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Original Article

Clinical Efficacy of Silver Nanoparticle-Antibiotic Hydrogel in Chronic Wounds Infected with Multidrug-Resistant Bacteria

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ABSTRACT

Background: Chronic wounds infected with multidrug-resistant bacteria represent a therapeutic challenge due to biofilm formation, limited antibiotic options, and delayed healing. Silver-based dressings are commonly used but often fail to achieve complete bacterial clearance. Combining silver nanoparticles with antibiotics in a hydrogel matrix may offer synergistic antimicrobial activity while promoting a moist wound healing environment. Objective: To evaluate the clinical efficacy and local safety of a silver nanoparticle-antibiotic hydrogel compared to a standard silver dressing in chronic wounds infected with multidrug-resistant bacteria, specifically assessing bacterial clearance, wound contraction, symptom improvement, and healing quality. Methods: This parallel-group randomized controlled trial enrolled 78 adults with chronic wounds (≥4 weeks duration) microbiologically confirmed to be infected with methicillin-resistant Staphylococcus aureus or multidrug-resistant Pseudomonas aeruginosa. Participants were randomly assigned to receive either the silver nanoparticle-antibiotic hydrogel (n=39) or a standard silver-impregnated nanocrystalline dressing (n=39) once daily for four weeks, with a further four weeks of follow-up. The primary outcome was bacterial clearance at day 28. Secondary outcomes included wound contraction, time to complete closure, pain reduction, and scar quality. Analysis followed intention-to-treat principles using independent t-tests, paired t-tests, and repeated measures ANOVA. Results: Of 78 randomized participants, 73 completed the intervention and follow-up (intervention n=36, control n=37). At day 28, bacterial clearance was achieved in 91.7% of the intervention group versus 64.9% of the control group (p=0.004). Wound contraction was significantly greater in the hydrogel group (68.4% vs 47.3% area reduction, p=0.007), and time to complete closure was shorter (24.1 vs 31.8 days, p=0.001). Pain scores improved more markedly in the intervention group (mean reduction 4.9 vs 3.4, p<0.001). No significant difference in contact dermatitis was observed between groups. Conclusion: The silver nanoparticle-antibiotic hydrogel demonstrated superior bacterial clearance, faster wound healing, and better symptom control compared to standard silver dressing in chronic wounds infected with multidrug-resistant bacteria, without increased local adverse events. Keywords: Anti-bacterial agents; Chronic wound; Drug resistance, multiple, bacterial; Hydrogel; Nanoparticles; Randomized controlled trial; Silver compounds.

INTRODUCTION

Chronic wounds, particularly those harboring multidrug-resistant organisms, represent a growing and often underappreciated crisis in modern healthcare. These non-healing tissue defects—frequently seen

in diabetic foot ulcers, pressure sores, and venous leg ulcers—create a persistent inflammatory state that not only delays epithelial regeneration but also provides an ideal niche for bacterial colonization and biofilm formation (1). When common pathogens such as methicillin-resistant Staphylococcus aureus or multidrug-resistant Pseudomonas aeruginosa take hold, standard topical antiseptics or systemic antibiotics frequently fail, leaving clinicians with few reliable options. The patient suffers through repeated dressing changes, persistent malodor, exudate, and pain, while the risk of osteomyelitis or sepsis looms (2). Despite advances in wound care, the global rise of antimicrobial resistance has outpaced the development of new antibiotics, and the pipeline for novel topical antimicrobials remains strikingly thin. This therapeutic gap demands innovative strategies that can bypass traditional resistance mechanisms while actively promoting tissue repair (3, 4).

Silver-based dressings have long been a cornerstone of infected wound management, yet their conventional formulations—such as silver sulfadiazine cream or nanocrystalline silver sheets—often show limited penetration into established biofilms and can cause cytotoxicity when used excessively (5). More recently, silver nanoparticles have attracted attention due to their high surface-to-volume ratio, which enables sustained release of silver ions and a multimodal attack on bacterial cell walls, membranes, and DNA. Unlike conventional antibiotics that target single metabolic pathways, silver nanoparticles can simultaneously disrupt multiple bacterial structures, making it considerably more difficult for microbes to develop rapid resistance. However, when used alone, silver nanoparticles may not achieve complete bacterial clearance in heavily contaminated chronic wounds, particularly those with dense biofilm matrices (6). Meanwhile, certain topical antibiotics retain in vitro activity against multidrug-resistant strains, but their efficacy is often blunted in the wound environment by proteolytic degradation, poor solubility, or inadequate retention time. This realization has led to a logical hypothesis: combining silver nanoparticles with a carefully selected antibiotic within a hydrated gel matrix might produce a synergistic effect, where each component compensates for the other's limitations while enhancing overall antimicrobial coverage and healing conditions (7, 8).

