

Incontinence-associated dermatitis (IAD) study: Blinded assessment and treatment with zinc oxide-based ointment



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ABSTRACT

Background and objective: For prevention and treatment of incontinence-associated dermatitis (IAD), structured skin care regimens including gentle cleansing and a skin protectant are recommended. This trial compared two zinc oxide-based skin ointments used for the treatment of IAD.

Methods: Two-arm, randomised controlled trial with independent, blinded outcome assessment. Population: children >12 years and adults with urinary and/or faecal incontinence and IAD. Following informed consent, participants were randomised to receive a structured skin care regimen for one week with either Calmoseptine Ointment or Desitin Maximum Strength Diaper Rash Paste. Primary outcome: percentage of participants completely healed, defined as an IAD severity score of zero on the Kennedy Skin Condition Assessment Tool. Secondary outcomes: daily IAD severity scores; daily size of area affected by IAD; daily pain and itch.

Results: Treatment groups were equivalent at baseline in terms of IAD severity scores, area affected and demographic characteristics. Frequency and type of incontinence were similar throughout the study period. In the Calmoseptine group, significantly higher numbers of participants were completely healed on day 6 ($p=0.009$) and there were greater reductions in area affected on all follow-up days ($p=0.000$). A higher prevalence of more severe IAD remained in the Desitin group on days 4 ($p=0.024$), 5 ($p=0.035$) and 6 ($p=0.039$).

Conclusions: Used within a structured skin care regimen for treatment of IAD, Calmoseptine is more effective than Desitin in terms of complete healing and reduction of area affected.

BACKGROUND

Incontinence-associated dermatitis (IAD) is an inflammation of the skin associated with exposure to urine or stool. It is one of several types of moisture-associated skin damage (MASD) caused by prolonged contact with body secretions or moisture of various kinds¹⁻⁴. IAD can occur not only in all parts of the perineum and perigenital area but can extend to the inner and posterior thighs and gluteal regions and may lead to extensive skin destruction⁵. It is often accompanied by secondary bacterial and fungal infection, commonly candidiasis. Although few studies have determined the incidence of fungal infection in IAD, one found that of 198 patients with urinary, faecal or double incontinence,



nearly one in five IAD patients had evidence of co-existing cutaneous candidiasis^{6,7}. IAD can result not only in physical harm to patients, but also in extreme itching and in some cases pain that has been likened to that of burns.

The aetiology of IAD is multifactorial. The normal barrier function of healthy skin can be undermined by increased pH levels resulting from ammonia in urine, which affects skin cells' fatty acid content and the lipid barrier. Normal stool is also alkaline, as is perspiration, which commonly occurs when diapers are worn. Overgrowth of microorganisms from urine or stool can create changes in the skin's normal flora that can lead to irritation or infection and further undermine the skin's barrier mechanism. Skin that is already compromised by these effects can be further damaged by pressure, shear or friction resulting from a patient's bedbound status, repositioning, diaper use and cleansing⁸.

IAD is a common problem in patients with urinary, faecal or double incontinence and can affect any age group. Estimates for the prevalence of IAD are affected by the settings and populations studied, which vary from 5.6% to 50%³. In a survey conducted over 24 hours of all adult medical, surgical and critical care patients (n=976) in three US hospitals in 2005, 35% were catheterised and excluded from further examination. Of the remainder, 20.3% (n=198) were incontinent of urine (2.6%), stool (13.0%) or both (4.7%) in the previous 24 hours. Of these uncatheterised incontinent patients, 27% (n=54) had IAD, 5.5% of the total survey population⁷. A similar survey of all paediatric patients in a US university-affiliated hospital found that of 252 patients, nearly 60% were incontinent of urine, stool or both and of these 16% developed diaper-related dermatitis⁹. Factors that increase the risk of IAD include prolonged contact with wetness, occlusion of the skin through prolonged wearing of wet diapers, increasing age, and the coexistence of urinary and faecal incontinence¹⁰.

Treatment of IAD aims to halt and reverse its progression and to heal the affected area. Consensus guidelines recommend a structured skin care regimen that includes gentle perineal skin cleansing and moisturisation after each episode of incontinence, particularly if faecal matter is present. Vigorous cleaning is discouraged as it may damage previously compromised skin, and combination preparations are encouraged as they reduce the amount of patient handling and the potential for discomfort^{3,6}. The application of a skin protectant is recommended to reduce the skin's contact with urine and/or stool, at least daily and more frequently in those affected by frequent or high-volume incontinence episodes³.

