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ARTICLE

Comparison of Efficacy and Safety between Two Silver-Containing Dressings in the Treatment of Deep Partial-Thickness Thermal Burns: A Multicenter, Double-Blind, Non-Inferiority, Randomized Clinical Trial

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Abstract

Aims/Background Silver-containing dressings are commonly utilized in burns treatment by virtue of their excellent antibacterial properties. Further research is needed to determine the type of silver-containing dressing that is more effective and safer for burns treatment. Pyperbranched polyamide-Ag dressing (HBPs-Ag dressing) is a modified polyamide dressing with a uniform coating of the Amino-terminated hyperbranched polymer (HBP-NH_2)/Ag^+ compound on its surface. This study aimed to evaluate the efficacy and safety of a silver ion-containing dressing (HBPs-Ag) for wound contact layer in the treatment of deep partial-thickness burns versus a silver-impregnated tulle dressing (Atrauman Ag).

Methods This study was conducted between October 2019 to January 2021 at six sites in China. A total of 132 patients with deep partial-thickness burns (aged 18–65 years, injury occurring within 72 hours, burns <30% total burn surface area) were randomized 1:1 to HBPs-Ag group (study group) or Atrauman Ag group (control group). Data were obtained and analyzed, including total efficacy, wound healing rate, wound healing time, rate of negative bacterial culture from wound secretions, systemic response, skin or tissue irritation, local skin color changes, wound swelling, wound pain and adverse events.

Results For partial thickness burns, the HBPs-Ag dressing was not inferior to Atrauman Ag dressing because the total efficiency of HBPs-Ag group (98.3%) was comparable to that of Atrauman Ag group (94.7%) ($p > 0.05$). There were no significant differences in efficacy, wound healing rate, wound healing time, and rate of negative bacterial culture from wound secretions between the two groups ($p > 0.05$). There were no statistical differences in all safety indicators tested between the two groups ($p > 0.05$). Silver was detected in the blood or urine of only 5 patients (3.79%).

Conclusion The HBPs-Ag dressing was not inferior to Atrauman Ag dressing in deep partial-thickness burns treatment, with both of them showcasing comparable efficacy and safety.

Clinical Trial Registration Chinese Clinical Trial Registry (ChiCTR2100049814)

Key words: burns; silver compounds; dressings; wound healing; randomized controlled trial

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Introduction

Deep partial-thickness burns refer to wounds extending into deep (reticular) dermis, presenting huge challenges in treatment (Gibson et al, 2021). During the healing process of the deep partial-thickness burns, exudation, necrotic cuticular layer and tissues would accumulate on the wound surface, leading to infection, delayed wound healing, scarring, and potentially fatal complications such as sepsis, and multi-organ dysfunction (Gacto-Sanchez, 2017). Due to severity of the condition, distribution of pathogenic bacteria, and level of drug resistance across different regions and time periods, patients with deep partial-thickness burns often require hospitalization. In China, burn patients face an increased risk for nosocomial infections, marked by the highest incidence rate among all diseases, and unfortunately, the clinical communities see a declining number of topical antibiotics capable of effectively controlling infections, raising the mortality rate by 8.5–11 times (Jin et al, 2022; Tan et al, 2022).

The primary approach to burn wound care is to keep the wound clean and covered, and implement the necessary measures to prevent wound infections. Numerous types of wound dressings with antibacterial properties have been successfully developed, with most physicians agreeing that appropriate use of wound dressings could reduce the frequency of dressing changes, shorten the length of hospitalization, and improve patient comfort (Markiewicz-Gospodarek et al, 2022). The antibacterial property is considered the most crucial feature and requirement of a wound dressing, followed by its ability to alleviate pain (Dumville et al, 2016). Silver-containing dressings represent a common option for the treatment of deep partial-thickness burns (Pamuk Cebeci and Acaroğlu, 2019). Since the 1960s, following the discovery of silver sulfadiazine, silver ion-based agents and dressings have been widely used in the treatment of burn wounds, as well as acute and chronic wounds, because of silver's proven antibacterial properties against wound pathogens (Meredith and Forbes, 2023). Despite the superior antimicrobial and bactericidal capability, silver dressing is cytotoxic to fibroblasts when present in high concentrations (Brouillard et al, 2018). Nevertheless, the mechanisms of action, efficacy, safety, and adverse effects of silver-containing dressings require further exploration.

Studies have reported that Aquacel-Ag dressing could shorten wound healing time and effectively minimize inflammatory reactions in burn patients compared to silver sulfadiazine (Gao et al, 2017; Wu et al, 2023). However, the use of silver-containing dressings may result in adverse reactions such as exacerbated local pain, allergies, pigmentation, liver and kidney damage, interaction with other drugs, and the rate of silver release from dressings might be linked to several adverse reactions (Cutting et al, 2007; Kumar et al, 2018). Choosing appropriate base materials for dressings can delay silver release, reduce the stimulation of new cells and granulation tissue, effectively alleviate or resolve unwanted side effects such as pain and pigmentation, prolong the bactericidal time of dressings against a broad spectrum of pathogens, and maintain a broad-spectrum, anti-infection barrier (Mondal et al, 2020).

At present, studies of silver-containing dressings focus more on the investigation of different types of silver agents and dressing substrates (Francisco et al, 2023; Gao et al, 2016; Salleh et al, 2022). Variations in silver agent concentration, distribution, and release rate can result in differences in therapeutic effects, and the compatibility of silver agents with carrier matrices requires further investigation. Conducting multicenter clinical trials is necessary to establish a rational application of different silver-containing dressings for treating burn wounds. Therefore, the purpose of this study was to compare two slow-release silver ion-containing dressings—silver ion antibacterial functional dressing and Atrauman Ag dressing. Both dressings have been on the market for many years and are widely used to treat deep partial-thickness burns in China (Li et al, 2020). The silver ion carriers for both dressings consist of glycerol-infused polyamide fine mesh yarn, which slowly releases silver ions through silver metal (silver fiber method) or hyperbranched polyamide-silver complex (silver impregnation method, containing Ag^{+}), exerting an antibacterial effect.