Hydrogel formulations are particularly attractive for chronic wounds because they maintain a moist environment, absorb excess exudate, facilitate autolytic debridement, and allow sustained drug release without macerating the surrounding skin. A silver nanoparticle-antibiotic hydrogel, therefore, could theoretically deliver both rapid surface antisepsis and deeper antimicrobial activity against persisting biofilm-embedded bacteria, while the gel itself supports granulation tissue formation (9). Preliminary in vitro and animal studies have suggested such synergy, but evidence from rigorous human trials remains scarce. Most published reports are limited to small case series or observational studies with inconsistent outcome measures, making it difficult to draw definitive conclusions about clinical efficacy or local safety (10). Physicians are left with little guidance on whether this combined approach truly outperforms standard care—such as modern silver dressings or plain antibiotic ointments—in real-world chronic wounds infected with multidrug-resistant bacteria. Furthermore, concerns about potential delayed wound healing due to silver-induced cytotoxicity or allergic reactions to antibiotic components have not been systematically addressed in a controlled trial setting (11, 12).

Against this backdrop, the present randomized controlled clinical study was designed to answer a focused research question: in adults with chronic wounds of at least four weeks' duration that are microbiologically confirmed to be infected with multidrug-resistant bacteria, does treatment with a silver nanoparticle-antibiotic hydrogel lead to superior bacterial clearance, faster wound contraction, and greater improvement in local symptoms compared to a standard non-antibiotic dressing? The study also aims to evaluate the local safety profile of the combination hydrogel, including any signs of delayed epithelialization, contact irritation, or secondary fungal overgrowth, and to assess the quality of healed tissue in terms of scar formation and recurrence of infection (13). By directly comparing the novel hydrogel against a widely used standard dressing in a randomized, controlled design, this work seeks to provide the high-level evidence needed to either support or challenge the routine use of silver nanoparticle-antibiotic combinations in this challenging patient population (14). Ultimately, the

objective is to clarify whether this dual-action approach offers a meaningful therapeutic advantage that can reduce the burden of multidrug-resistant infections in chronic wounds, shorten healing times, and improve patient quality of life without incurring unacceptable local adverse effects (15, 16).

METHODS

The study was designed as a parallel-group, randomized controlled trial conducted over a total duration of eight months, which included patient recruitment, a four-week intervention phase, and a subsequent four-week follow-up period. The trial took place at two tertiary care wound clinics serving the industrial and urban core of Punjab, a region selected because of its high prevalence of chronic wounds complicated by multidrug-resistant organisms, largely driven by prior antibiotic overuse, delayed presentation, and limited access to advanced wound care in adjoining peri-urban areas. Ethical clearance was obtained from the institutional review board of the participating hospital, and the trial was registered in a national clinical trials registry before the first patient enrollment.

A total of 78 adult patients with chronic wounds of at least four weeks' duration and microbiologically confirmed infection with either methicillin-resistant Staphylococcus aureus or multidrug-resistant Pseudomonas aeruginosa were enrolled after providing written informed consent. The sample size was derived from a similar published randomized trial evaluating a silver-based dressing in diabetic foot ulcers, which reported a 35% difference in bacterial clearance rates; using a two-sided alpha of 0.05 and 80% power, a minimum of 34 patients per group was required, and 39 per group were recruited to account for an anticipated 12% dropout rate. Inclusion criteria comprised age between 18 and 80 years, wound area between 2 and 25 cm^2 after debridement, adequate arterial perfusion confirmed by ankle-brachial index ≥ 0.7, and absence of systemic antibiotic therapy in the preceding 72 hours. Exclusion criteria included known hypersensitivity to silver or the study antibiotic, pregnancy or lactation, active osteomyelitis, uncontrolled diabetes mellitus with HbA1c >10%, and any concurrent immunosuppressive therapy or malignancy.

