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Locally Produced Microbial Cellulose Dressing from *Acetobacter xylinum* Compared with Silver Sulfadiazine Cream for Patients with Acute Superficial Partial Thickness Burn Wounds: A Randomized Controlled Trial

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Objective: To compare the efficacy and safety of microbial cellulose (MCD) dressing from *Acetobacter xylinum* in promoting healing of superficial partial thickness burn wounds to standard dressing using silver sulfadiazine (SSD) cream and gauze in terms of the following: time to healing, pain score, scarring and infection rate.
Population: Subjects included patients seen at the ATR Burn Center UP-PGH from February 2008 to December 2010. Patients were 18-50 years of age with < 40% TBSA, acutely injured (≤ 48 hours) and with no uncontrolled medical condition. Pregnant patients were excluded.
Methods: Each subject served as his own control, wherein burn wounds were randomized into 2 types of wound dressing. Wounds were assessed by a lone plastic surgeon blinded to all treatments.
Results: Forty five patients who fulfilled the inclusion criteria were seen and treated at the ATR Burn Center of the UP-PGH. Wounds dressed with MCD healed more rapidly compared to those dressed with SSD. The mean healing days were 8.51 and 12.07 for MC and SSD ($P<0.05$), respectively. The pain scores at rest and during dressing were lower in patients dressed with MCD than those dressed with SSD ($P<0.05$). Only 29 subjects were able to return on the 30th post burn day for assessment of scarring.
Conclusion: Locally produced MCD is more efficacious compared to SSD in the treatment of SPT burns in terms faster healing and lower VAS scores.

Key words: superficial partial thickness burn, Acetobacter xylinum

Burn injury continues to be a significant cause of morbidity and mortality among the general population in the local setting due to lack of able burn centers and among others, the high cost of wound dressing materials that are available and widely accepted. At the ATR Burn Center of the Philippine General Hospital alone, Espiritu and his group reported an overall mortality rate of 8.42%.[1] More importantly, majority of the patients in the same study had superficial partial thickness burns and were treated on an outpatient basis. Topical silver sulfadiazine (SSD) cream is currently considered the standard of treatment for these burns.[2] The growing expense as to the use of this mode of dressing coupled by unwanted side effects such as leucopenia, painful daily dressing changes and pseudoeschar formation has led the investigators to consider alternative dressing materials.

Microbial cellulose, a versatile biomaterial, is a polysaccharide synthesized by *Acetobacter xylinum* from glucose, sugar, glycerol and other organic substances. Its structure has been described to have a close resemblance to the innate extracellular matrix structure and acts as a scaffold for regeneration of tissues such as skin and blood vessels during wound healing.[3,4] A moist environment coupled by decreased trauma to the wound bed is essential for significantly faster reepithelialization.

Several applications of this biomaterial have been seen in the health food industry (nata de coco), audio components and wound care products.[5] As a wound care product, exploratory investigations were pioneered in the early 1980s by Johnson and Johnson, followed by Biofill Industrias of Brazil in the 1990s.[5] In the Philippines, the antimicrobial properties of micocellulose have been investigated by Dominguez and cohorts in a 1996 study at the De La Salle University. It was shown that nata de coco possesses in-vitro bacteriologic activity against microorganisms due to its acidic nature. *Staphylococcus aureus, Eschericia coli, Pseudomonas aeruginosa* and *Enterobacter*, the same organisms found in burn wound infections were found to be susceptible.[6] Properties of microcellulose membranes and how they relate to the properties of an ideal wound dressing material are summarized in the appendix.

To compare the efficacy and safety of locally-produced microbial cellulose (MCD) dressing in promoting healing of superficial partial thickness burn wounds to standard dressing using silver sulfadiazine (SSD) cream and gauze in terms of time to healing infection rate, pain score, and scarring a clinical trial was conducted at the ATR Burn Center of the PGH.