The current study is a multicenter randomized controlled trial involving blinded evaluators to assess the therapeutic efficacy and safety of the two dressings.

Methods

Study Design and Participants

This multicenter, double-blind, non-inferiority randomized clinical study was conducted from October 2019 to January 2021 at six sites in China. The six hospitals and the number of patients included from each institute are as follows: The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, 1 case; The Second Affiliated Hospital of Kunming Medical University, 7 cases; The First Affiliated Hospital of University of South China, 8 cases; Nanning Second People's Hospital, 17 cases; Wuhan Third Hospital, 97 cases; and The First Affiliated Hospital of Zhengzhou University, 8 cases. Patients were assessed against the key inclusion criteria during the screening visit to evaluate their eligibility for the study: (1) patients admitted to hospital within 72 hours after burns; (2) adults aged 18–65 years with total burn surface area (TBSA) $<30\%$; (3) all deep partial-thickness burn wounds regarded as observation areas, but special burns (at/on face, eyes, ears, neck, fingers, toes, perineum, genitals) were excluded. Their wounds were observed for the presence of infection (but not signs of serious infection or systemic infection). Our subjects were affected by thermal burns, caused by hot liquid (water, soup, oil, etc.), steam, high-temperature gas, flame, hot metal liquid or solid (such as molten steel, steel ingot). Burns are classified by Four-degree depending on the depth and severity of penetration of the skin's surface, the burn surface area can be quickly estimated by using the "rule of nines" (Fan et al, 2017). According to this method, burns are classified into several grades: I (damage to the epidermal stratum corneum, hyaline layer, and granular layer), superficial II (damage to the entire epidermis, down to the hair layer, or to the papillary layer of the dermis), deep II (damage to the dermis below the papillary level, but some dermis remains), III (damage to the entire skin layer, with total destruction of the

epidermis, dermis and its attachments), and IV (damage to muscles and even bones and internal organs). Burn surface area was determined by using the palm method, which involves comparing the size of a palm with all fingers held together to the surface area of burns; the size of one palm is loosely equivalent to 1% of the body surface area. The nine-point rule sets the whole body surface area at 100%, with the head, face, and neck accounting for 3%; the hands, both forearms, and both upper arms accounting for 5%, 6%, and 7%, respectively; the anterior and posterior torso accounting for 13%; the perineum accounting for 13%; the perineum accounting for 1%; and the buttocks, feet, calves, and thighs accounting for 5%, 7%, 13%, and 21%, respectively.

Key exclusion criteria of this study include: (1) subjects who had participated in any clinical trial within three months of admission; (2) subjects who had previously used silver dressing or had history of industrial silver exposure (e.g., jewelry, photographic development, silver welding, etc.); (3) subjects with electrochemical burns, radiation burns, severe immune system diseases, severe complications or systemic infection, serious primary diseases such as cardiovascular, cerebrovascular, liver, kidney or hematopoietic system, mental illness, diabetes; (4) subjects who were pregnant (or having plans to become pregnant) and breastfeeding; (5) subjects with allergic constitution or allergies to silver; and (6) those who may not be able to complete the study for other reasons or who the investigator considers should not be included. As shown in Fig. 1, the patients with deep partial-thickness burns were assessed for study eligibility during the screening visit. All patients provided written informed consent before enrolment.

This study is registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn/showprojEN.html?proj=131091; Registration No. ChiCTR2100049814) and has been accepted by the Center for Medical Device Evaluation. The eligible patients were randomized 1:1 to Pyperbranched polyamide-Ag dressing (HBPs-Ag dressing) group (study group; dressing (Batch number: 20171211) acquired from Changsha Hairun Biotechnology Co., Ltd. Changsha, China) or Atrauman Ag group (control group; dressing (Batch number: 700631115, 700733116) acquired from Paul Hartmann Ag, Heidenheim, Germany). This study was carried out in compliance with good clinical practice (GCP) requirements, the Declaration of Helsinki, as well as relevant laws and regulations in China. All ethics committees from participating hospitals had approved of the trial. Both the patients and the public were not involved in the design, implementation, reporting or dissemination of the study.

Sample Size

The total efficiency is the primary evaluation index of effectiveness in this clinical trial, and the efficiency rate is estimated to be 91% based on preliminary clinical observations. The significance level α was set as 0.025 (one-sided), the test confidence 1-β was set as 0.8, and the non-inferiority margin δ of this study was defined as –15%. The formula $n_E = n_C = 2\pi \times (1-\pi) \times \frac{\left(Z_{1-\alpha}+Z_{1-\beta}\right)^2}{(\Delta)^2}$ was employed to calculate the sample size required for both the study and control groups, which was about 58 cases considering about 12% of that were potentially