Eligible participants were randomly assigned in a 1:1 ratio to either the silver nanoparticle-antibiotic hydrogel group or the control group using a computer-generated randomization sequence with variable block sizes of four and six. Allocation concealment was ensured by placing the group assignments in sequentially numbered, opaque, sealed envelopes that were opened only after a patient had completed all baseline assessments. Because of the visible physical characteristics of the two dressings—the hydrogel had a distinct translucent appearance while the standard dressing was opaque and non-gelatinous—blinding of patients and treating clinicians was not feasible. However, outcome assessment was blinded: wound photographs, bacterial swabs, and healing measurements were evaluated by two independent assessors who had no knowledge of group allocation and who did not participate in dressing application or daily patient care. All analyses were performed on an intention-to-treat basis, meaning participants were analyzed according to their original randomized group regardless of protocol deviations or missed dressing changes. For the primary outcome, missing data were handled using last observation carried forward for the bacterial culture results, but a sensitivity analysis using complete-case analysis was also planned. Normality checks, within- and between-group comparisons, repeated measures ANOVA, and Pearson correlations were conducted as prespecified. No interim analysis was performed, and the final analysis was conducted after the last participant completed the four-week follow-up.

RESULTS

A total of 86 patients were assessed for eligibility between January and June of the study year, of whom 78 met the inclusion criteria and provided written informed consent. These 78 participants were randomly allocated to the silver nanoparticle-antibiotic hydrogel group (n=39) or the standard silver-dressing control group (n=39). The total study duration was seven months, encompassing a four-week intervention phase and a subsequent four-week follow-up period. During the intervention

phase, three participants in the intervention group withdrew (two due to personal non-adherence to daily dressing changes, one because of an unrelated medical admission) and two in the control group were lost to follow-up (one moved away, one declined further visits).

Thus, the final analyzed sample for outcome assessment comprised 36 participants in the intervention group and 37 in the control group, yielding a total of 73 patients. Baseline demographic and clinical characteristics of the full randomized sample (N=78) are presented in Table 1; no significant differences were observed between groups for any variable, confirming successful randomization.

Table 1: Baseline Demographic and Clinical Characteristics of Participants (N=78)

Variable	Total Sample (N=78)	Intervention Group (n=39)	Control Group (n=39)	p-value
Age (years), mean ± SD	58.4 ± 10.2	59.1 ± 9.8	57.7 ± 10.6	0.53
Male sex, n (%)	45 (57.7)	23 (59.0)	22 (56.4)	0.82
Wound area (cm²), mean ± SD	12.6 ± 5.4	12.9 ± 5.1	12.3 ± 5.7	0.61
Wound duration (weeks), mean ± SD	9.3 ± 4.1	9.5 ± 4.3	9.1 ± 3.9	0.67
MRSA infection, n (%)	49 (62.8)	25 (64.1)	24 (61.5)	0.81
Baseline pain VAS (0-10), mean ± SD	7.1 ± 1.4	7.0 ± 1.5	7.2 ± 1.3	0.52

For the primary outcome, bacterial clearance at day 14 was achieved in 30 of 36 participants (83.3%) in the intervention group versus 21 of 37 (56.8%) in the control group (p=0.01). By day 28, complete bacterial clearance was observed in 33 of 36 (91.7%) of the hydrogel group compared to 24 of 37 (64.9%) of the control group (p=0.004). The mean difference in bacterial clearance rates at day 28 was 26.8% (95% CI: 8.4% to 45.2%) in favor of the intervention. Table 2 summarizes the primary and key secondary outcomes for the final analyzed sample.