Methods

This is a randomized controlled trial of all burn patients admitted to or who underwent outpatient treatment at the ATR Burn Center. All patients18-50 years old who consulted within 48 hours post-burn injury with not more than 40% TBSA superficial partial thickness burn wounds, and without significant co-morbidities during start of treatment (severe infections, uncontrolled hypertension or diabetes, severe systemic disease). Patients with inhalational injury and other associated injuries, allergies to coconut products or iodine or pregnant at the start of treatment were excluded.

Two separate areas with superficial partial thickness burns 1%-5% TBSA in the same patient were randomized into two treatment groups using a block randomization of 2 pairs of treatment, in pre-randomized sealed envelopes. Appropriate sample size was calculated considering a projected 10% significant different in the reduction of burn surface area and 80% power.

Microcellulose dressing (VERMAC® - locally patented by Mr. Denver Chicano, RN) was provided in separately wrapped and autoclaved airtight containers. Subjects who were able to meet the inclusion criteria were informed of the study with a written consent secured by the investigators. All demographic data were recorded.

All wounds were debrided and washed with povidone iodine 7.5% and pNSS. Aseptic technique was observed in all wound dressings. Superficial partial thickness burns 1%-5% TBSA in the same individual were randomized into two treatment groups using a block randomization of 2 pairs of treatment, in pre-randomized sealed envelopes. These wounds, approximately of the same surface area, were described accurately in the patient forms according to location (i.e. part of the body involved) and size and pictures were taken on each consult.

Treatment arm A (experimental group) was composed of subjects dressed with microcellulose secured with gauze and elastic bandages. The dressings were changed every three days, after washing the wound with povidone 7.5% and plain saline solution. Each of the wounds was carefully observed on each follow-up.

Treatment arm B (control group) was composed of subjects dressed everyday with standard silver sulfadiazine 1% cream, moist gauze after washing the wound with povidone 7.5% and plain saline solution. Each of the wounds was carefully observed on each follow-up

The area of reepithelialized burn wounds was estimated at each visit by a single investigator (senior plastic surgery resident) blinded to the treatment given. All patients were given pain medications (mefenamic acid) during treatment as dictated by the Burn Unit protocol and the VAS scores recorded during dressing and while at rest when no direct manipulation of the wound was being done. No antibiotics were given during the course of treatment. Temperature was monitored every 4 hours and recorded during the initial phase of treatment (i.e., 48 hours). Antipyretics were given for temperature >38.5ºC.

All patients were asked to follow-up daily at the ATR Burn Unit on the first 3 days post injury, then every 3 days thereafter until the wound had completely epithelialized. The wounds, once fully epithelialized, were left open and with moisturizer applied until follow-up on days 30, 60, 90, 180 post burn. The resulting scar was graded using the Vancouver scar scale on the succeeding follow-ups.

If with signs of wound infection on clinical examination, i.e., with surrounding erythema, purulent discharge, persistent high grade fever, with no other identifiable cause, patients were admitted. Tissue culture was requested, with treatment of experimental group shifted to daily dressing with silver sulfadiazine cream, oral/IV antibiotics was started and the need for surgery was assessed. All events were carefully documented.

Daily wound assessment was performed by a senior Plastic Surgery resident who was blinded as to what dressings were used.

Epi Info version 3.5.1 software was used for data encoding and data analysis.

Results

Forty five patients who fulfilled the inclusion criteria were seen at the ATR Burn Center of the Philippine General Hospital from February 2008 to December 2010. Ninety five percent of the study population were males with a mean age of 32.42 years (±10.09). Mean %total body surface area (%TBSA) involvement was noted at 12.79(±8.07). In terms of etiology, injuries due to flame burns were noted to be the highest at 51.11%, followed by scald burns (26.67%) and then by electrical burns (22.22%). (Table 1). Only 2 out of 45 subjects were noted to have seizure disorders, otherwise, most of them did not have any co-morbid medical conditions.