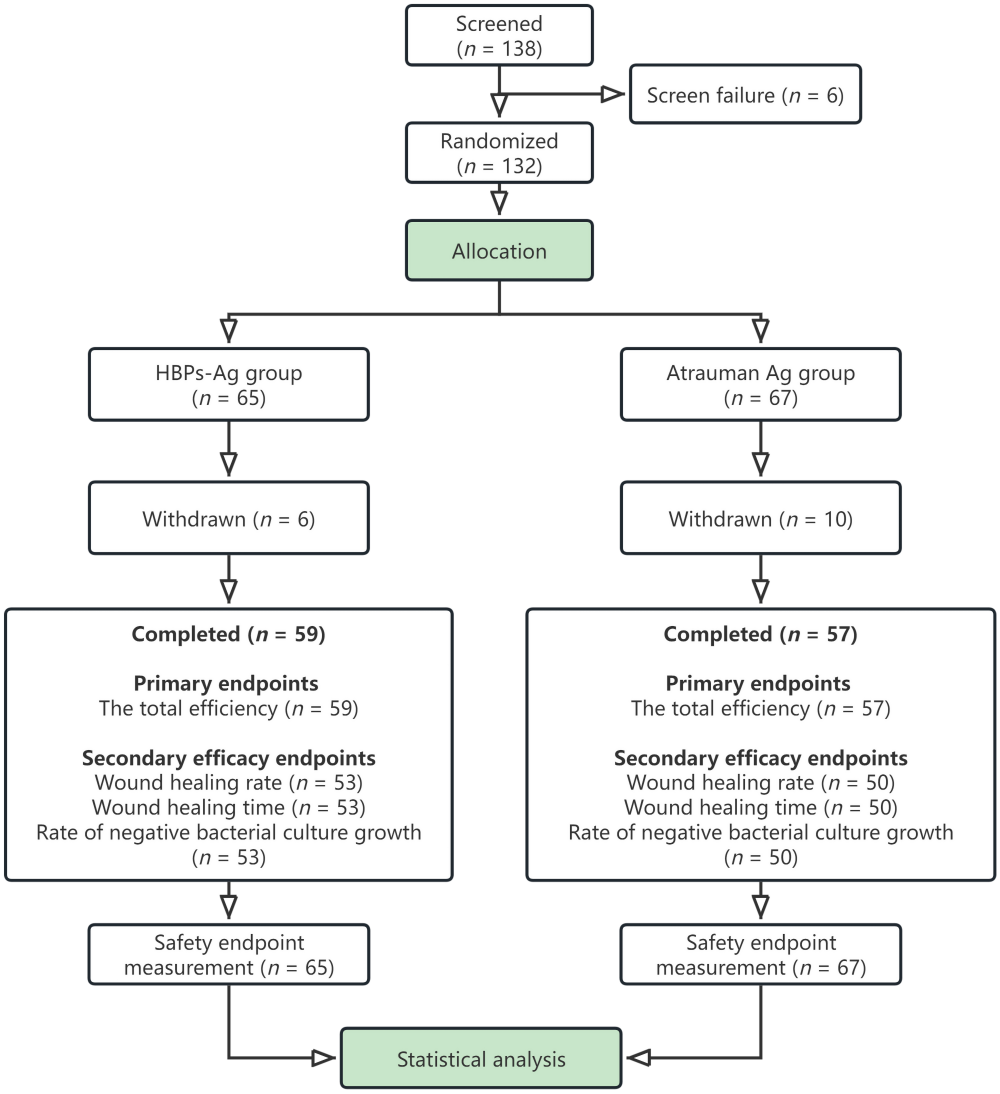

Fig. 1. Consolidated Standards for Reporting Trials (CONSORT) diagram depicting the subject recruitment and outcome measurement workflow of this clinical trial of two silver-containing dressings. The figure was created with Microsoft Office Visio 2016 (version 16.0, Microsoft Corporation, Redmond, WA, USA). HBPs-Ag, Pyperbranched polyamide-Ag.

unqualified or withdrawn. A total of 132 participants were needed for making up the samples of the final study and control groups, with each requiring 66 subjects. A total of 138 patients were screened in this study, of which 6 failed to be screened, 132 patients were enrolled, and 16 patients dropped out, leaving behind 116 patients (as Fig. 1). Of the 16 patients who dropped out of the study, 10 patients were lost to follow-up and 6 patients experienced other traumatic injuries.

Materials and Methods

The investigational silver dressings were applied to the deep partial-thickness burns area from day 1. The burns area of each patient (except the special area burns at regions such as face, eyes, fingers, toes, perineum, genitalia, etc.), who met the inclusion criteria, were used as the observation wounds. All deep partial-thickness burns applied with dressings were observed for ≤21 days. The observation time is

defined as the duration from the first application of the silver dressing to the last evaluation of the wound condition. The entire research process is shown in Fig. 2.

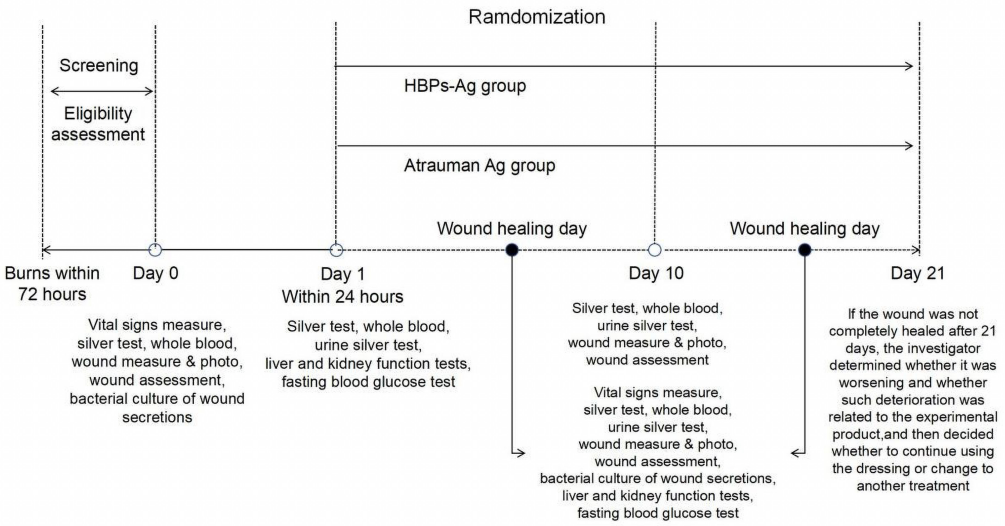

Fig. 2. Study design and assessment. Patients with deep partial-thickness burns were assessed for study eligibility during the screening visit. Different types of dressings were randomly assigned to the subjects included and applied to the wounds on day 1, and changed every 1–3 days based on the patient's condition. If the wounds were not healed within 10 days, additional dressing changes were conducted until the complete epithelialization. Wound assessment was performed on days 0, 10, and the day of wound healing. If the wound was not completely healed on day 21, reasons for delayed healing owing to the product were ruled out by the assessors. The figure was created with Microsoft Office Visio 2016 (version 16.0, Microsoft Corporation, Redmond, WA, USA).