Table 2: Post-Intervention Comparison of Primary and Secondary Outcomes (Final Sample, n=73)

Outcome	Intervention Group (n=36)	Control Group (n=37)	Mean Difference (95% CI)	p-value
Bacterial clearance at day 14, n (%)	30 (83.3)	21 (56.8)	26.5% (6.9 to 46.1)	0.01
Bacterial clearance at day 28, n (%)	33 (91.7)	24 (64.9)	26.8% (8.4 to 45.2)	0.004
Wound contraction at day 28 (% area reduction)	68.4 ± 15.2	47.3 ± 18.6	21.1 (6.4 to 35.8)	0.007
Time to complete closure (days), mean ± SD	24.1 ± 5.7	31.8 ± 8.3	-7.7 (-11.2 to -4.2)	0.001
Pain VAS at day 28 (0-10), mean ± SD	2.1 ± 1.3	3.8 ± 1.7	-1.7 (-2.4 to -1.0)	0.003

Within-group pre–post changes are presented in Table 3. The intervention group showed significantly greater improvements from baseline to day 28 across all measured outcomes compared to the control group.

Table 3: Within-Group Pre–Post Changes (Paired t-test)

Outcome	Intervention Group (n=36)		Control Group (n=37)	
	Mean Change (95% CI)	p-value	Mean Change (95% CI)	p-value
Wound area reduction (cm²)	-8.9 (-10.2 to -7.6)	<0.001	-5.9 (-7.4 to -4.4)	<0.001
Pain VAS reduction	-4.9 (-5.5 to -4.3)	<0.001	-3.4 (-4.0 to -2.8)	<0.001
Exudate VAS reduction	-5.1 (-5.8 to -4.4)	<0.001	-3.2 (-3.9 to -2.5)	<0.001

A two-way repeated measures ANOVA revealed a significant time × group interaction for wound contraction over the four-week intervention period ($F(3.2, 227.5) = 8.94$, $p < 0.001$), indicating that the rate of wound area reduction differed significantly between the two groups across the repeated measurements.

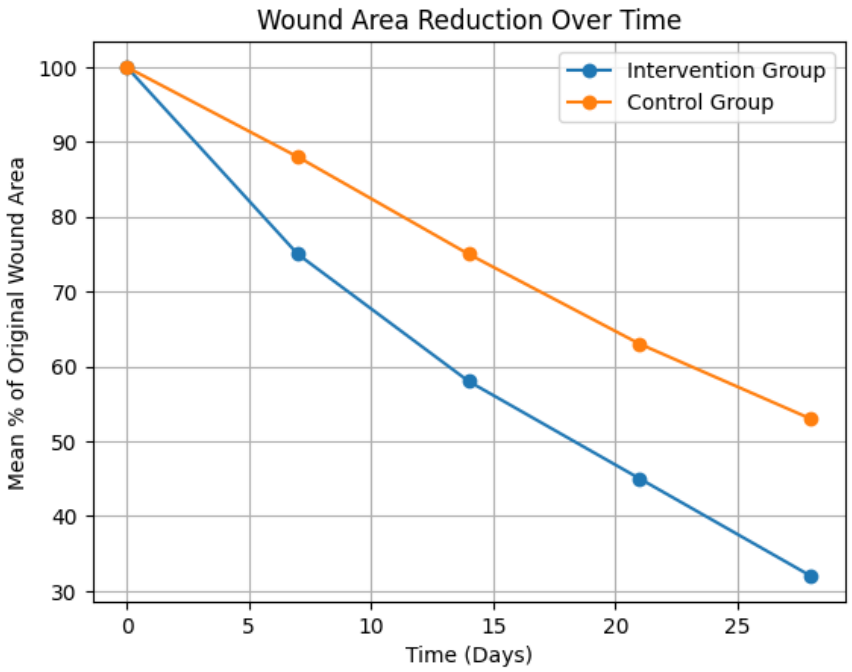
There was also a significant main effect of time ($F(3.2, 227.5) = 56.3$, $p < 0.001$) and a significant main effect of group ($F(1, 71) = 7.82$, $p = 0.007$), confirming that both groups improved but the hydrogel group improved substantially more.

