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A prospective double-blinded comparative analysis of framycetin and silver sulphadiazine as topical agents for burns: A pilot study

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ABSTRACT

Burn wound sepsis remains the leading cause of mortality if conservative methods of wound management are employed. Topical agents are still the mainstay of such wound management in the developing world. Non availability of agents like Mafenide or silver ion dressings in the developing world due to corporate strategies or cost concerns necessitates a search for alternatives to silver sulphadiazine, which is the gold standard. We report the use of framycetin 1% cream (Soframycin®) in 20 patients of major burns (ranging from 15% to 40% TBSA), and in a double blinded study quantitatively comparing the bacterial load on day 4 and day 7 with a group of similar patients in whom silver sulphadiazine was used. The age group of the 40 patients was 10–50 years and they were without any co-morbid condition. All bacterial isolates from the 40 patients were also tested for framycetin sensitivity. Serial kidney function tests were done on all patients, and patients in the framycetin group underwent an audiometric testing at a mean time of 28 days. All results were statistically analyzed. It was noted that there was no statistically significant difference in the colony counts on days 4 and 7 between the two groups. As a corollary, it was also evident that there was no statistically significant difference in the rise in colony counts from day 4 to day 7 in the two groups. Sixty-four percent of all bacterial isolates were sensitive to framycetin, although, this could not be compared with sensitivity to silver sulphadiazine. It was not possible to do assays for framycetin levels in blood but no patient developed nephrotoxicity or ototoxicity with its use. According to our pilot study results framycetin appears to be an alternative to silver suphadiazine as a topical agent for major burns. Framycetin application is also painless and it leads to no discoloration of the wound.

1. Introduction

Burns is still a major cause of mortality and morbidity in most of the developing world. Its management involves huge expenditure, time, effort, patience and diligence. The burn victim is under major physical, physiological and psychological stress. After the initial resuscitation, up to 75% of mortality in burn patients is related to infection [1]. Preventing

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infection, recognizing when it occurs, and treating it successfully presents considerable challenges. It has been evident that systemic antibiotics do not play a major role in prevention of invasive burn wound sepsis [2]. This is due to of the presence of necrotic avascular tissue around the burn wound which does not allow systemic antibiotics to reach the area of concern. Early excision and grafting is probably the best procedure to eliminate potentially necrotic and infected tissue and prevent development of sepsis. However, this procedure is very demanding in terms of work hours, blood bank support and operating theatre time, and is not amenable in an extremely high volume unit like ours, where there may be 4–5 major burn admissions per day [3]. Thus, we still need to develop cost-effective alternatives in wound management techniques to strengthen the armamentarium to prevent burn wound sepsis.

Framycetin is a sulphated salt of Neomycin B, in the aminoglycoside group. It has not been sufficiently evaluated in management of major burns, though, it has been used in the treatment of minor burns for many years. Data of its antibacterial spectrum obtained from European pharmacopeia (www.actavis.bg) [4] shows it to be active against *Staphylococcus* spp., including coagulase-negative *Staphylococci*, *Escherichia coli*, *Klebsiella* spp., *Salmonella*, *Shigella*, *Enterobacter* spp., *Proteus* spp., *Serratia marcescens*, *Pasteurella* spp., *Vibrio* spp., *Borellia*, *Leptospira* spp. and *Mycobacterium tuberculosis* including also *Streptomycin*-resistant strains. It shows comparatively high activity against some strains of *Pseudomonas aeruginosa*. Resistance to framycetin is hardly achieved even after very prolonged use [4]. This broad spectrum antibiotic is usually bactericidal in action. Although, the exact mechanism of action has not been fully elucidated, the drug appears to inhibit protein synthesis in susceptible bacteria by binding to ribosomal subunits [5]. The available literature suggests its toxic nature, when introduced parenterally, is nephrotoxicity and ototoxicity. However, like neomycin its absorption from the oral route is minimal. It is highly water soluble. With reference to the wide use of framycetin in otorhinolaryngology and others, it is accepted that the ototoxicity risks are insignificant after topical application [4]. No safe blood level for the drug is mentioned in literature.

There are a number of studies which elucidate the role of silver sulphadiazine (SSD), and its efficacy has been proven beyond doubt. SSD has a wide spectrum of bactericidal activity against both gram-positive and gram-negative organisms. Organisms that are susceptible to topical silver sulphadiazine include *Staphylococcus aureus*, *S. epidermidis*, *beta-hemolytic streptococci*, *Klebsiella*, *Escherichia coli*, *Enterobacter* (*including E. cloacae*), *Citrobacter*, *Proteus*, *Pseudomonas*, *Morganella morganii*, *Providencia*, *Serratia*, and *Candida albicans* [6]. In contact with body fluids, it is converted to sulfhydryl groups and proteins to free sulphadiazine, which can be systemically absorbed especially when applied to second or third degree burns. Systemic concentrations of sulphadiazine are detectable in some patients. Roughly 10% of sulphadiazine can be absorbed, while only 1% of free silver is absorbed [6]. Within 72 h, 60–80% of the absorbed drug can be collected in the urine either as metabolites or unchanged [6].