Basic Wound Treatment and Study Assessments

Before the silver dressings were applied, the wounds should be routinely disinfected. The wounds and surrounding skin should be cleaned and dried. Silver dressings of appropriate size were selected and gently applied to the wound in a single layer, and covered with 16 single layers of sterile gauze, prior to fixing them properly. Large-area wounds could be covered with several pieces of dressing spliced together. The dressings were cut according to the wound shape, if the area was too small. Dressings were changed every 1–3 days based on the patient's condition, and the patient was given medications while monitoring for any abnormal reactions was ongoing.

Epithelialization of the burn area, signs of inflammation and infection were assessed during dressing changes. If any subject was healed ahead of schedule, usage of silver dressing was terminated. But if the wound was not completely healed after 21 days, the investigator would determine whether it was worsening and whether such deterioration was related to the silver dressings, prior to making decision regarding subsequent treatment—continued application of the dressing or switching to another treatment. Other non-observation wounds were treated as usual during the trial, based on the subject's condition, but silver-containing products (including drugs and devices) were not used.

Primary Endpoints

Total Efficiency

Total efficiency is the ratio of the number of subjects who are cured and show marked effects from the therapy to the total number of subjects. According to the wound healing rate at the time of the last dressing removal, the curative effect can be classified into four grades: cured (100% wound healing rate), markedly effective (wound healing rate $\geq$70% and $<$100%), effective (wound healing rate of $\geq$30% and $<$70%), and ineffective (failure in wound infection control, necessitating a change to skin grafting or other treatment).

Secondary Efficacy Endpoints

Wound Healing Rate and Wound Healing Time

$$\text{Wound healing rate } (\%) = [(\text{Ai} - \text{Af})/\text{Ai}] \times 100$$

Where Ai represents the initial wound area and Af represents the final wound area.

The wound area evaluation was performed by two researchers using the ImageJ program (version 1.51p, National Institutes of Health (NIH), Bethesda, MD, USA), after photographing and recording, and the average value was determined. The assessors were blinded during the evaluation. The assessment of the wound area was conducted by two designated research doctors who did not participate in the trial operation, and the blind assessment was carried out, and the average value of the wound area calculated by the two doctors was taken. Biological sample analysis testers will use blind state analysis and will not know the subject random code and test grouping during sample analysis testing.

Wound healing time refers to the days to achieve complete epithelialization (wound healing rate = 100%). If the wound was not fully healed at the time of the last dressing removal, the healing time of the wound was not evaluated.

Rates of Negative Bacterial Culture Growth

Wound secretions were collected for bacterial culture. The bacteria that were successfully cultured were recorded, and the rates of negative bacterial culture before and after dressing were calculated and compared between the two groups.

Rate of negative bacterial culture growth (%) = (Pre-treatment culture-positive bacterial cases – Culture-positive bacterial cases during observation)/Pre-treatment culture-positive bacterial cases $\times$ 100.

Safety Endpoints

Safety endpoints included the incidence of adverse events (AEs) and changes in clinical laboratory variables (hematology, blood chemistry, and urinalysis), electrocardiograms, systemic reactions, local skin/tissue irritation, changes in skin color, wound swelling, wound pain and vital signs.

Wound swelling was graded using the scale for swelling and edema: grade 1 (immediate rebound with 2 millimeter [mm] pit); grade 2 (less than 15-second rebound with 3–4 mm pit); grade 3 (rebound greater than 15 seconds but less than 60

Table 1. Efficacy study endpoint and evaluation method.

Study endpoints	Statistical analysis methods
Total efficiency	[P] z-test (FAS/PPS), confidence interval approach (FAS/PPS) [S] Summary (FAS/PPS)
Wound healing rate	[P] *t*-test (FAS/PPS) [S] Summary (FAS/PPS)
Wound healing time	[P] Wilcoxon rank sum test (FAS/PPS) [S] Summary (FAS/PPS)
Rate of negative bacterial culture growth	[P] Fisher's exact test (FAS/PPS) [S] Summary (FAS/PPS)

[P]: Primary; [S]: Supplemental. Full analysis set (FAS) refers to a complete dataset that includes all subjects randomized, regardless of whether they adhered to the planned course of treatment. In practice, however, full follow-up of all subjects is often difficult to achieve. Therefore, a full analysis set is often used for analysis. Per protocol set (PPS) is defined as a subset of the full analysis set in which subjects have no major violations of the trial protocol in terms of enrollment criteria, treatment received, and measurements of the primary indexes, and have good adherence.

seconds with 5–6 mm pit); and grade 4 (rebound between 2 and 3 minutes with an 8 mm pit). Wound pain was assessed using 4-point Verbal Rating Scale (VRS): 0 (no pain); 1 (slight pain); 2 (moderate pain); and 3 (severe pain). Adverse events were observed and recorded until the last follow-up, and were rated as positively relevant, possibly relevant, possibly irrelevant, definitely irrelevant, and undetermined.

