raised MIC after serial passage [6]. Hence an in vitro study was planned for screening the development of resistant mutants of *Staphylococcus aureus* by exposure to Sofinox cream, Fucidin cream and T Bact ointment and its whole genome sequencing.

Study Objectives

1. To determine the Minimum Inhibition Concentration of Sofinox cream, Fucidin cream, T Bact ointment against *Staphylococcus aureus*.
2. To screen for the development of resistant mutants of *Staphylococcus aureus* by exposure to Sofinox cream, Fucidin cream and T Bact ointment
3. Genetic analysis by Whole Genome Sequencing of resistant mutants.

Methodology

Study Design

In-vitro experimental study

Study Setting

Department of Microbiology, Kasturba Medical College, Manipal (NABL, NABH, NAAC and AAHRPP accredited) and Melaka Manipal Medical College Manipal. The whole-genome sequencing was carried out at Medgenome Laboratory Bengaluru.

Materials & Methods

a) Topical antimicrobials: The Sofinox cream (Apex Laboratories, Chennai, contains Sodium fusidate IP equivalent to Fusidic acid IP 2% w/w in a cream base containing Biopolymer (Poly— (1,4)- 2- amino-2-deoxy-D-glucose q.s) Fucidin cream (Leo, Denmark contains Fucidin 2%) and T Bact ointment (Mupirocin I P 2.0% w/w India) were obtained and stored according to their product insert recommendations and evaluated within their stated shelf life.

b) Bacteria: Sofinox cream, Fucidin cream and T bact ointment were tested against strains of *S. aureus* (ATCC 25923, ATCC 43300, ATCC 700699, 2 clinical isolates of methicillin-sensitive *S. aureus* (MSSA) and 2 methicillin-resistant *S. aureus* (MRSA). The inoculum was freshly prepared by growing the organism in Blood agar and incubating for 24 hrs. The cells were suspended in Trypticase soy broth prior to the assay procedure.

c) Minimum inhibitory concentration testing: [7] Minimum Inhibitory Concentration (MIC) of Sofinox cream, Fucidin cream and T Bact ointment against the test strains were determined by agar dilution method in Mueller Hinton Broth, following Clinical Laboratory Standards Institute (CLSI) guidelines.

d) Resistance development assay: [8] The bacterial suspension of *S. aureus* (ATCC 25923, ATCC 43300, ATCC 700699), 2 clinical isolates of methicillin-sensitive *S. aureus* (MSSA) and 2 methicillin-resistant *S. aureus* (MRSA) in the 96-well microtiter plate were exposed to a sub-MIC concentration of the drug for 6 hours at 37°C. The MIC was determined as mentioned above5. This process of sublethal concentration exposure and MIC determination was carried out for 70 passages and were assessed for an increase in MIC value at each passage. The resistant mutants isolated during this process were reported with the number of the passage required for the development of resistance with their MIC value.

e) Whole Genome Sequencing: The DNA was extracted using DNA Minikit (QIAGEN, Hilden Germany) from the reference strains and strains showing higher MIC following passage was sent to Medgenome Lab Bengaluru for genome analysis.

Results

Sofinox cream: The Sofinox cream showed the MIC value of 16 μg for MRSA standard strains ATCC 43300, ATCC700699, MSSA standard strain ATCC 25923, MSSA clinical isolates and 32 μg for clinical isolates of MRSA (Table 1). When all the strains were subjected to sub MIC concentration of respective MIC values, ATCC700699 strain showed a one-fold rise in MIC by 59th passage, strain ATCC 43300 by 67th passage, ATCC 25923 by 62nd passage and one of the MSSA clinical isolates by 48th passage as shown in Table 2 and Figures. The MRSA clinical isolates and one of the MSSA clinical isolates did not develop resistant mutants until 70 passages.

Table 1 MIC value of the drugs to bacteria tested

Strain	**Sofinox**	**Fucidin**	**T Bact**
	Minimum Inhibitory concentration (g)		
Staphylococcus aureus ATCC 700699	16	16	16
Staphylococcus aureus ATCC 43300	16	64	16
Staphylococcus aureus ATCC 25923	16	64	32
Methicillin sensitive *Staphylococcus aureus* Clinical isolate	16	16	16
Methiciliin sensitive *Staphylococcus aureus* Clinical isolate	16	64	32
Methiciliin resistant *Staphylococcus aureus* Clinical isolate	32	64	16
Methiciliin resistant *Staphylococcus aureus* Clinical isolate	32	64	16