However, there is a scarcity of research evidence relating to the treatment of existing IAD. The quality of much of the research that has been conducted has been considered poor, often affected by methodological issues and low sample sizes¹¹. Recent extensive reviews of the literature identified few studies that evaluated treatment-focused

regimens^{3,6,11}. The most frequently used skin protectants in the prevention or treatment of IAD are petrolatum, zinc oxide or dimethicone-based ointments. Although they are widely used, there is little research into their efficacy, possibly because these products can be marketed without such evidence^{12,13}. Reviews found only one published randomised trial that considered the effectiveness of zinc-based ointments for treatment of IAD^{3,6,11,14}. The reviews called for high-quality research evaluating the effectiveness of regimens and products used in the treatment of IAD^{3,6,11}.

This paper reports a randomised controlled trial that compared the use of two leading topical zinc oxide-based diaper rash ointments in a structured skin care regimen for the treatment of IAD in hospitalised adults and older children. The study aimed to compare the effectiveness of the two products in completely healing or improving IAD.

METHODS

Study design and patient eligibility

The study was a single-centre, randomised, controlled, assessor-blinded clinical trial. Patients were assigned to receive a structured skin care regimen with either of two zinc oxide-based topical ointments for IAD. The study was conducted in Philippine General Hospital, a tertiary, government-funded university hospital in Manila, the Philippines, which admits both private and charity patients.

All participants were inpatients at the Philippine General Hospital. Older children (≥ 12 –17 years old) and adults (≥ 18) who had urinary and/or faecal incontinence or were functionally incontinent and had IAD were potentially eligible for inclusion. Additional inclusion criteria included: signed informed consent or assent; reasonable expectation that they would be hospitalised for seven days in order to complete the study; no known allergy to any treatment ingredients; IAD score ≥ 3 according to the Kennedy Skin Condition Assessment Tool (described later). Exclusion criteria included: pre-existing pressure ulcer Stage 3 or 4 or other full-thickness wound within the study area; active dermatological condition that may affect healing of IAD, or history of such; acute or chronic medical condition such that trial participation may affect medical care; treatment within previous week with other topical IAD treatments or agents that may affect IAD healing; known allergy to any treatment ingredients.

Patients were allowed to withdraw from the study at any time. In addition, automatic withdrawal could occur on discharge from the hospital, upon attending physicians' request for therapeutic reasons, addition of topical therapeutic agents such as topical antibiotics or antifungals to the study IAD treatment, deviation from the structured skin care regimen for more than 24 hours, occurrence of a pressure ulcer Stage 3 or 4 within the study area, serious adverse event, or worsening medical condition. Withdrawals were not



Figure 1: Blinded assessment procedure by WOCN

replaced, and the data up to withdrawal day were included in intention-to-treat (ITT) analyses.

Randomisation and blinding

Randomisation was computer-generated. Treatment allocation was assigned by the surgical research unit, which was not linked to the study team. Blinding of participants and study clinical staff was not possible because the investigational products differ in appearance and odour. However, assessment of the primary IAD severity score outcome was conducted by independent Wound, Ostomy and Continence Nursing Certification Board (WOCNCB)-certified wound care expert assessors who were blinded to treatment allocation.

Structured skin care regimen and products

All patients recruited to either arm of the trial received a structured care regimen for treatment of IAD for six days following study entry. At least twice daily and as required by incontinence episodes, treatment and care was provided by nurses and nursing aids trained in the study regimen to

ensure its consistent implementation. Wet or soiled diapers were removed and the affected area was gently cleansed with plain saline, a polihexanide wound cleansing solution, gauze pads and soft tissue. Vigorous cleansing and scrubbing was strictly avoided. A thin layer of the study topical ointment was applied prior to putting on a new diaper. IAD kits containing all the materials required were prepared for each patient daily, including the same brand of diapers for all patients, skin cleansing products and materials, and the assigned study ointment.

Participants were assigned to one of the two zinc oxide-based topical ointments: Calmoseptine Ointment or Desitin Maximum Strength Diaper Rash Paste. The primary active ingredients of Calmoseptine are zinc oxide (20%), which forms a moisture barrier, and menthol, which soothes skin discomfort. Other ingredients include chlorothymol (antiseptic and antifungal), glycerin (emollient with water-retaining properties that absorbs moisture from inflamed tissues and mucous membranes), lanolin (moisturising skin conditioner with good skin penetrability, which facilitates the absorption of other ingredients), sodium bicarbonate (antipruritic), phenol (antiseptic) and thymol (antiseptic, antifungal and deodoriser). The active ingredients of Desitin Maximum Strength Original Paste are 40% zinc oxide, lanolin, petrolatum (moisturising ointment base) and cod liver oil (skin moisturiser and protectant).

Data collection and outcome measures

Upon recruitment to the study and initiation of the structured skin care regimen (day 0), data were collected using standard case report forms on IAD outcomes (Kennedy IAD severity score, total area affected by IAD), participant characteristics (age, sex, height and weight, public or private patient status) and health status (incontinence episodes in the preceding 24 hours, ambulatory status, primary diagnosis and co-morbidities, medications, albumin levels). On subsequent days (days 1–6) data were collected on incontinence episodes in the preceding 24 hours and IAD outcomes. At each data collection, high-definition photographs were taken using

Box 1: The Kennedy Skin Condition Assessment Tool. Skin is assessed according to the three domains, in which a score is attributed in line with the descriptions for each. The Kennedy IAD severity score is the sum of scores for the three domains.