Statistical Analysis

According to the research purpose, data type and corresponding distribution characteristics, descriptive statistics and statistical analysis methods were selected accordingly. The Kolmogorov-Smirnov test was used to determine whether the data met the normal distribution requirement. Normally distributed data are expressed as mean ± standard deviation, and comparisons between groups were achieved using the independent samples *t*-test. Data that are not normally distributed are expressed as median (upper and lower quartiles), and comparisons between groups were performed using the Mann-Whitney *U* test. Categorical data are expressed as count and percentage, and comparisons between groups were conducted using the chi-square test or Fisher's exact probability method. Mauchly's sphericity test was implemented to determine whether the covariance matrices of the variables were uniform. The repeated measurements were analyzed using analysis of variance (ANOVA), and the Fisher's Least Significant Difference pairwise comparison method was employed to investigate differences between different measurement time points. The comparison of non-normal data block multiple groups uses the Friedman-M test. All statistical tests were two-sided, and a $p \leq 0.05$ was considered statistically significant unless otherwise noted. All statistical analyses were performed using SAS V9.4 statistical analysis software (version 9.4, SAS Institute Inc., Cary, NC, USA) (Table 1).

Table 2. Comparison of basic information between the HBPs-Ag and Atrauman Ag groups.

Variable		HBPs-Ag group (n = 59)	Atrauman Ag group (n = 57)	$\chi^2/t/Z$	p-value
Gender	Male	40 (67.8)	39 (68.4)	0.005	0.942
	Female	19 (32.2)	18 (31.6)		
Age (years)		40.59 ± 12.40	40.88 ± 11.04	–0.130	0.897
BMI (kg/m^2)		23.69 ± 3.71	23.68 ± 3.18	0.012	0.990
TBSA		1549.95 (1068.00, 2592.50)	1778.90 (1162.25, 2414.10)	–0.511	0.609
Observation area		194.90 (94.80, 445.40)	247.40 (142.00, 473.30)	–0.815	0.415
Burn area of the body surface (%)		9.00 (6.00, 15.00)	10.00 (7.00, 15.00)	–0.704	0.482

BMI, body mass index; TBSA, total burn surface area.

Results

Basic Information

A total of 132 patients were enrolled, of which 116 had completed the trial and 16 had dropped out. Additionally, all 132 participants took part in the safety survey. Table 2 indicates that there were no significant differences in gender, age, body mass index (BMI), total burn surface area (TBSA), test area, and burn area of the body surface (%) between the HBPs-Ag group and the Atrauman Ag group ($p > 0.05$). The basic information of the two groups was comparable.

Epithelialization and Infection

The per protocol set (PPS) included 116 patients who completed the study, of which 20 patients were cured, 92 patients showed marked effect, 4 patients demonstrated effective outcomes, and 0 patients exhibited ineffective results. With both cured patients and those showing marked effect combined, there were 112 of them. In the HBPs-Ag group (n = 59), 9 patients were cured, 49 patients showed marked effect, 1 patient demonstrated effective outcomes, and 0 patients exhibited ineffective results There were a total of 58 patients who had been cured and showed marked effect in the HBPs-Ag group, with a total efficiency rate of 98.31%. In the Atrauman Ag group (n = 57), 11 patients were cured, 43 patients showed marked effect, 3 patients demonstrated effective outcomes, and 0 patients exhibited ineffective results. There were a total of 54 patients who had been cured and showed marked effect in the Atrauman Ag group, with a total efficiency rate of 94.74%. The total efficiency rate of the HBPs-Ag group outperformed that of the Atrauman Ag group by 3.57%; the lower limit of unilateral 97.5% confidence interval (CI) was –3.10%, higher than the non-inferiority threshold of –15% ($p < 0.001$) (as Fig. 3).

The wound healing rate, wound healing time and rate of negative bacterial culture growth are detailed in Table 3. The wound healing rate in the HBPs-Ag and Atrauman Ag groups was 93.76 ± 12.10% and 93.91 ± 13.95%, respectively. The wound healing time in the HBPs-Ag and Atrauman Ag groups was 11 days (9, 14) and 12 days (10, 17), respectively. No statistical differences were found between the two groups in terms of wound healing rate, wound healing time and rate of negative bacterial culture growth ($p > 0.05$).

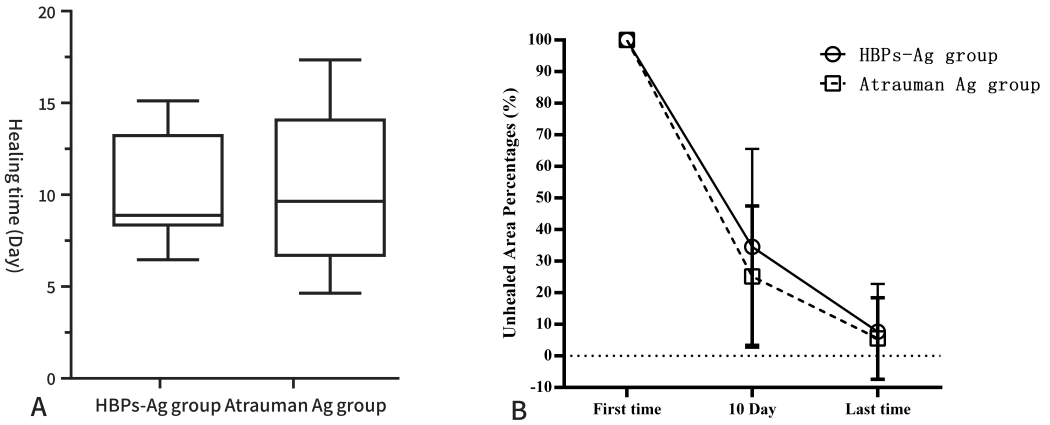

Fig. 3. Comparative analysis of wound healing: HBPs-Ag vs. Atrauman Ag. (A) Box plot depicting the comparison of wound healing time between the Pyperbranched polyamide-Ag (HBPs-Ag) and Atrauman Ag groups. (B) The trends of unhealed area percentages across different time points in the HBPs-Ag and Atrauman Ag groups.