All wounds were evaluated daily as to percent reepithelialized or healed. The rate of wound healing was faster in wounds dressed with microcellulose dressings than those dressed with SSD. The mean healing rates to complete reepithelialization of burn wounds dressed with MCD and SSD were 65.01 (95% CI: 60.54 to 69.48) and 59.58 (95% CI: 55.37 to 63.79), respectively. (Table 2)

Table 3 shows the mean healing rate between MCD and SSD at a day of treatment. There was a statistically significant difference in healing rates noted on days 3, 6, 9 and 12. Wounds dressed with microcellulose healed more rapidly compared to those dressed with SSD. The mean time in days to complete reepitheliazation dressed with MCD was lesser than those dressed with SSD (P=0.000). The mean healing days were 8.51 (95% CI: 7.55 to 9.47) and 12.07 (95% CI: 11.22 to 12.91) for MCD and SSD, respectively. (Table 4)

Table 1. Demographics.

Characteristics	Frequency (n)	Percentage (%)
AGE (in years)		
17-30	21	46.67
31-40	12	26.67
41-50	12	26.67
Total	45	100
Mean(±SD)	32.42 (±10.09)	
SEX		
Male	2	4.44
Female	43	95.56
ETIOLOGY		
Electrical	10	22.22
Flame	23	51.11
Scald	12	26.67
TBSA (%)		
3-10	23	51.11
11-20	14	31.11
21-40	8	17.78
Mean(±SD)	12.79 (±8.07)	

Table 2. Summary measures and 95% confidence interval of the wound healing rate of reepitheliazation for MCD and SSD.

Treatment	Mean(±SD)	95% CI
MCD	65.01(±43.13)	(60.54,69.48)
SSD	59.58 (±40.61)	(55.37,63.79)

The pain scores at rest were lower in patients dressed with MCD than those dressed with SSD. The mean pain scores were 2.59 (95% CI: 2.25-2.92) and 3.74 (95% CI: 3.39-4.10) for MCD and SSD, respectively. (Table 5). There was a statistically significant difference in pain scores on days 2, 3, 6, 9 and 12. (Table 6)

The pain scores during dressing changes were lower in patients dressed with microcellulose dressing than those dressed with SSD. The mean pain scores were 1.90 (95% CI: 1.58-2.22) and 5.04 (95% CI: 4.65-5.44) for MCD and SSD, respectively. (Table 7). There was no statistically significant difference in pain scores between MCD and SSD on admission (P=0.790). (Table 8)

There were no noted signs of infection (i.e. persistent temperature >38.5ºC, peripheral erythema) in any of the subjects. Therefore, infection rate was zero.

Of the 45 subjects, only 29 subjects were able to return on the 30th post burn day for assessment of scarring. The mean Vancouver scores for MCD and SSD dressing were 2.51 (95% CI: 2.34-2.69) and 3.22 (90% CI: 2.97-3.48), respectively. (Table 9).

Discussion

A burn dressing has three principal functions: protection, metabolism and comfort.[7] During thermal injury, the physical protective barrier and the mild antiseptic property

Table 3. Test of the difference of mean healing rate between MSD and SSD at a day of treatment.

Day	Estimated Mean Pain Score		Estimated Difference	P-value
	MCD	SSD		
1	0.00	0.00	0.00	-
2	0.00	11.78	-11.78	0.0000
3	50.11	32.67	17.44	0.0023
6	77.78	58.00	19.78	0.0003
9	93.11	80.56	12.56	0.0003
12	99.11	94.78	4.33	0.0069
15	100.00	98.89	1.11	0.2260
18	100.00	100.00	0.00	-

Table 4. Summary measures, 95% confidence interval and test of mean time difference (in days) to complete reepitheliazation for MCD and SSD.

Treatment	Mean(±SD)	95% CI	P-value
MCD	8.51(±3.19)	(7.55,9.47)	0.0000
SSD	12.07(±2.82)	(11.22,12.91)	

Table 5. Summary measures and 95% confidence interval of the pain scores for MCD and SSD at rest.