Domain	Attributable domain scores			
	0	1	2	3
Area of skin breakdown	None	Small area (<20 cm ²)	Moderate area (20–50 cm ²)	Large area (>50 cm ²)
Skin redness	No redness	Mild redness (blotchy and non-uniform)	Moderate redness (severe in spots, but not uniform)	Severe redness (uniformly severe in appearance)
Erosion	None	Mild erosion involving only epidermis	Severe erosion involving epidermis and dermis with little or no exudate	Severe erosion involving epidermis and dermis with moderate volume and persistent exudate





Figure 2: Validation of measurements and IAD scoring at the monitor

standard operating procedures to facilitate subsequent blind assessment of the primary outcome. Photographs included a measuring guide and were taken at least three times, both with flash and without. Care was taken to ensure the dignity, privacy and comfort of participants. Residual ointment was meticulously removed using mineral oil so that photographs would not provide blinded assessors with information about which ointment was used.

The primary outcome was complete healing of IAD, defined as a Kennedy IAD severity score of zero. The Kennedy IAD severity score is a cumulative severity score ranging from zero (no IAD) to nine generated by the IAD Skin Condition Assessment Tool developed by Kennedy and Lutz, which requires assessors to attribute scores of zero to three for three domains: area of skin breakdown, skin redness or inflammation, and erosion (Box 1). The sum of these scores is the IAD severity score^{6,15}. No fully validated score for assessing the extent or severity of IAD existed at the beginning of the study. For determination of final trial results for the primary outcome, sets of photographs for each patient on each treatment day were assessed by WOCNCB-certified wound care specialists in the United States (US) who were blinded to treatment allocation, independent of both the sponsors and the investigating team and were not involved in any other aspect of the study, and Kennedy IAD severity scores were attributed.

Prior to the start of the study, a WOCNCB-certified international skin and wound care specialist conducted training for relevant study personnel on the use of the Kennedy tool. A new photographic scale for assessing the intensity of IAD-associated redness in brown skin was developed to ensure consistent assessment of redness in skin tones common in the Philippines¹⁶.

The assessment process was piloted alongside other study processes. Throughout the trial, clinical assessment of the primary IAD severity score outcome, supervised by an investigator blinded to allocation, was used to monitor study participants' progress and safety and efficacy of the treatments. WOCNCB-certified wound care specialists in the US validated on-site assessments and measurements. Educational updates on wound care were provided to the study investigators through the WoundPedia International Interprofessional Wound Care Course¹⁷.

Secondary outcomes included: time to complete healing in days; IAD severity score at baseline and on each study day; size of area affected by IAD at baseline and on each study day; pain scores and itch scores at baseline and on each study day; study participant satisfaction with treatment at final assessment; and adverse events.

The size of IAD-affected area was calculated by multiplying the longest portion of the affected area measured in a head-to-toe orientation by the widest portion of the affected area measured from side to side (in centimetres). On occasions where there were more than one non-contiguous area affected by IAD, these were measured separately and the areas added together. IAD-associated pain was assessed using either a visual analogue scale (VAS) or the Wong Baker Pain Scale. The Wong Baker Pain Scale is a simple visual instrument originally designed for assessing pain in children, but has been used in adult populations. A range of six simple faces represents six degrees of pain, ranging from zero (no pain at all) to five (as much pain as the patient can imagine experiencing)¹⁸. Itch associated with IAD was assessed using VAS or the "Itch Man Scale", a validated scale originally developed to assess itch associated with the healing of burns in paediatric patients^{19,20}. A range of five simple pictures represents five degrees of itch, ranging from zero (no itch at all) to four (itches terribly). Both the Wong Baker Pain Scale and the Itch Man Scale have been shown to correlate closely to VAS measurements^{21,22}.

Statistical analysis

Means and standard deviations (SDs) of scale baseline characteristics (such as age and area measurements) and frequency tabulations of categorical characteristics (such as sex) are presented and compared between groups using *t* tests and chi-squared tests as appropriate. Percentages of participants completely healed at any time during the study and at each of the follow-up days were calculated and compared between the two groups using the chi-squared test. For ordinal, categorical outcome variables (Kennedy IAD severity scores, Wong Baker Pain Scale, Itch Man Scale) the percentages of groups at each level of rash, pain and itch and median levels were calculated for day 0 and days 1, 2, 3, 4, 5 and 6 after treatment commencement and chi-square tests were used to compare distributions. For scale outcome variables (pain and itch visual analogue scales,

size of area affected) the mean score for each group was calculated for each day, along with standard deviations and compared using *t* tests. Analysis of covariance was used to compare the difference in effect on days 1, 2, 3, 4, 5 and 6 of the intervention and comparator treatments, adjusting for baseline levels. Subgroup analyses (defined by age group, diabetes, incontinence status and IAD severity score) were performed to test for differences in treatment effectiveness. Post hoc subgroup analyses were conducted to consider the effect of potential confounding factors identified when participants' baseline characteristics were analysed. The level for statistical significance was set a priori for all analyses at $p=0.05$. Analysis was conducted in IBM SPSS Version 20²³.