Efficacy Comparison between the Two Groups

We found that the wound area at various time intervals did not satisfy the sphericity test ($F = 127.472$, $p < 0.001$), necessitating result correction. Results indicated that there was no significant difference between the two groups ($F = 0.137$, $p = 0.712$), while a significant difference was observed among time points ($F = 28.877$, $p < 0.001$). Moreover, no statistically significant difference in burn area was detected concerning the interaction between groups and time points ($F = 0.088$, $p = 0.787$). Moreover, day 0 measurement exceeded that on day 10 and the day the wound healed, underscoring the therapeutic efficacy of both dressings, and no significant difference in efficacy between the two types of dressings was observed. Additional details are outlined in Table 4.

Safety Results

The 65 subjects in the HBPs-Ag group were treated with dressings, the mean duration of treatment was 13.2 ± 6.4 (day), meanwhile in the Atrauman Ag groups, 67 subjects were treated with dressings, the mean duration of treatment was 13.5 ± 5.7 (day), both compliance of device use was good. Twenty-six of subjects in the HBPs-Ag group (42.62%) experienced AEs versus 35 subjects in the Atrauman Ag group (57.38%). All AEs detected were classified as lower than grade 2 (less severe), and most of the AEs were weakly correlated to devices (Table 5). There were no statistical differences in all the safety indexes tested between two groups ($p > 0.05$).

Comparisons of Blood and Urine Silver Concentrations at Different Time Points

Silver was not detected in the first and last blood samples or the initial urine samples in both HBPs-Ag and Atrauman Ag groups. Additionally, no significant differences in blood and urine silver concentration on day 10 and in final urine

Table 3. Comparison of total efficiency rate, wound healing rate, wound healing time and rate of negative bacterial culture between the HBPs-Ag and Atrauman Ag groups.

Variable		HBPs-Ag group (n = 59)	Atrauman Ag group (n = 57)	$\chi^2/t/Z$	p-value
Cured		9 (15.25)	11 (19.30)	1.557	0.459
Markedly effective		49 (83.05)	43 (75.44)		
Effective		1 (1.69)	3 (5.26)		
Ineffective		0 (0.00)	0 (0.00)		
Total efficiency		58 (98.3)	54 (94.7)		
Wound healing rate		93.76 ± 12.10	93.91 ± 13.95	–0.060	0.952
Wound healing time		11 (9, 14)	12 (10, 17)	–1.032	0.302
Rate of negative bacterial culture growth	Number of culture-positive cases before treatment	2	7	0.085	0.771
	Number of culture-negative cases after treatment	2	5		

Table 4. Comparison of wound area and healing between the HBPs-Ag and Atrauman Ag groups.

	HBPs-Ag group (n = 59)	Atrauman Ag group (n = 57)	Z	p-value
Wound area (cm^2)				
Day 0	95.45 (31.34, 188.3)	84.15 (47.3, 190.18)	–0.224	0.823
Day 10	20.05 (7.85, 58.3)	16.15 (5.05, 63.65)	–0.438	0.661
Wound healing	1.6 (0.15, 8.7)	0.5 (0.1, 5.9)	–0.980	0.327
M*	55.070	68.000		
p-value	<0.001	<0.001		

M*, Friedman-M test.

silver concentration were observed between the two groups ($p > 0.999$, $p > 0.999$, and $p = 0.988$). Further information can be found in Table 6.

Silver was detected in four blood samples of this study, of which three belonged to the Atrauman Ag group (id: 27, 122, 156) and one belonged to the HBPs-Ag group (id: 136). Silver was also detected in two urine samples, of which one belonged to the Atrauman Ag group (id: 122) and one belonged to the HBPs-Ag group (id: 22). Samples 27, 122, 156 and 136 all had silver detected in blood tests on day 10, while samples 22 and 122 had silver detected in final urine tests. At the same time, silver was found in both urine and blood samples from patient id: 122 of the Atrauman Ag group. Compared with parameter before treatment, the mean increase in blood silver concentration after treatment was 0.824 ng/mL in the HBPs-Ag group and 2.352 ng/mL in the Atrauman Ag group. The mean increase in urinary silver excretion after treatment was 1974.242 ng/mL in the HBPs-Ag group and 3645.104 ng/mL in the Atrauman Ag group. Further details can be found in Table 6.

Table 5. Safety profiles of the HBPs-Ag and Atrauman Ag groups.