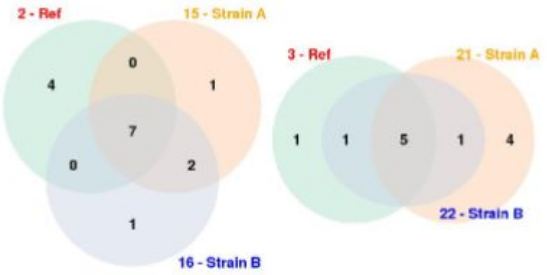
Table 2 Resistant Mutant development by 50 serial passage to sub MIC exposure

Strain	Sofinox	Fucidin	T Bact
	Minimum Inhibitory concentration (g)		
Staphylococcus aureus ATCC 700699	16 upto 58 passage and 32 upto 70^{th} passage	16 upto 35 passage 64 till 56 passage and 128 upto 70 passage.	16 upto 60 passages, 32 upto 70 passages
Staphylococcus aureus ATCC 43300	16 upto 66 passage, 32 upto 70 passage	64 upto 56 passage and 128 upto 70 passage	16 upto 58 passage 32 till 70 passage
Staphylococcus aureus ATCC 25923	16 upto 61 passage, 32 upto 70 passage	64 upto 56 passage and 128 upto 70 passage	32 upto 21 passage 64 upto 68 passage 128 till 70 passage
Methiciliin sensitive *Staphylococcus aureus* Clinical isolate	16	16 upto 35 passage 64 up to 56 passage, 128 till 70 passage	16 upto 65 passage 32 till 70 passage
Methiciliin sensitive *Staphylococcus aureus* Clinical isolate	16 upto 47 passage 32 upto 70 passage	64	32 upto 11passage 64 upto 70 passage
Methiciliin resistant *Staphylococcus aureus* Clinical isolate	32	64	16 upto 47 passage 32 till 62passage 64 till 70 passage
Methiciliin resistant *Staphylococcus aureus* Clinical isolate	32	64 upto 61 passage, 128 upto 70 passage	16 upto 17 passage 64 till 66 passage 128 till 70 passage

Table 3 Resistant mutant development.

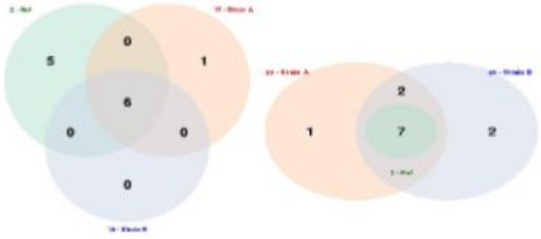
Strain	**Sofinox**	**Fucidin**	**T Bact**
	Minimum Inhibitory concentration (g)		
Staphylococcus aureus ATCC 700699	One fold rise	Four fold rise	One fold rise
Staphylococcus aureus ATCC 43300	One fold rise	One fold rise	One fold rise
Staphylococcus aureus ATCC 25923	One fold rise	One fold rise	Two fold rise
Methicillin sensitive *Staphylococcus aureus* Clinical isolate	No change	Four fold rise	One fold rise
Methiciliin sensitive *Staphylococcus aureus* Clinical isolate	One fold rise	No change	One fold rise
Methiciliin resistant *Staphylococcus aureus* Clinical isolate	No change	No change	One fold rise
Methiciliin resistant *Staphylococcus aureus* Clinical isolate	No change	One fold rise	Four fold rise

Fig 1: WGS analysis Sofinox cream:



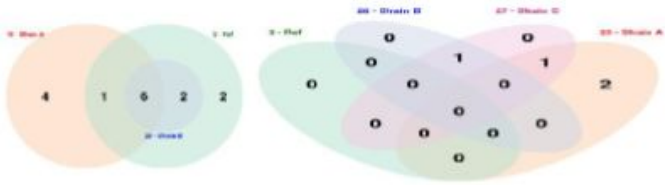
1. No variant in FusA gene
2. 5 AR specific mutations were identified
3. The AR-specific mutations were not significant - not in the protein coding region or missense
4. No significant increase in mutations after antibiotic passage

Fig 2: WGS analysis Fucidin cream:



1. No variant in FusA gene
2. 1 AR specific mutations was identified
3. The AR-specific mutations were significant
4. Significant increase in mutations after antibiotic passage. The mutation count is more than that from the Sofinox treatment

Fig 3: WGS analysis of T Bact:



1. No variant in FusA gene
2. 4 AR specific mutations were identified

Fig: 4: MIC value for *Staphylococcus aureus* ATCC 700699

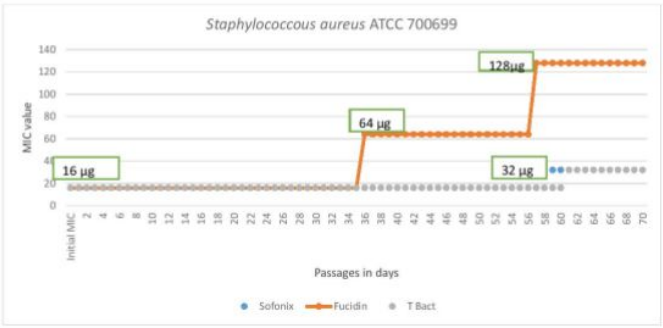


Fig.5: MIC value for *Staphylococcus aureus* ATCC 43300

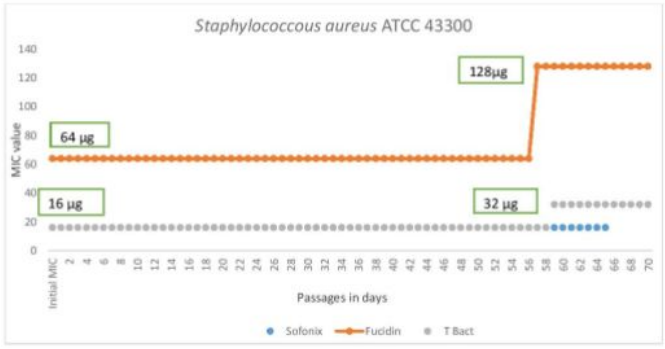


Fig. 6: MIC value for *Staphylococcus aureus* ATCC 25923

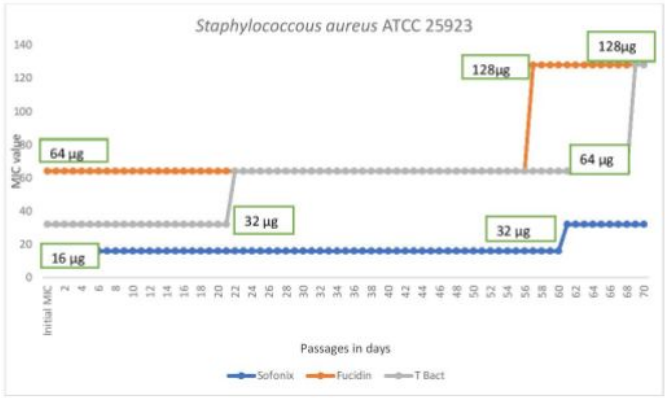


Fig.7: MIC value for *Staphylococcus aureus* ATCC Clinical Isolate 1.

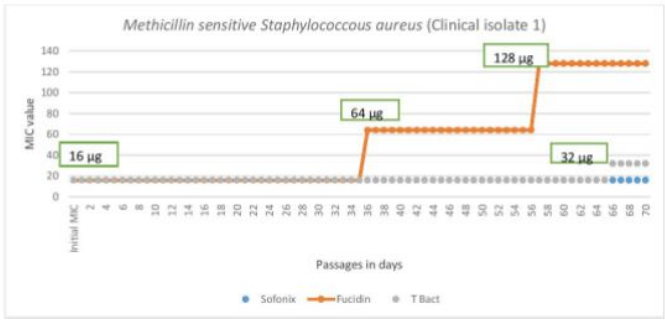


Fig. 8: MIC value for Methicillin sensitive *Staphylococcus aureus* Clinical isolate 2

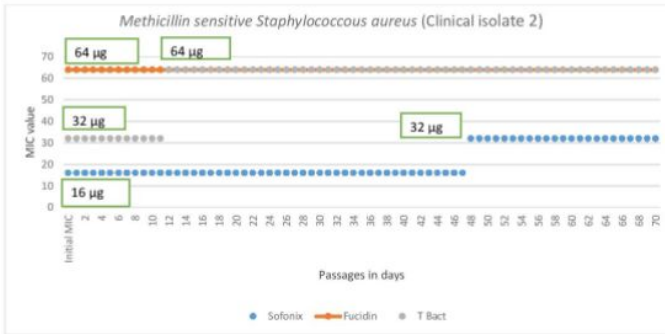


Fig: 9: MIC value for Methicillin resistant *Staphylococcus aureus* Clinical isolate1.