Sample size calculation

In the absence of published evidence relating specifically to the IAD healing rate of either product in adults and older children, sample size calculations were based on clinical experience in the US. It was considered that in a population with IAD of varying degrees of severity including established IAD at the higher end of the Kennedy Scale, a difference of 20% between the two products in complete healing rates would represent a clinically important finding. To have an 80% power to detect a 20% difference in the primary outcome measure at a 5% confidence level, a total sample size of 118 was required. An additional 20% were recruited to allow for withdrawals and drop-outs. Thus a total sample of 142 was recruited.

Ethical considerations

The University of the Philippines Research Ethics Board approved the study protocol. Written, informed consent was obtained from all participants aged 18 and above. In addition, and in accordance with national guidance and World Health Organization recommendations, written, informed assent was obtained from the parent/next of kin/guardian of minors aged ≥ 12 –17^{24,25}. Participant information leaflets and consent/assent forms were available in plain English and Tagalog, and in simplified age-appropriate formats for minors aged 12–15.

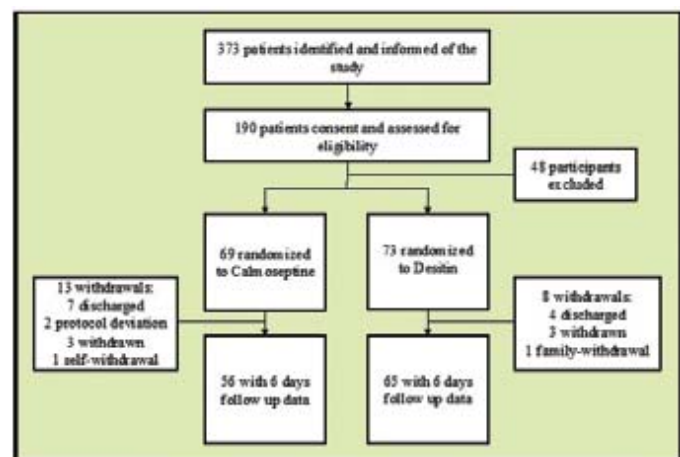


Figure 3: Study participant flow diagram

Table 1: Baseline demographic and clinical characteristics of study participants by treatment group

	Calmoseptine (n 69)	Desitin (n 73)	<i>p</i> value
Female — n (%)	53 (76.8)	52 (71.2)	.449 ^c
Age — mean (SD)	58.8 (19.5)	59.1 (15.7)	.919 ^t
Private — n (%)	36 (52.2)	29 (39.7)	.137 ^c
Body mass index — mean (SD)	22.8 (5.1)	23.7 (5.5)	.328 ^t
Bedbound — n (%)	68 (98.6)	70 (95.9)	.338 ^c
Antibiotics — n (%)	59 (85.5)	59 (80.8)	.457 ^c
Steroids — n (%)	6 (8.7)	16 (21.9)	.030 ^c
Diabetes mellitus — n (%)	15 (21.7)	18 (24.7)	.681 ^c
Albumin — mean (SD) [n]	25.6 (7.4) [27]	23.9 (8.3) [35]	.422 ^t
Kennedy IAD severity score — median (range)	6 (3–9)	5 (3–8)	.868 ^c
Total IAD area — mean cm ² (SD)	227.8 (160.1)	202.7 (186.9)	.393 ^t
VAS pain — mean (SD) [n]	3.2 (2.7) [38]	2.4 (2.5) [46]	.144 ^t
Wong Baker Pain — median (range) [n]	2 (0–6) [6]	4 (0–8) [9]	.119 ^c
VAS itch — mean (SD) [n]	1.6 (2.2) [38]	1.5 (2.2) [46]	.838 ^t
Itch Man — median (range) [n]	1.5 (0–4) [6]	2 (0–3) [9]	.733 ^c

^c Chi-square test

^t *t* test

RESULTS

Between December 2012 and March 2014, 373 patients were identified who were considered to be potentially eligible and were invited to participate in the study. Of these, 190 (50.9%) consented to participate, of which 48 were excluded for the following reasons: pressure ulcers > Stage 2 ($n=7$), active dermatologic conditions that may affect IAD healing ($n=1$), medical conditions such that participation may constitute a risk or interfere with their care (15), previous treatment with agents that may affect IAD healing (8), hospital stays expected to be less than seven days (15), assessed to have Kennedy severity scores of less than 3 (21).