Safety variable			HBPs-Ag group (n = 65)	Atrauman Ag group (n = 67)	t/χ^2	p-value
Medical device exposure			13.20 ± 6.40	13.50 ± 5.70	0.536	0.596
Compliance of device usage	Good		64 (100.0)	67 (100.0)	-	-[a]
	Moderate		0 (0.0)	0 (0.0)		
	Bad		0 (0.0)	0 (0.0)		
Patients experiencing adverse events			26 (42.62)	35 (57.38)	0.298	0.585
Occurrence of adverse events	Day 1		12 (46.15)	16 (45.71)	–0.141	0.888
	Day 2		8 (30.77)	11 (31.43)		
	Day 3		1 (3.85)	1 (2.86)		
	Day 4		3 (11.54)	2 (5.71)		
	Day 6		0 (0.0)	1 (2.86)		
	Day 7		1 (3.85)	1 (2.86)		
	Day 8		1 (3.85)	0 (0.0)		
	Day 10		0 (0.0)	1 (2.86)		
	Day 12		0 (0.0)	1 (2.86)		
	Day 14		0 (0.0)	1 (2.86)		
Systemic responses	Day 1	No	61 (93.8)	62 (92.5)	0.089	0.766
		Yes	4 (6.2)	5 (7.5)		
	Day 10	No	33 (100.0)	38 (95.0)	-	0.497[b]
		Yes	0 (0.0)	2 (5.0)		
	On the day of wound healing	No	63 (98.4)	64 (100.0)	-	1.000[b]
		Yes	1 (1.6)	0 (0.0)		
Skin or tissue irritation	Day 1	No	60 (92.3)	60 (89.6)	0.303	0.582
		Yes	5 (7.7)	7 (10.4)		
	Day 10	No	31 (93.9)	36 (90.0)	0.033	0.856
		Yes	2 (6.1)	4 (10.0)		
	On the day of wound healing	No	63 (96.9)	62 (92.5)	<0.001	>0.999
		Yes	1 (1.5)	2 (3.0)		
Color changes of local skin	Day 1	No	1 (50.0)	2 (50.0)	-	1.000[b]
		Yes	1 (50.0)	2 (50.0)		
	Day 10	No	2 (6.1)	6 (15.0)	0.706	0.401
		Yes	31 (93.9)	34 (85.0)		
	On the day of wound healing	No	11 (17.2)	11 (17.2)	0.000	1.000
		Yes	53 (82.8)	53 (82.8)		
Wound swelling and wound pain	Day 1	No	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	–0.689	0.491
		Yes	1.00 (1.00, 1.50)	1.00 (1.00, 1.00)	–0.433	0.665
	Day 10	No	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	–0.582	0.561
		Yes	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	–1.451	0.147
	On the day of wound healing	No	2.00 (2.00, 3.00)	2.00 (2.00, 2.00)	–1.760	0.078
		Yes	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	–0.436	0.663

[a] No statistical test could be performed; [b] Fisher's exact probability method was used.

Table 6. Comparison of blood and urine silver concentrations at different time points between the HBPs-Ag and Atrauman Ag groups.

Variable			HBPs-Ag group (n = 65)	Atrauman Ag group (n = 67)	Statistical value	p-value
Blood silver concentration	Day 1	No	65 (100.0)	67 (100.0)	-	-[a]
		Yes	0 (0.0)	0 (0.0)		
	Day 10	No	64 (98.46)	64 (95.5)	<0.001	>0.999
		Yes	1 (1.54)	3 (4.5)		
	On the day of wound healing	No	65 (100.0)	67 (100.0)	-	-[a]
		Yes	0 (0.0)	0 (0.0)		
Urine silver concentration	Day 1	No	65 (100.0)	67 (100.0)	-	-[a]
		Yes	0 (0.0)	0 (0.0)		
	Day 10	No	64 (98.5)	66 (98.5)	<0.001	>0.999
		Yes	1 (1.5)	1 (1.5)		
	On the day of wound healing	No	64 (98.5)	67 (100.0)	<0.001	0.988
		Yes	1 (1.5)	0 (0.0)	<0.001	0.988

[a] No statistical test could be performed.

Discussion

This study is a multi-center double-blind randomized controlled trial (RCT) that evaluated the efficacy and safety of silver dressings, which presents the preliminary clinical exploration of two distinct silver-containing mesh dressings for burn wounds. Patients with burn wounds suffer a high incidence of infections, of which nosocomial infections account for the most common type of infection in this category of patients (Kiley and Greenhalgh, 2023). Infections can cause delays in healing, and administering antibiotics during hospitalization aids in the screening of pathogenic microorganisms that are increasingly resistant to antibiotics. It has been reported that antibiotics may also induce changes in gene expression that increase the virulence and spread of pathogenic microorganisms (Lachiewicz et al, 2017). Deep burn patients require prolonged treatment courses and are vulnerable to infections. Severe infections and complications attributed to deep burns may deteriorate to a point where no drugs can effectively resolve the burn wounds. Thus, having an ideal dressing is of great management significance to burns as well as all types of acute and chronic wounds because it can improve healing and help address the growing issue of antibiotic treatment failure (Yao et al, 2021). In this study, we examined silver-containing dressings with antibacterial property and conducted comprehensive evaluations of the efficacy and safety of two such dressings. We also observed adverse reactions in burn patients and obtained clinical evidence to support the introduction of silver ions from silver-containing dressings into the fluid circulation of burn patients.

HBPs-Ag dressing is loaded with modified polyamide-silver complex in the mesh, which is mainly composed of silver ions and modified polyamide amino group. The primary functional component of the HBPs-Ag dressing requires a simpler procedure in application and lower cost than other methods used for burn

treatments. The amino group of modified polyamide exists only in the molecular structure, addressing problems such as easy oxidation of silver ions and uncontrolled release. The preparation method for this type of dressing is simple and does not lead to contamination with other impure elements. Atrauman Ag dressing consists of a polyamide tulle dressing chemically coated with metallic silver and impregnated with a non-petroleum triglyceride-based ointment—a standard silver-containing dressing commonly used in the clinic. The carrier of the HBPs-Ag dressing is the same as the Atrauman Ag dressing, which is the polyamide fine mesh. This material is applied to the wound and can slowly release silver ions to reduce excessive contact between silver ions and wound cells, thereby reducing potential adverse reactions while maintaining antibacterial activity. An ideal dressing should be able to absorb excess exudates and maintain a barrier that prevents bacteria from entering. Given the continuous wound exudation in the early stages of deep partial-thickness burns, the HBPs-Ag dressing is not packed with glycerol, which acts as a lubricant and moisturizer. This is because, in the presence of glycerol, the dressing would slide on the degenerated necrotic skin, causing discomfort and raising the need for more frequent dressing changes, thereby constituting a bigger financial burden on patients. In the later stages of deep partial-thickness burns, vaseline gauze can be added between the HBPs-Ag dressing and the wound to balance the wound's moisture level and protect the nascent epithelial tissue (Wei, 2015).