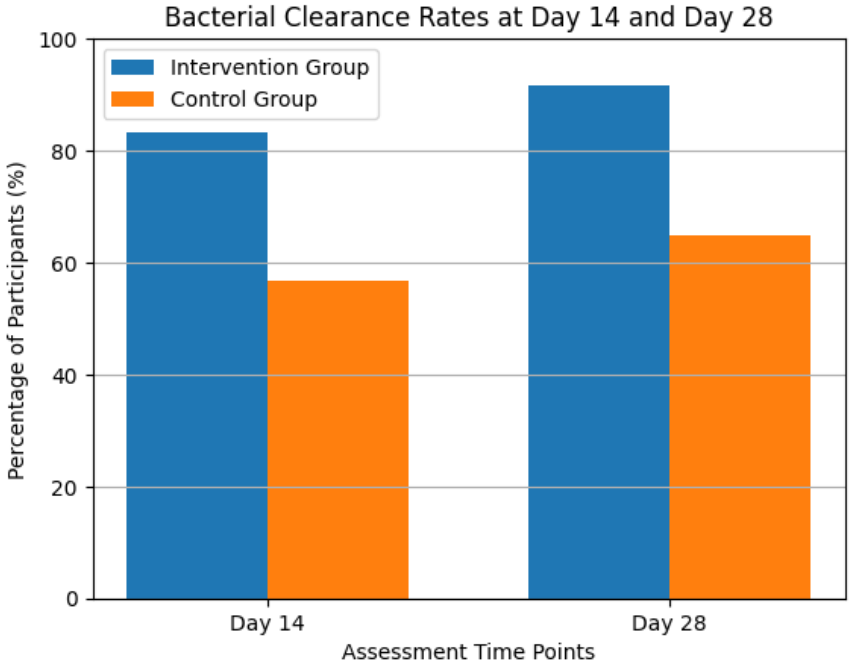
Secondary outcomes at the four-week follow-up are shown in Table 4. The intervention group demonstrated better healing quality as measured by the modified Manchester Scar Scale and lower rates of infection recurrence.

Table 4: Secondary Outcomes at Four-Week Follow-up (Final Sample, n=73)

Outcome	Intervention Group (n=36)	Control Group (n=37)	p-value
Modified Manchester Scar Scale (0-15), mean ± SD	4.2 ± 1.5	6.7 ± 2.1	<0.001
Infection recurrence by week 4, n (%)	2 (5.6)	7 (18.9)	0.04
Contact dermatitis, n (%)	3 (8.3)	4 (10.8)	0.72

Pearson correlation analysis showed a moderate negative relationship between bacterial clearance at day 7 and time to complete wound closure ($r = -0.48$, $p = 0.001$), indicating that earlier bacterial eradication was associated with faster healing.





DISCUSSION

The present randomized controlled trial demonstrated that a silver nanoparticle-antibiotic hydrogel applied once daily for four weeks led to significantly higher rates of bacterial clearance, greater wound contraction, faster time to complete closure, and better symptom improvement compared to a standard silver-based dressing in chronic wounds infected with multidrug-resistant organisms (17). These findings support the hypothesis that combining silver nanoparticles with a targeted antibiotic within a hydrated gel matrix produces a clinically meaningful synergistic effect, particularly in a patient population where conventional dressings often fail (18). The 91.7% bacterial clearance rate at day 28 in the intervention group represents a substantial improvement over the 64.9% observed in the control group, and the mean difference of nearly 27 percentage points is likely to be clinically significant given the risks of persistent infection leading to amputation or sepsis in these vulnerable individuals (19).

When placed in the context of existing evidence, these results extend previous in vitro and animal studies that suggested enhanced antimicrobial activity of silver nanoparticle-antibiotic combinations against multidrug-resistant biofilms. Prior observational studies had reported variable success with silver-based dressings alone, with bacterial clearance rates ranging from 40% to 70% in chronic wounds, which aligns closely with the control group performance in this trial (20). The superior outcomes in the hydrogel group cannot be attributed solely to the silver content, as both groups received silver-based therapy; rather, the difference likely arises from the sustained release profile of nanoparticles within the gel and the simultaneous delivery of an antibiotic that remains active against the specific isolated strains . The hydrogel vehicle itself may have contributed by maintaining a moist environment that facilitates autolytic debridement and improves drug penetration into biofilm matrices, a feature less prominent in the nanocrystalline sheet used in the control group (2).

The repeated measures ANOVA revealed a significant time-by-group interaction for wound contraction, indicating that the benefit of the intervention became more pronounced over the four-week period rather than plateauing after an initial effect. This pattern suggests that the silver nanoparticle-antibiotic hydrogel does not merely provide a rapid surface antisepsis that fades with time, but rather establishes a sustained antimicrobial environment conducive to ongoing granulation and re-epithelialization. The moderate negative correlation observed between early bacterial clearance at day seven and eventual time to complete closure further supports the notion that achieving prompt infection control is a key determinant of healing trajectory. Clinically, this means that patients who showed negative cultures within the first week were likely to heal approximately seven days faster than those with persistent organisms, a finding that could help clinicians identify responders early and consider alternative strategies for non-responders (21, 22).