Table 2: Urinary and faecal incontinence, urethral catheterisation and nature of stool passed for each study day by treatment group

		Calmoseptine	Desitin	p value (chi-square)
Day 0	n	69	73	
	UI in previous 24 hrs — n (%)	47 (68.1)	50 (68.5)	.961
	Urethral catheter	22 (31.9)	23 (31.5)	
	FI in previous 24 hrs — n (%)	59 (85.5)	65 (89.0)	.527
	Loose/ watery stool — n (%)	19 (32.2)	24 (36.9)	.581
Day 1	n	69	73	
	UI in previous 24 hrs — n (%)	46 (66.7)	53 (72.2)	.477
	Urethral catheter	22 (31.9)	20 (27.4)	
	FI in previous 24 hrs — n (%)	50 (72.5)	52 (71.2)	.871
	Loose/ watery stool — n (%)	22 (44.0)	22 (42.3)	.863
Day 2	n	68	73	
	UI in previous 24 hrs — n (%)	45 (66.2)	53 (72.6)	.706
	Urethral catheter	22 (32.4)	19 (26.0)	
	FI in previous 24 hrs — n (%)	49 (72.1)	56 (76.7)	.527
	Loose/ watery stool — n (%)	19 (39.6)	19 (33.9)	.551
Day 3	n	66	69	
	UI in previous 24 hrs — n (%)	47 (71.2)	54 (78.3)	.429
	Urethral catheter	18 (27.3)	15 (21.7)	
	FI in previous 24 hrs — n (%)	54 (81.8)	55 (79.7)	.756
	Loose/ watery stool — n (%)	17 (31.5)	22 (40.0)	.354
Day 4	n	61	67	
	UI in previous 24 hrs — n (%)	43 (70.5)	51 (75.0)	.847
	Urethral catheter	17 (27.9)	16 (23.5)	
	FI in previous 24 hrs — n (%)	47 (77.0)	52 (76.5)	.938
	Loose/ watery stool — n (%)	13 (27.1)	19 (36.5)	.311
Day 5	n	59	65	
	UI in previous 24 hrs — n (%)	42 (71.2)	48 (73.8)	.947
	Urethral catheter	16 (27.1)	16 (24.6)	
	FI in previous 24 hrs — n (%)	43 (72.9)	53 (81.5)	.250
	Loose/ watery stool — n (%)	17 (39.5)	19 (35.8)	.711
Day 6	n	56	65	
	UI in previous 24 hrs — n (%)	40 (71.4)	49 (75.4)	.527
	Urethral catheter	15 (26.8)	16 (24.6)	
	FI in previous 24 hrs — n (%)	42 (75.0)	51 (78.5)	.653
	Loose/ watery stool — n (%)	13 (31.0)	15 (28.8)	.824

One hundred and forty-two patients were enrolled in the study. Of these, 121 completed the seven-day study with data for six days' daily follow-up (Figure 1). Four participants were withdrawn by physicians for treatment of fungal infections in the IAD area and two because treatment for their primary diagnoses made continuing in the study impractical.

Eleven were discharged or self-discharged from the hospital before study completion. One participant withdrew from the study without giving a reason and one was withdrawn by a family member because worsening health status made continuing in the study impractical. Two were withdrawn following protocol treatment deviation. The primary

Table 3: Numbers completely healed, total IAD area (cm²) and change in IAD area from baseline (cm²) for each study follow-up day by treatment group

	Calmoseptine		Desitin		p value
	n (%) completely healed	n	n (%) completely healed	n	
Day 1	1 (1.4)	69	0	73	.302 ^c
Day 2	2 (2.9)	68	1 (1.4)	73	.518 ^c
Day 3	2 (3.0)	66	3 (4.3)	69	.685 ^c
Day 4	4 (6.6)	61	4 (5.9)	68	.874 ^c
Day 5	6 (10.2)	59	4 (6.2)	65	.412 ^c
Day 6	14 (25.0)	56	5 (7.7)	65	.009 ^c
Ever healed during study	15 (21.7)	69	7 (9.6)	73	.046 ^c
Ever (complete follow-up)	14 (25.0)	56	7 (10.8)	65	.039 ^c
	Mean (SD) total IAD area	n	Mean (SD) total IAD area	n	
Day 1	183.9 (134.1)	69	219.1 (195.6)	73	.216 ^t
Day 2	154.8 (120.1)	68	188.6 (188.9)	73	.210 ^t
Day 3	127.2 (115.8)	66	203.2 (200.8)	69	.008 ^t
Day 4	109.1 (129.0)	61	199.0 (189.9)	68	.002 ^t
Day 5	96.8 (126.8)	59	174.2 (147.2)	65	.002 ^t
Day 6	82.1 (111.9)	56	163.7 (144.5)	65	.001 ^t
	Mean change in IAD area from baseline (SD)	n	Mean change in IAD area from baseline (SD)	n	
Day 1	-43.9 (82.6)	69	+16.4 (44.2)	73	.000 ^t
Day 2	-75.9 (96.4)	68	-14.1 (72.0)	73	.000 ^t
Day 3	-100.6 (115.4)	66	-2.7 (81.8)	69	.000 ^t
Day 4	-112.2 (102.7)	61	-7.5 (93.5)	68	.000 ^t
Day 5	-119.3 (100.3)	59	-30.2 (168.2)	65	.001 ^t
Day 6	-136.6 (114.2)	56	-40.7 (174.6)	65	.001 ^t