The current clinical trial demonstrated that the efficacy of the two types of dressings tests were comparable, indicating that both dressings were similarly effective. Furthermore, there were no statistical differences between the time taken for healing or wound healing rates. Neither functional ingredients nor the addition of glycerol affected the overall wound healing. The rates of negative bacterial culture from wound secretions in both groups were relatively low, implying that the use of silver-containing dressings could reduce the probability of wound infections by virtue of the dressings' widely recognized feature—antibacterial property. The efficacy of these two types of dressings is consistent with their performances reviewed elsewhere (Cancio, 2021).

Studies have shown that compared with non-silver ion preparations or dressings commonly used clinically, silver ion preparations or dressings are not particularly excellent in counteracting infections and are may even inhibit wound healing and trigger pain, among other limitations (Haidari et al, 2020; Iljas et al, 2021). Adverse reactions experienced by patients using the silver-containing dressings in this trial were assessed with safety indicators. The assessment results showed that all AEs were below grade 2 or less severe, and most of the AEs had weak correlation to devices. In addition, the four adverse reactions that may be related to the dressings occurred in the same patient who applied the experimental dressing on the same day, all of which were associated with abnormal blood biochemical indicators, with no high concentrations of blood and urine silver detected. Subsequent investigations revealed that alcohol consumption while being hospitalized was the actual cause of these abnormal indicators.

In this study, the majority of patients were found to have silver ion concentrations in body fluids ten days after burn incident, but the overall measurement

rate of silver concentration among the subjects remained low, with only 5 patients (3.79%) across both groups. Of these 5 patients, silver ions were only detected in the blood and urine sample of 1 patient, while silver ions were only detected in the blood samples of the other 4 patients. In these 5 patients, the increase of blood silver concentration and urinary silver excretion after treatment was lower in HBPs-Ag group than in Atrauman Ag group. Silver ions in the patient's body are derived from silver-containing dressings, and the blood and/or urine concentration depends on the condition of wounds and the area where dressings are applied. Previous study has reported skin penetration of silver ions from silver-containing dressing, a process that could be accelerated in the event of skin damage (Brouillard et al, 2018). Presently, there are no cases or studies reporting a potential correlation between silver concentration and occurrence of serious adverse events, especially in patients suffering critical burns; however, some preliminary studies have suggested that the accumulation of silver in the body up to 3.8–6.0 g can lead to silver poisoning (Hadrup et al, 2018; Kharkar et al, 2020). The primary pathway of silver excretion is through excretion into the intestine via bile and then expulsion, followed by excretion in urine (Hadrup et al, 2022). It is important to note that silver ions face greater difficulty than silver nanoparticles in gaining entry into the systemic circulation, which is also so much more challenging as the wounds heal (Lansdown and Williams, 2004).

This study has some limitations. First, regardless of how strict the inclusion and exclusion criteria were applied in subject selection, there were still differences in terms of demographic characteristics, wound characteristics, and especially the physical properties, chemical properties, and silver release characteristics of silver-containing products. Despite the simple use and low costs of the dressings utilized in the HBPs-Ag group, these dressings have not yet passed the market pricing evaluation and have not been applied in clinical settings. As a result, the economic benefits of their clinical application cannot be accurately evaluated. Due to the limitations in manpower and material resources, this study used a limited sample size, which barely meets the statistical requirements during sample size determination, thus limiting statistical inference.

Conclusion

We conducted a comparison between two silver-containing dressings, in terms of their efficacy and safety, for the treatment of adult patients with deep partial-thickness burns. Both types of dressings were found to be similarly effective and safe for treating deep partial-thickness burns. Further research is underway to investigate the long-term efficacy and safety, as well as cost-effectiveness, of these treatments, including their impact on scarring and pigmentation.

Key Points

- The total efficiency of the HBPs-Ag dressing was higher than that of the Atrauman Ag dressing.
- No significant differences were found between the two types of dressings, in terms of efficacy, wound healing rate, wound healing time, and rate of negative bacterial culture from wound secretions.
- There were no statistical differences in any safety indicators between the two types of dressings.
- The efficacy and safety profiles of the HBPs-Ag dressing were comparable to those of the Atrauman Ag dressing in the treatment of deep partial-thickness burns.

Availability of Data and Materials

All data included in this study are available from the corresponding authors upon reasonable request.

Author Contributions

ZY and WX wrote the first draft and revised the manuscript. WX and SL designed the research and coordinated the multi-center study. SL and MJ were involved in the analysis and interpretation of the data. ZY, SL, WZ, DL, GY, ZC, JZ, WL, ZZ were involved in data acquisition and interpretation, and ensured that data accuracy or integrity. All authors contributed to revising the manuscript critically for important intellectual content and approved the final version. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the good clinical practice (GCP) requirements, the Declaration of Helsinki, as well as relevant laws and regulations in China. An informed consent was obtained from each patient. This study was approved by all ethics committees: Ethics committee of Tongren Hospital of Wuhan University, Wuhan Third Hospital, approval number: 2018 Ethics Review (25)-Year 1; Ethics committee of Nanning Second People's Hospital, approval number: 2019010A; Ethics committee of The First Affiliated Hospital of Zhengzhou University, approval number: MD-2019-042; Ethics committee of The First Affiliated Hospital of University of South China, approval number: [2019] MD Ethics Review (01-05); Ethics committee of The Second Affiliated Hospital of Kunming Medical University, approval number: Review-PJ-2020-48; Ethics committee of The First Affiliated Hospital of Hunan University of Traditional Chinese Medicine, approval number: HN-LL-2019-004-02.

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Conflict of Interest

The authors declare no conflicts of interest related to the use of two dressings in this study. The authors declare no conflict of interest.

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