The comparable antibacterial spectrum as mentioned above for the two drugs and a report by Sawhney and Sharma in 1990 on the use of framycetin in major burns [7] prompted the senior author to use framycetin cream (1%) in burn management. Over the past 18 years there has been an extremely high level of satisfaction amongst burn specialists in the department which was never reported. Thus, in 2005 a pilot study was designed to further provide a scientific basis for its use as a topical agent in major burns.

2. Patients and methods

This prospective, double blinded study was performed in the department of Burns and Plastic Surgery, Lok Nayak Hospital, Delhi, over a period of 1 year from March 2006. The study was approved by the ethical committee of Lok Nayak Hospital. We limited our investigation to study the topical containment of bacterial colonization by both the agents towards the end of the first week, and to the bacterial sensitivity and clinical safety profile of framycetin. Since both the topical agents are white, creamy, of similar consistency, without any smell and with similar appearance in the wound, the user (dresser) could be easily blinded. 40 burn patients were studied by randomization. Topical agent for each patient was decided by cherry picking of 'lottery chits' from a jar having 20 chits for silver sulphadiazine and 20 chits for framycetin. All patients were then dressed daily with a 1 mm layer of the respective topical agent after a shower or cleaning the wounds with saline. Rest of the burn management was according to the procedure laid out in an earlier publication [3].

Burn patients were included in the study by following criteria.

2.1. *Inclusion criteria*

1. Patients between the ages of 10–50 yr. Older children were included as they obey commands, are sufficiently cooperative and their exclusion would have prolonged the period of study. The youngest patient in SSD group was 13 years, and 15 years in the framycetin group.
2. Patients presenting within 6 h of burn.
3. Patients having only flame burns or scalds.
4. Burns between 15% and 40% TBSA. Burns <15% TBSA were excluded as they are not routinely admitted in our burns ward for want of beds and those >40% TBSA have several other variables introduced, like septicaemia, which make evaluations more complicated for a pilot study.

2.2. *Exclusion criteria*

1. Patients with co-morbid conditions like chronic respiratory problems, ischemic or other cardiac disease and diabetes, etc.
2. Patients with inhalation injury.

The wounds were assessed by quantitative and qualitative estimation of the bacterial load, and also by culture sensitivity to framycetin. The microbiologist was blinded to the topical agent used for the patient. Punch biopsies (5 mm) from the wound were taken on day 4 and day 7, and transported to the microbiology lab in sterile containers. The tissue biopsies were

weighed, homogenized with 1 ml saline, and then 0.01 ml of it cultured on to Blood agar and Maconkey's plates. Biopsy specimens were cultured using lawn-culture technique to get individual colonies. Subsequently, bacterial colony count was done and approximated to per gram of tissue. All the isolates, from both groups, were then tested for sensitivity with 100 μg framycetin discs® (Himedia laboratories, India). Semi-quantitative counts were done, and plates were tested for antibiotic susceptibility using the Kirby Bauer method (official method of the United States Federal Drug Analysis). In the situation of 'confluent' growth i.e. when the bacteria have grown all over the plate and individual count was not possible, it was assumed that the colony forming units were over 10^5. We have also seen that since the amount of bacterial solution taken is about 0.01 ml (taken through micropipettes), when the bacterial counts reach between 80 and 100 on extrapolating the numbers the counts were greater than 10^5. Thus, we have taken confluent growth to mean any count greater than 10^5. This figure also assumes clinical relevance in terms of development of septicemia. Bacterial subcultures were done on all plates, irrespective of confluence or not, and antibiotics, if required were started according to the sensitivity reports.

The data was statistically analyzed to study:

1. significance of individual colony counts on day 4 between the two groups,
2. significance of individual colony counts on day 7 between the two groups,
3. statistical significance of rise in colony counts from day 4 to day 7 between the two groups,
4. age distribution,
5. percentage burn distribution.

Unpaired two-tail *P*-value, using non-parametric test was used with the assumption that the sample does not follow Gaussian distribution (for the points 1–3, and 5), and assumption that the sample follows Gaussian distribution (for the point 4).

Serial kidney function tests (KFT) were done for all 40 subjects till all wounds healed. The 20 patients in the framycetin group were further studied for ototoxicity by an audiometric evaluation near the time of discharge or at first follow up visit. It was not feasible to conduct audiometric testing at the time of admission to the burns unit to develop a point of reference. Blood estimations for framycetin levels and culture sensitivity to silver sulphadiazine were not possible.