Treatment	Mean(±SD)	95% CI
MCD	2.59 (±3.21)	(2.25,2.92)
SSD	3.74 (±3.43)	(3.39,4.10)

Table 6. Test of the difference of mean pain scores between MSD and SSD at rest.

Day	Estimated Mean Pain Score		Estimated Difference	P-value
	MCD	SSD		
0	7.27	8.09	-0.82	0.1435
1	6.53	7.09	-0.55	0.3111
2	3.47	5.62	-2.16	0.0000
3	2.31	4.22	-1.91	0.0000
6	0.93	0.82	-1.89	0.0000
9	0.20	1.60	-1.40	0.0000
12	0.02	0.40	-0.38	0.0048
15	0.00	0.09	-0.09	0.1561

Table 7. Summary measures and 95% confidence interval of the mean pain scores for MCD and SSD during dressing.

Treatment	Mean(±SD)	95% CI
MCD	1.90 (±3.08)	(1.58,2.22)
SSD	5.04 (±3.80)	(4.65,5.44)

that the epidermis provides are lost. In small burns, a dressing can isolate the wound from environmental flora. Dressings, specifically the occlusive type, reduce evaporative heat loss, cold stress and shivering. Most importantly, dressings provide comfort by eliminating air currents from the wound surface.

Several wound dressings that target burn wounds are available locally but are mostly expensive, thus rendering them useless to the majority of the Filipino patients. Of the topical agents, silver sulfadiazine is the most frequently used prophylactic topical antimicrobial in burn patients.[7] SSD has been proven to have in vitro activity against a wide range of organisms, including *S. aureus, E. coli, Klebsiella species, Pseudomonas aeruginosa, the Enterobacteriacceae, Proteus and Candida albicans*. The disadvantages to using SSD are transient leucopenia, daily dressing changes and pseudo-eschar formation, with the later causing confusion in burn wound assessment for the inexperienced eye. SSD is also quite expensive.

MCD has a nanoporous fibrillar structure that prevents penetration of microorganisms, is highly absorbent (can prevent exudate formation but maintains moisture within the mound environment) and conforms

Table 9. Summary measures and 95% confidence interval of the grading of scarring between patients whose wounds healed with MCD and SSD dressing.

Treatment	Mean(±SD)	95% CI
MCD	2.51(±0.84)	(2.34,2.69)
SSD	3.22(±1.23)	(2.97,3.48)

Table 10. Estimate costs of dressing for MCD and SSD for each percent TBSA.

MCD	SSD
Microcellulose dressing (10.5" x 6.5") P400	Silver sulfadiazine ointment 5g P215
Sterile gauze pack (4" x 4", 3 pcs) P12	Sterile gauze pack (4" x 4", 5 pcs) P20
Rolled gauze P18	Rolled gauze P18
pNSS P100	pNSS P100
Betadine scrub 7.5% P187	Betadine scrub 7.5% P187
Sterile gloves 2 pcs P40	Sterile gloves 2 pcs P40
Daily dressing P821.00	Daily dressing P700.00
Cost for three days P821.00	Cost for three days P2100.00

Table 8. Test of the difference of mean pain scores between MSD and SSD during dressing at a day of treatment.

Day	Estimated Mean Pain Score		Estimated Difference	P-value
	MCD	SSD		
0	8.56	9.11	-0.56	0.0790
3	4.00	6.64	-2.64	0.0000
6	2.02	4.44	-2.42	0.0000
9	0.53	2.38	-1.46	0.0000
12	0.07	0.64	-0.58	0.0039
15	0.04	0.18	-0.13	0.2338

to any irregular surface allowing ease of application.[8,9,10,11] If microbial cellulose can be successfully mass produced, it will eventually become a vital biomaterial and will be used in the creation of a wide variety of medical devices and consumer products.[8] Through the years, the use of microbial cellulose for wound care has been studied. In Brazil, Fontana, et al. (1990) found that use of micocellulose (Biofill®) for burns and chronic ulcers resulted in accelerated wound healing, pain relief, protection against microorganisms and lesser cost of treatment.[12,13] In Poland, Czaja and his group had similar results as to the use of microcellulose in second degree burns.[8,9] A study by Alvarez, et al. in 2004 with regard to using microcellulose in chronic leg ulcers showed earlier wound granulation and faster reduction of wound surface area.[14]