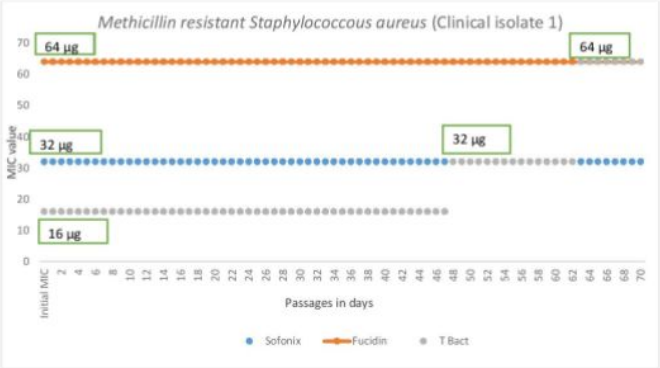
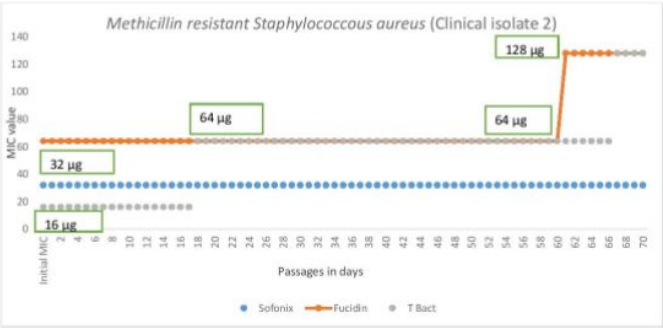


Fig: 10: MIC value for Methicillin resistant *Staphylococcus aureus* Clinical isolate2.



WGS analysis of the strains with Sofinox cream treatment (Fig 1), it was noted that 150 significant genetic variations to MSSA (ATCC 25923) reference strain and 84 number for MRSA (ATCC 700699) reference strain. *S. aureus* (ATCC 43300) and MSSA clinical isolate 1 showed raise in MIC, but there were no significant genetic mutations documented.

Fucidin cream: The Fucidin cream showed the MIC of 16 μg for MRSA standard strain ATCC700699, and one of the clinical isolates of MSSA and MIC value was 64 µg for the rest of the isolates (Table1). When all the strains were subjected to sub MIC concentration of respective MIC values, the MRSA standard strain ATCC700699 and one of the MSSA clinical isolate showed a four-fold rise in MIC by 36th passage (From 16 µg to 64 µg) and raised 128 µg by 70th passage as shown in Table 2. ATCC 43300 and ATCC 25923 showed a one-fold rise in MIC by the 57th passage, and one of the MRSA clinical strain showed a one-fold rise in MIC by the 62nd passage. One each of MSSA and MRSA clinical isolates did not develop resistant mutants even up to 70 passages.

WGS analysis of the strains with Fucidin cream treatment(Fig2), it was noted that 185 number of significant genetic variations to one of the clinical isolate of MSSA followed by 102 to MRSA standard strain ATCC700699, Standard strain ATCC 43300, ATCC 25923 and one of a clinical isolate of MRSA showed 95, 85 and 76 number of genetic variations respectively.

T Bact: The T Bact ointment showed the MIC of 16 µg for MRSA standard strain ATCC700699, *Staph aureus* ATCC 43300, one of the clinical isolates of MSSA, MRSA clinical isolates and MIC value was 32 µg for *S. aureus* ATCC 25923 and one of a clinical isolate of MSSA (Table 1). When all the strains were subjected to sub MIC concentration of respective MIC values, all the seven isolates developed resistant mutants. The MRSA standard strain ATCC700699 showed a one-fold rise in MIC by 61st passage, ATCC 43300 by 59th passage, One of the MSSA clinical isolate by 66th passage and another by 12th passage. ATCC 25923 strain showed one fold rise by 22nd passage and another fold rise by 69th passage (32 to 64 to 128 µg), One of the MRSA strain showed a two-fold surge in MIC by 63rd passage (32 by 48th passage and 64 by 63rd passage) and another MRSA stain showed a four-fold rise in MIC by 67th passage (64 by 18th passage and 128 by 67th passage) as shown in Table 2 and Figures.

WGS analysis of the strains with T Bact ointment treatment(Fig 3), it was noted that 158 number of significant genetic variations with Standard strain ATCC 25923 and one of the clinical isolate of MSSA, followed by 150 variations for ATCC 700699, 115 with ATCC 43300 and variations ranged from 89 to 85 with another strain of clinical isolate of MSSA and two clinical strains of MRSA.

The WGS analysis of the resistant strains did not show mutations in the resistant genes like fus A, fusB, fus C, fus D and mupR and showed genetic variations (SNP's) and mutations at a chromosomal level as discussed.