3. Results

The application of framycetin was painless and there was no wound discoloration. No patient died in this study group. There were 80 wound biopsy samples. Age, gender, % TBSA burn and colony counts on day 4 and day 7 for each patient are given in Table 1 (framycetin) and Table 2 (silver sulphadiazine). Confluent growth was defined when individual colony count was not possible. This was arbitrarily taken as 10^5 for all statistical measurements.

Qualitative bacterial sensitivity testing provided 97 bacterial isolates from 80 wound biopsies. 62 of these bacteria were sensitive to framycetin. The qualitative culture sensitivity profile of bacterial isolates to framycetin is provided in Table 3. Thus, 64% of all bacteria isolated were sensitive to framycetin. Pseudomonas isolates had a high level of sensitivity to the agent (73%) with good sensitivity patterns for E. coli, Staphyococcus and Klebsiella. The number of isolates of Acinetobacter, Citrobacter and Proteus were too few to make any conclusions.

The samples were well matched for age with the mean age for framycetin group being 30.95 years (range 15–50 years) and

Table 1 – Subject distribution and quantitative estimation of colonies in framycetin group.

S. no.	Age	Sex	% TBSA Burn	Day 4 Colony count (gm)	Day 7 Colony count (gm)
1	21	M	25	29	2288
2	30	F	20	44	1667
3	35	F	40	Confluent	Confluent
4	26	F	15	162	333
5	17	F	35	0	Confluent
6	47	F	30	0	834
7	15	F	35	503	Confluent
8	27	M	20	35	1181
9	50	M	15	0	90
10	29	M	20	32	960
11	23	M	25	621	724
12	35	M	35	3541	6666
13	16	M	15	0	3487
14	41	F	20	3315	4715
15	29	F	40	4966	7433
16	48	M	25	255	10,695
17	31	F	20	0	9876
18	42	M	30	26	90
19	19	F	30	110	Confluent
20	38	M	25	213	5420

Table 2 – Subject distribution and quantitative estimation of colonies in silver sulphadiazine group.

S. no.	Age	Sex	% TBSA Burn	Day 4 Colony count (gm)	Day 7 Colony count (gm)
1	31	M	25	172	3642
2	23	M	15	0	118
3	18	M	20	0	38
4	45	M	35	3306	4415
5	50	F	25	440	615
6	25	M	30	204	1575
7	27	F	35	2156	2809
8	20	F	25	4560	7549
9	39	F	40	102	Confluent
10	19	F	40	315	Confluent
11	38	F	25	600	1234
12	23	M	10	0	512
13	47	F	30	0	2167
14	30	M	35	2984	6452
15	13	M	25	200	456
16	28	M	20	45	832
17	24	M	35	4232	Confluent
18	33	F	25	86	298
19	38	M	40	365	1765
20	43	M	35	0	231

Table 3 – Bacterial isolate profile and sensitivity to framycetin.

S. no.	Bacteria	Number isolated	Number sensitive to framycetin	Sensitivity percentage
1	Klebsiella	41	23	56
2	*E. coli*	11	7	64
3	*Staph aureus*	18	12	63
4	Pseudomonas	22	16	73
5	Acinetobacter	1	1	100
6	Citrobacter	2	2	100
7	Proteus	3	1	33

Table 4 – Statistical analysis on day 4 of the colony counts for the framycetin and silver sulphadiazine groups.

Title	Framycetin	Silver sulphadiazine
Mean	1192.65	988.4
Standard deviation	2518.8	1531.5
Sample	20	20
Standard error of mean	563.22	342.46
Median	77	202
Normality test KS	0.3898	0.3501

for silver sulphadiazine group being 30.7 years (range 13–50 years). The '*p*' value for unpaired *t*-test was 0.9440, which implies that the age difference was insignificant. Both the groups were also well matched in terms of % TBSA burns, with mean TBSA burn for framycetin group at 26% and 28.5% for silver sulphadiazine group.

Statistical study of the significance of individual colony counts on day 4 between the two groups is summarized in Table 4. The Mann–Whitney two-tailed result is 0.6068, which is non significant. Thus, there was no statistical difference between the colony counts on day 4 between the two groups. Statistical study of the significance of individual colony counts on day 7 between the two groups is summarized in Table 5. The Mann–Whitney two-tailed result is 0.2285, which is again non significant. Thus, there was no statistical difference between the colony counts on day 7 between the two groups. As a corollary from results in Tables 4 and 5 it is evident that there is no statistical difference in the rise in colony counts from day 4 to day 7 between the two groups. Although, there is a significant (and expected) quantum rise in colony counts from day 4 to day 7, in both the groups.