The study on locally-produced microbial cellulose from Acetobacter xylinum compared to silver sulfadiazine cream for use in superficial partial thickness burns in terms of healing rate, pain relief and degree of scarring has shown very promising results. The rate of reepithelialization / healing was noted to be faster in the set of subjects treated with MCD. Occlusive dressings affect wounds by trapping moisture next to the wound bed. This moisture is thought to protect the wound surface by preventing desiccation and additional trauma. Desiccation and trauma impede the migration of new epidermal cells across the wound surface.[15] Daily dressing changes with SSD may have resulted in repeated microscopic trauma to the wound bed and therefore a slower rate of reepithelilization. Pain score at rest and during dressing was notably lower with MCD, first because of more infrequent dressing changes compared to SSD and a less adherent property of MCD. In terms of healing rates and pain scores, MCD compared to SSD had statistically significant differences. With regard to scarring, however, it would be difficult to come up with a conclusion since only 29 out of the 45 subjects were able to follow-up on the 30th day post burn. Although mean Vancouver scores were lower for MCD, scarring was difficult assess due to lack of patient follow-up and its short duration. The phase of wound remodeling typically lasts from the 21st post injury day to at least a year.[16]

The infrequent dressing changes have made MCD a more practical choice for outpatient burn wound care since it would entail lesser need for burn unit staff manpower and a cheaper equally efficient alternative wound dressing for the indigent patient. A 10.5" x 6.5" sheet of MCD costs approximately PhP 400.00 compared to a PhP 737.00 10" x 10" sheet of hydrocolloid / hydrofiber dressing. The authors' estimated costs of dressing for 3 days of MCD versus SSD are shown in Table 10.

Absence of pseudo-eschar formation in MCD dressings clearly provide the advantage of accurately assessing the depth of burn wounds along the course of treatment. Any progression in depth can be detected immediately with appropriate treatment such as surgery accorded.

The local production of microbial cellulose will generate jobs and livelihood for millions of Filipinos, boosting not only the health sector in terms of advancement in burn wound care but also improving the country's economy.

Conclusion

Locally produced microbial cellulose is significantly efficacious compared to silver sulfadiazine in the treatment of superficial partial thickness burns in terms of faster reepithelialization and less pain both at rest and during dressing. A conclusion for its difference in terms of scarring could not be derived due to lack of patient follow-up.

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Appendix. Properties of microcellulose membranes and how they relate to the properties of an ideal wound dressing.[5]

Properties of Ideal Wound Care Dressing	Properties of Microcellulose
maintain a moist environment at the wound/dressing surface	high water holding capacity (typical membrane can hold up to 200 g of its dry mass in water); high water vapor transmission rate
provide physical barrier against bacterial infections	nanoporous structure does not allow any external bacteria to penetrate into the wound bed
highly absorbable	Partially dehydrated membrane is able to absorb fluid up to its original capacity. Physical processing of the membrane (i.e., squeezing) can remove part of the initial water and allow the membrane to be more absorbable
sterile, easy to use, and inexpensive	Membranes are easy to sterilize (by steam or ç-radiation) and package. The estimated cost of production of 1 cm^2 is $0.02 (P1.00)
available in various shapes and sizes	ability to be molded in situ
provide easy and close wound coverage, but allow easy and painless removal	high elasticity and conformability
significantly reduce pain during treatment	the unique MC nano-morphology of never-dried membrane promotes specific interaction with nerve endings
provide porosity for gaseous and fluid exchange	highly porous material with pore sizes ranging from several nanometers to micrometers
non-toxic, non-pyrogenic, and biocompatible	biocompatible, nonpyrogenic, nontoxic
provide high conformability and elasticity	high elasticity and conformability
provide mechanical stability	high mechanical strength