SD Standard deviation

^c Chi-square test

^t t test

diagnoses of those enrolled were cerebrovascular disease (30.3%), cancer (15.5%), pneumonia (13.4%), gastrointestinal pathology (11.3%), sepsis (7.7%), pulmonary disease (4.9%), cardiovascular disease (4.2%), neurological conditions (3.5%), trauma (3.5%), diabetes-related complications (2.8), renal disease (2.1%) and substance abuse (0.7%).

The baseline characteristics of the study participants are presented in Table 1. Mean age was 59.0 (SD 17.5) and a majority (73.9%) was female. Of the participants, 97.2% were bedbound and all were in diapers on all study days. Chi-squared and *t* tests found that the two treatment groups were only statistically significantly different in terms of treatment with steroids (6 participants, 8.7% in the Calmoseptine group; 16, 21.9% in the Desitin group; *p*=0.030). No statistically

significant differences were observed between the groups in terms of incidence of urinary or faecal incontinence, urethral catheterisation or nature of stool passed (Table 2).

Amongst the whole study population, percentages of patients completely healed, mean total areas affected by IAD and mean changes in those areas are reported in Table 3. Amongst the whole trial population, 15.5% were assessed to have completely healed at some point during follow-up. On follow-up day 6, significantly higher numbers of participants were completely healed in the Calmoseptine group. Overall, significantly higher numbers in the Calmoseptine group were completely healed at some point during the follow-up period than in the Desitin group. Chi-square tests found statistically significant differences in the distributions of Kennedy

severity score between the groups on days 4 ($p=0.026$), 5 ($p=0.045$) and 6 ($p=0.020$), with higher numbers of more severe IAD remaining in the Desitin group. Treatment with Calmoseptine was associated with statistically significantly smaller affected areas from day 3 onwards, and with greater reductions from baseline in the affected area on all follow-up days (Table 3). Analyses of covariance (ANCOVA), adjusting for baseline area affected, indicated that Calmoseptine was associated with significantly greater reductions in area affected on days 1 ($F=29.18$, $p=0.000$), 2 ($F=18.41$, $p=0.000$), 3 ($F=34.18$, $p=0.000$), 4 ($F=40.53$, $p=0.000$), 5 ($F=18.34$, $p=0.000$), and 6 ($F=19.67$, $p=0.000$).

However, a statistically significantly greater proportion of participants in the Desitin group were receiving steroids, which can retard wound healing. The majority of these participants were cancer, neurology, pneumonia or pulmonary disease patients. To take this potential confounding factor into account, post hoc subgroup analyses were conducted comparing treatment groups of participants who did and did not receive steroids. Amongst those who received steroids, no participants were completely healed during the six-day follow-up period. No statistically significant differences in total IAD area were detected between the two groups on any day. Treatment

Table 4: Numbers not receiving steroids completely healed, total IAD area (cm^2) and change in IAD area from baseline (cm^2) for each study follow-up day by treatment group