Table 5 – Statistical analysis on day 7 of the colony counts for the framycetin and silver sulphadiazine groups.

Title	Framycetin	Silver sulphadiazine
Mean	4822	3234
Standard deviation	4115.6	3579.5
Standard error of mean	920.8	800.4
Median	4101	1665.5
Normality test KS	0.1902	0.2173

Serial kidney function tests conducted on all 40 patients were within normal limits. The audiometric testing in framycetin group was done at a mean time of 28 days and it revealed no derangement in any of the patients. Thus, the use of framycetin did not lead to any nephrotoxicity or ototoxicity.

4. Discussion

Many agents have been reported to be successful in containing burn wound infection [6,8,9]. It is a good strategy for burn units largely pursuing conservative wound management techniques to continuously switch topical agents to prevent the development of resistance. Some agents like Mafenide and silver impregnated dressings still remain unavailable in many developing countries because of corporate strategies. This necessitates the search and use of alternative topical agents.

There have been a few studies which have discussed the role of framycetin in minor burns [10,11]. However, it is quite fortuitous that there is not a single study which analyzes the use of framycetin in major burns. The only article documenting the use of framycetin in major burns is by Sawhney and Sharma [7]. By clinical evaluation, qualitative bacterial culture profile and blood culture estimation they found framycetin to be useful in management of major burns. The quantitative estimation of bacterial load and side effect profile of the topical agent was not addressed in that paper. In fact, a relatively recent article [12] mentions the use of topical antimicrobials like bacitracin and neomycin but there is no mention of the use of framycetin; even though framycetin and neomycin belong to the same group of drugs.

As mentioned earlier, the antibacterial spectrum of framycetin closely matches the spectrum for SSD, which is further confirmed by our study. Not only that, even after its use for past 18 years, 64% of all bacterial isolates are still sensitive to framycetin, while the sensitivity to pseudomonas is 73%. The percentage of overall sensitivity may appear to be low but clinical absence of septicaemia points to a higher level of containment. SSD has also been used uninterruptedly for a similar period and this is the main reason for increase in bacterial loads between day 4 and day 7 in each group. It would have been very informative to know the sensitivity pattern for SSD, but unfortunately discs for SSD are not available in India. Attempts to create discs of SSD in our laboratory were also not very successful as they could not be standardized. From this study it is also observed that the quantitative analysis of bacterial loads on day 4 and day 7 are similar for the two drugs, and by corollary, the rise in bacterial load on day 7 is also comparable. This obviously implies that the level at with the wound infection gets contained by the two drugs is very similar, at least in the first week of treatment.

In contact with body fluids, SSD it is converted to sulfhydryl group to free sulphadiazine, which can be systemically absorbed especially when applied to second or third degree burns. Systemic concentrations of sulphadiazine are detectable in some patients. Roughly 10% of sulphadiazine can be absorbed, while only 1% of free silver is absorbed [13]. Within 72 h, 60–80% of the absorbed drug can be collected in the urine either as metabolites or unchanged [13]. Since framycetin is

water soluble, there is fear of absorption of the drug leading to nephrotoxicity or ototoxicity. Perhaps, this is the reason why the drug has not been reportedly used in major burns. We were unable to obtain a spectrophotometric blood assay to ascertain framycetin levels in our patients. Our enquiries revealed that this assay was also not available across major burn units of the world. Thus, we had to rely on serial KFTs and audiometric tests to determine its toxicity. It was heartening to note that we did not get a permanently deranged KFT report in any patient who was part of the study. No patient complained of difficulty in hearing on admission or later in follow up. This was also documented by audiometric tests done at a mean time of 28 days from admission.

We initiated our study with the hypothesis that SSD was better than framycetin as a topical agent and hence if this had been the outcome of the study, 20 patients per arm would have been sufficient for a >90% power. Since our study prima facie reveals a level of comparable efficacy between framycetin and SSD as topical agents in <40% TBSA burns it is now necessary to study more than 2000 patients for a >95% power. Just as the efficacy of SSD has been proven beyond doubt results of our pilot study indicate that there is a need to further study and develop framycetin as a topical agent for burn management. It is also pertinent to note that there is not a single study with so many patients comparing silver ion dressings and yet they are as much a gold standard as SSD. Besides, other outcome measures need to be studied as well, like the level of eschar penetration, blood levels of framycetin with topical application, septicaemic episodes, period of hospitalization and cost analysis etc. in a multi-centric trail.

Disclaimer

Authors have no financial interest in the drug framycetin. Sanofi Aventis which currently manufactures and distributes Soframycin cream® was not aware of this study.

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