Discussion

Bacterial skin infections are the most common infectious diseases, and *Staphylococcus aureus* is the important pathogen associated with a skin infection. Topical antimicrobials are used for the prevention and treatment of skin infections[9]. In the clinical setting, topical antibiotics are used for 7 to 10 days, and if not cured, the antibiotics are changed, and in diabetic ulcers, it is used for about 4 – 6 weeks [10]. But the risk of using topical antibiotics is the development of bacterial resistance.

Multiple-passage studies determine the effect of selective pressure of antibiotics on microorganisms, resulting in the cumulative acquisition of mutations at the genetic level [11].

In the present study, resistant mutants were developed to sofinox by only one strain of *Staphylococcus aureus* (clinical isolate of MSSA) by 48th passage and with the one-fold rise in MIC value. Even WGS analysis showed no major genetic changes when exposed to serial passages. Both phenotypic and genotypic analysis results were suggesting, Sofinox cream had less potential to gain drug resistance by genetic mutations/variations even after reaching the threshold serial passages. One of the clinical isolates of MSSA and MRSA did not develop resistance for Fucidin cream till 70 passages. The Fucidin cream developed resistant mutants early for two strains (MRSA standard strain ATCC700699 and one of the MSSA clinical isolates by 36th passage), and the MIC value raised four-fold when compared to Sofinox, which developed mutants by 48th passage to one of the clinical isolates of MSSA and MIC value raised only two-fold.

WGS analysis of the strains with Fucidin cream treatment showed significant genetic variations to one of the clinical isolates of MSSA followed by MRSA standard strain ATCC700699. In contrast, Standard strain ATCC 43300, ATCC 25923 and one of a clinical isolate of MRSA showed minimum variations.

All the strains of *Staphylococcus aureus* studied showed the development of resistant mutants to T Bact. Four strains showed a one-fold rise in MIC value, two strains showed a two-fold rise, whereas one of the isolates showed a four-fold MIC increase value. The resistant mutants developed early, by 12th passages by one of the strains.

WGS analysis of the strains with T Bact ointment treatment showed significant genetic variations with Standard strain ATCC 25923 and one of the clinical isolates of MSSA, followed by

ATCC 700699, ATCC 43300, and minimum variations ranged with another strain of clinical isolate of MSSA and two clinical strains of MRSA.

In the present study, it was observed that Sofinox cream had less potential of resistant mutant development after serial passage both phenotypically and genotypically. D Dobie et al. [12] showed a limited understanding of fusidic acid resistance at the genetic, epidemiological, and clinical level, but there is a lack of good quality studies examining the clinical efficacy of topical fusidic acid in the skin and soft tissue infections.

A report from McDougal LK et al.[13] showed that the mupA gene is typically present on the mobile genetic elements. These plasmids typically carry resistance determinants to other antimicrobial agents (macrolides, gentamicin, tetracycline, and trimethoprim), suggesting that mupirocin use can result in drug resistance in *S. aureus*. In the present study, we observed no mupA gene present in the chromosomal region of tested strains but showing mutations and their consistency with MIC reports.

Antonov et al.[14], in their study, observed that there are high rates of Mupirocin resistance in MRSA isolates (55.4%), and MRSA was a strong preexisting risk factor for acquiring resistance to mupirocin. Another study reported 4.81% resistance of *S. aureus* clinical isolates to Mupirocin, and it was of high-level resistance by MIC[15]. They concluded that the resistance is bound to rise with the increased usage of mupirocin.15 In the present study, all the strains showed a rise in MIC, indicating high resistance potential.

Fritz et al.[16] reported no mutations within the mupA coding sequence when mupA gene was discordant and submitted for sequencing after alignment with the reference strain. This suggests the possibility of alternative mutation within the promoter region or other regulatory element, resulting in disparate results between genotypic and phenotypic testing. In our study, there was a discordant result obtained by genotypic characterization.

Conclusion

Sofinox cream had low resistance potential in vitro compared to Fucidin, whereas T Bact ointment had more resistance development potential. When the WGS analysis of the strains showing raise in MIC was analysed, even though major mutants in target genes were not observed, variations and mutations were noted at the chromosomal level. Strains exposed to T Bact showed more genetic variation followed by Fucidin cream, and the least variation was with Sofinox. Hence, the study shows that Sofinox cream is less likely to develop resistance compared to Fucidin cream and T Bact phenotypically and genotypically. Therefore, there is a less likely chance of developing resistant mutants with the topical use of Sofinox cream, even up to 8 weeks. This will be definitely an advantage of Sofinox in the management of skin and soft tissue infections.

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Disclosures

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