	Calmoseptine		Desitin		<i>p</i> value
	n (%) completely healed	n	n (%) completely healed	n	
Day 1	1 (1.6)	63	0	57	.339 ^c
Day 2	2 (3.2)	62	1 (1.8)	57	.609 ^c
Day 3	2 (3.3)	60	3 (5.6)	54	.563 ^c
Day 4	4 (7.0)	57	4 (7.5)	53	.915 ^c
Day 5	6 (10.9)	55	4 (7.8)	51	.589 ^c
Day 6	14 (26.9)	52	5 (9.8)	51	.025 ^c
Ever healed during study	15 (23.8)	63	7 (12.3)	57	.103 ^c
Ever (complete follow-up)	14 (26.9)	52	7 (13.7)	51	.096 ^c
	Mean (SD) total IAD area	n	Mean (SD) total IAD area	n	
Day 0	232.1 (163.5)	63	208.3 (204.6)	57	.482 ^t
Day 1	186.7 (137.1)	63	222.1 (214.0)	57	.277 ^t
Day 2	156.3 (122.0)	62	191.3 (207.6)	57	.260 ^t
Day 3	126.7 (117.3)	60	210.4 (220.2)	54	.012 ^t
Day 4	109.8 (131.5)	57	208.3 (208.6)	53	.004 ^t
Day 5	97.6 (128.4)	55	174.9 (153.1)	51	.006 ^t
Day 6	81.6 (113.1)	52	164.6 (152.6)	51	.002 ^t
	Mean change in IAD area from baseline (SD)	n	Mean change in IAD area from baseline (SD)	n	
Day 1	-45.4 (85.9)	63	+13.8 (44.5)	57	.000 ^t
Day 2	-79.0 (99.6)	62	-17.0 (80.2)	57	.000 ^t
Day 3	-105.5 (119.2)	60	-1.5 (88.7)	54	.000 ^t
Day 4	-116.8 (103.9)	57	-4.0 (102.5)	53	.000 ^t
Day 5	-123.8 (102.3)	55	-36.9 (184.3)	51	.003 ^t
Day 6	-142.7 (116.2)	52	-47.3 (193.6)	51	.004 ^t

SD Standard deviation

^c Chi-square test

^t t test



Figure 4: IAD illustration at Initial day

with Calmoseptine was associated with statistically significantly greater reductions from baseline in affected area on days 1 ($p=0.013$) and 2 ($p=0.022$). Analyses of covariance (ANCOVA), adjusting for baseline area affected, indicated that Calmoseptine was associated with significantly greater reductions in area affected on days 1 ($F=7.30$, $p=0.014$) and 2 ($F=6.50$, $p=0.020$).

Analysis of outcomes amongst participants who had not received steroids, revealed the confounding effect of a higher proportion of steroid use in the Desitin group. However, although the levels of statistical significance were less, the results reflect those for the whole study population, with significantly greater proportions healed completely at day 6. Chi-square tests found statistically significant differences in the distributions of Kennedy severity score between the groups on days 4 ($p=0.024$), 5 ($p=0.035$) and 6 ($p=0.039$), with higher numbers of more severe IAD remaining in the Desitin group. As with the whole study population, treatment with Calmoseptine amongst those not receiving steroids was associated with statistically significantly smaller affected areas from day 3 onwards, and with greater reductions from baseline in the affected area on all follow-up days (Table 4). Analyses of covariance (ANCOVA), adjusting for baseline area affected, indicated that Calmoseptine was associated with significantly greater reductions in area affected on days 1 ($F=21.40$, $p=0.000$), 2 ($F=13.66$, $p=0.000$), 3 ($F=29.20$, $p=0.000$), 4 ($F=35.91$, $p=0.000$), 5 ($F=14.37$, $p=0.000$), and 6 ($F=15.73$, $p=0.000$).

The majority of participants who provided data on pain and itch chose to use VAS instruments: 39 in the Calmoseptine group and 46 in the Desitin group at baseline. Overall, the structured care regimen produced marked reductions in both pain and itch over the follow-up period. However, no statistically significant differences were observed between the two treatment groups in terms of pain or itch on any treatment day, either in *t* tests or ANCOVA adjusting for



Figure 5: Improvement of IAD at Day 5

baseline levels. Too few participants chose to use the pictorial scales for meaningful analysis (six in the Calmoseptine group, nine in the Desitin group). No adverse medical events occurred during the study.

No statistically significant differences were detected in terms of complete healing at any time during the study or on each day in subgroup analyses between age-groups 12–29, 30–49, 50–69 and 70 or over. No statistically significant difference was detected between those whose IAD did or did not heal completely during the study and baseline IAD severity score or presence of diabetes mellitus. Neither complete healing nor reduction in area affected was statistically significantly associated with the number of days upon which either urinary or faecal incontinence occurred, or whether stool was well formed or liquid. No association was detected between participants' median Kennedy severity scores and the frequency or type of incontinence.

DISCUSSION

The study was a randomised controlled trial of topical treatments for IAD, providing evidence for the effectiveness of two products in a clinical area in which there is a paucity of high-quality research. Although both products had beneficial effects in the context of a structured skin care regimen for the treatment of IAD, Calmoseptine was more effective than Desitin in terms of complete healing and in terms of reducing the total area affected. Use of steroids appeared to retard the healing of IAD. Age, diabetes, baseline severity of IAD and frequency or type of incontinence did not affect the likelihood of complete healing or the reduction in area affected.

The primary reasons for hospital admission amongst the study population might be considered typical of seriously ill, bedbound patients who are at high risk of developing IAD. The primary diagnosis of nearly one-third of those enrolled was cerebrovascular disease; cancer, pneumonia, gastrointestinal pathologies, sepsis and pulmonary disease

accounted for more than half. Around two-thirds of the participants experienced urinary incontinence on any given study day, with most of the rest having urethral catheters. Between two-thirds and three-quarters were faecally incontinent on different study days.