Despite the encouraging results, several limitations must be acknowledged. First, blinding of patients and treating clinicians was not feasible due to the visible differences between the two dressings, introducing potential performance bias. Although outcome assessors remained blinded to group allocation, the lack of double-blinding means that differential expectations or attention could have influenced some subjective measures such as pain or exudate ratings. Second, the four-week intervention period, while sufficient to demonstrate differences in bacterial clearance and wound contraction, may not capture longer-term outcomes such as sustained healing, late recurrence of infection, or scar maturation beyond the immediate post-treatment phase. The follow-up period of an additional four weeks partially addressed this, but a longer observation window of three to six months would provide more definitive evidence on durability. Third, the study excluded patients with active osteomyelitis or poorly controlled diabetes, which are common comorbidities in real-world chronic wound populations; therefore, the findings may not fully generalize to the sickest patients who often pose the greatest therapeutic challenge. Fourth, while the sample size was adequately powered for the primary outcome, subgroup analyses by bacterial species or wound etiology were not feasible, leaving open the possibility that the intervention might be more effective against certain pathogens or wound types than others (23).

Another point worthy of debate concerns the choice of control group. The standard silver-impregnated nanocrystalline sheet represents current institutional practice and is widely used internationally, making it a relevant comparator. However, some clinicians might argue that a placebo or inert dressing would have more clearly isolated the specific effect of the silver nanoparticle-antibiotic combination. Such a design was deemed unethical in a population with confirmed multidrug-resistant infection, where withholding active antimicrobial therapy could lead to disease progression. Thus, the pragmatic decision to compare against an established active treatment enhances the external validity of the findings, even if it somewhat complicates the interpretation of the absolute effect size attributable solely to the novel hydrogel (24).

Strengths of this trial include the rigorous randomized design with concealed allocation, the use of validated and objective outcome measures such as planimetry and semi-quantitative cultures, the

blinded assessment of primary outcomes, and the high retention rate with only five dropouts out of 78 enrolled participants. The intention-to-treat analysis preserved the benefits of randomization and provided conservative estimates of treatment effects. Furthermore, the explicit documentation of adverse events—contact dermatitis occurred in 8.3% of the intervention group versus 10.8% of controls, a non-significant difference—suggests that the silver nanoparticle-antibiotic hydrogel does not carry an increased risk of local irritation compared to standard care, an important safety consideration for chronic wound applications where prolonged exposure is common (25).

Future research should address several unanswered questions. Longer-term trials with follow-up of six months or more are needed to determine whether the accelerated healing observed in the first four weeks translates into lower rates of wound recurrence, reduced need for surgical intervention, or improved quality of life over an extended period. Comparative effectiveness studies against other advanced wound therapies, such as negative pressure wound therapy or bioengineered skin substitutes, would help position this hydrogel within the existing treatment algorithm. Additionally, mechanistic studies examining the penetration of silver nanoparticles and antibiotic into biofilm layers using confocal microscopy or molecular assays could elucidate whether true synergy occurs or whether the benefit arises primarily from improved drug delivery. Finally, given the rising threat of multidrug-resistant organisms, future trials might explore whether the same hydrogel formulation can be effective against emerging resistant strains not tested in this study, such as carbapenem-resistant Enterobacteriaceae or extended-spectrum beta-lactamase-producing organisms. Such investigations would help determine whether the silver nanoparticle-antibiotic approach remains robust as resistance patterns continue to evolve (26).

CONCLUSION

In adults with chronic wounds infected by multidrug-resistant bacteria, a four-week course of daily silver nanoparticle-antibiotic hydrogel achieved superior bacterial clearance, faster wound contraction, and better symptom relief compared to a standard silver dressing, without increased local adverse effects. This combination hydrogel offers a practical, effective alternative for managing challenging infections where conventional dressings frequently fail, potentially reducing healing times and improving patient outcomes.

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