Literature reviews and consensus statements on IAD have called for high-quality research in the area of prevention and treatment^{3,6,11}. The updated 2012 review and consensus statement on IAD called for trials that assess products and validate its recommendations regarding prevention and treatment regimens³. This study found that a structured treatment regimen in line with the consensus recommendations, involving gentle cleansing and the application of products that combine moisturisation and skin protectants, can successfully be used to treat IAD of any severity. Overall, the regimen resulted in complete healing at some point during the six-day follow-up of 15.5% of all participants. Mean areas affected by IAD were reduced throughout the follow-up period, so that it seems likely that the percentage of those completely healed would increase over time. The structured regimen also reduced both pain and itch markedly.

Used as the skin protectant component of such a regimen, Calmoseptine proved more effective than Desitin in treating IAD in terms of complete healing and in the reduction of the total area affected over a week. Calmoseptine's antiseptic, active ingredients may be a driving factor in the product's superiority in IAD healing. The results are in line with a previous study amongst 57 geriatric patients in which a zinc oxide ointment with antiseptic ingredients was shown to reduce skin redness and bacterial counts in pre-existing IAD compared with zinc oxide alone at both 7 and 14 days¹⁴.

That severity of IAD and healing outcomes were not related to the frequency and type of incontinence may appear counterintuitive. However, there is little evidence that clarifies the association between frequency and type of incontinence and IAD, and that which exists is conflicting. While a small number of studies have suggested those with faecal or double incontinence are more likely to develop IAD, others have found that this not the case^{3,7,23,26,27}. No studies were identified that have considered the effects of different frequencies or types of incontinence on treatment outcomes. This study suggests that the success of a structured skin care regimen is not affected by frequency or type of incontinence, or the nature of stool.

The effect of systemic steroids on wound healing in general, and IAD in particular, is not well established by high-quality research. Perioperatively, they are reported to slow healing and increase surgical wound complication rates in a dose-dependent manner²⁸. In this study, an imbalance of steroid administration between treatment groups afforded an opportunity to consider their effect on healing in IAD. The numbers of participants completely healed and reductions

in area affected were statistically significantly better in the Calmoseptine group in both the total study population and in the large subgroup not receiving steroids. However, the differences were less marked in the subgroup without steroids, suggesting that steroids adversely affected healing. Amongst those receiving steroids, the only statistically significant effects detected favoured Calmoseptine, but too few patients were available for these analyses to be considered robust.

Study strengths and weaknesses

The study has considerable strengths. Trained nursing personnel consistently delivered the structured skin care regimen, with identical cleansing products and techniques and containment products used in both treatment groups. Considerable training was conducted and a new scale for redness in brown skin tones was developed to ensure consistent assessment of IAD¹⁶. Outcomes were either blindly assessed, objective, or patient-reported, reducing the possibility of measurement bias. The sample size was adequately powered to detect a smaller effect size than was actually observed.

The fact that the manufacturer of one of the investigational products funded the trial may have been regarded as a potential source of bias. Several strategies were adopted at protocol stage to mitigate this: the trial was designed and conducted by fully independent clinical researchers at a national university hospital; the sponsor had no access to the treatment allocation of participants at any time during or after the trial and played no part in data analysis or reporting; and, to prevent reporting bias, the trial was registered with a publicly accessible clinical trial registry that requires publication of results.

Another potential source of bias was that it was not possible to blind the investigators to the treatment to which participants had been randomised as the products differ in odour, colour and consistency. In addition, investigators would be familiar with each since both were already being used in the hospital. To prevent bias, assessment of the primary outcome was conducted by WOCNCB-certified wound care specialists who were blinded to treatment allocation, were fully independent of both the sponsors and the investigating team and were not involved in any other aspect of the study.

However, the study's limitations must be acknowledged. This was a single-centre study with an entirely Filipino population that assessed the effectiveness of zinc-based topical products within a hospital-based, structured skin care regimen in hospitalised patients with moderate to severe IAD. As such, the generalisability of the results to other populations might be considered, although there is no reason to suspect that either product would be less effective in different racial groups or community-based patients with milder IAD.

CONCLUSIONS

A structured skin care regimen involving gentle cleansing, moisturisation and a skin protectant can successfully be used to treat IAD of any severity. Used as the skin protectant component of such a regimen, Calmoseptine is more effective than Desitin in terms of complete healing and reduction of area affected.

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Conflicts of interest

The trial was fully funded by Calmoseptine Inc. and all authors received payment for their work on the study. No other conflicts of interest are known. All research staff and planners, including partners, in any position to control or influence the process and content of this study have disclosed no financial and significant relationships with or financial interest in any commercial companies pertaining to this activity.

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