An open multicenter comparative randomized clinical study on chitosan

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ABSTRACT

Chitosan, a natural polysaccharide derivate from chitin, offers a promising alternative biomaterial for use in wound dressings. In this work, the safety and efficacy of a next-generation KA01 chitosan wound dressing in facilitating the healing of nonhealing chronic wounds was studied. This open multicenter comparative prospective randomized clinical study was conducted at three medical centers in China. A total of 90 patients (45 in test group and 45 in control group) with unhealed chronic wounds including pressure ulcers, vascular ulcers, diabetic foot ulcers, and wounds with minor infections, or at risk of infection, were treated with the next generation chitosan wound dressing as the test article or traditional vaseline gauze as a control. Baseline assessments were undertaken with the primary end point being wound area reduction. The secondary end points included pain reduction (using the NRS11 pain scale) at dressing change, wound exudate levels, wound depth and duration of the treatment. After 4 weeks treatment, the wound area reduction was significantly greater in the test group ($65.97 \pm 4.48\%$) than the control group ($39.95 \pm 4.48\%$). The average pain level in the test group was 1.12 ± 0.23 and 2.30 ± 0.23 in the control group. The wound depth was also lower in the test group 0.30 ± 0.48 cm than the control group 0.54 ± 0.86 cm. The level of exudate fell and the dressing could be removed integrally in both the test and control groups. The mean duration of the test group was 27.31 ± 5.37 days and control group 27.09 ± 6.44 days. No adverse events were reported in either group. In conclusion this open multicenter comparative prospective randomized clinical study has provided compelling evidence that the next generation chitosan wound dressing can enhance wound progression towards healing by facilitating wound reepithelialization and reducing the patients pain level. Furthermore the dressing was shown to be clinically safe and effective in the management of chronic wounds.

There are many advanced wound dressing materials commercially available for the treatment of both acute and chronic wounds. The choices predominately include hydrogels, hydrocolloids, gauzes, foams, and fibrous dressings, such as alginates and occlusive synthetic materials.[1,2] Research has demonstrated that when compared to traditional wound dressings such as gauze, the "more" advanced wound dressings are likely to help promote healing in chronic wounds more effectively.[3] The advantage of advanced wound dressings, such as alginate, hydrocolloids and foams are they exhibit high absorption and moisture retention capacity. This has been reported in numerous in vitro and in vivo studies.[4–6] The overall benefit of these wound dressings is that they provide a moist environment for enhancing wound healing rates.[7–9] Furthermore, wound dressings provide a barrier to invading microorganisms due to their inherent immobilising or sequestering ability.[10] The overall outcome is that this prevents the colonization and proliferation of microorganisms in the wound bed.

It has recently been reported that chitosan, a natural polysaccharide derivate from chitin, offers a promising alternative biomaterial for use in wound dressings due to its inherent ability to assist with wound pathophysiology.[4] Chitosan possesses some excellent inherent properties such as being nontoxic, nonirritating, nonimmunogenic, biodegradable, and biocompatibile.[6] Furthermore it has been reported to provide other benefits such as hemostasis and bacteriostatic ability.[11–16]

Recent research has reported that wound dressings composed of chitosan have significant potential for reducing wound healing times and pain, when compared to traditional gauze or alginate wound dressings.[17–19] Stone and colleagues have reported that a chitosan wound dressing can enhance wound reepithelialization when compared to conventional wound dressings.[1,20]

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• 18 years old or above; • Clinically diagnosed to be suffering from an unhealed or nonhealing chronic wound such as pressure ulcer (PU), venous leg ulcer (VLU), diabetic foot ulcer (DFU), minor infective wound; • An area of target wound between 1 and 200cm^2; • Only one target wound was selected if there were several wounds on one patient. In this case the unselected wounds were managed through the hospitals own standard protocols of care; • Read, agreed and signed the informed consent form; • Willing and able to accept the treatment according to the protocol.	• Unable or unwilling to sign the written informed consent; • Unable or unwilling to comply with the protocol; • Allergies to shellfish, i.e., shrimp and crabs; • Pregnant women; • Participating in other clinical trials; • Underlying or diagnosed serious diseases or deemed unsuitable for this clinical trial according to the judgment of the studies clinicians.

A novel next generation wound dressing composed of 100% chitosan fibers has been developed by Foshan United Medical Technologies Ltd to efficiently and effectively manage wound exudate and other variables impeding wound healing. To demonstrate the safety and efficacy of the new next generation chitosan wound dressing for the management of chronic wounds, this article describes an open multicenter comparative prospective randomized clinical study that was conducted at three hospitals in China. The study was designed to compare the performance of the new next generation chitosan dressing against traditional vaseline gauze in the management of chronic wounds measuring factors that include wound healing rate, wound exudate levels and pain levels.

MATERIALS AND METHODS

Study design

This open multicenter comparative prospective randomized clinical study was conducted from November 2012 to July 2013. A total of 90 patients were recruited from three centers in Guangdong Province, China: The First Affiliated Hospital of Shantou University Medical College, The Second Affiliated Hospital of Guangzhou Medical University and Southern Medical University Zhujiang Hospital. The trial reference was TP286 and was fully approved by the relevant ethics committee of each hospital. The approval reference numbers were 2102005, 2012-29-1, and KA01-3, respectively.

Patients over 18 years of age with nonhealing chronic wounds that presented with pressure ulcers, vascular ulcers, diabetic foot ulcers, chronic ulcers, and minor infected wounds, with a wound area of between 1 and 200 cm^2, were eligible for inclusion into the study. The inclusion and exclusion criteria is shown in Table 1 below.

Patients were excluded if they had an allergy to shrimps or crabs, or if they were pregnant women, or had some other serious diseases that may conflict with the clinical trial. Additional exclusion criteria included inability to sign the written informed consent and currently participating in other similar clinical trials. Written informed consent was obtained from each patient prior to being enrolled.

Randomizing grouping method

Layered section (layered from the center) randomizing grouping was applied. The randomizing grouping programmed was compiled using SAS9.2 and with the supplied seed number and section span. The subjects were divided into two groups (Control Group/Test Group) at the ratio of 1 : 1. The randomizing grouping for all 90 subjects was formed into a Random Code Table, i.e., the therapy allocation corresponding to a range of sequential numbers (01–90) was listed. The random code table was kept by a designated person (referred to as the Keeper) in each center. On the election of a patient, the clinician would request an allocation code from the Keeper. The Keeper, according to the sequential number of the patient enrolled and the Random Code Table determined the group (test or control) in which the subjects should be, and then informed the clinician. The clinician would then apply the chitosan wound dressing to the wound if the patient was in the test group or the vaseline gauze dressing if the patient was in the control group. The treatment of the patient would start and all information logged as per the approved protocol.

Products

The test dressing was a chitosan wound dressing (Foshan United Medical Technologies Ltd, Guangdong, China) at a size of 10 cm × 10 cm. The control dressing was a sterile Vaseline gauze (Shaoxing Zhende Surgical Dressing Co. Ltd, China) at a size of 10 cm × 10 cm.

Base line assessment

At the beginning of the study and prior to the application of the dressing (test or control), base line information was obtained including patient information, type of wound, location of wound, wound area, wound depth, status of

wound, exudation degree, wound colour, level of exudate, signs and symptoms of infection (erythema, pain, malodour, colour, granulation tissue, slough, purulent exudate) and conditions surrounding the skin (healthy, macerated, dry). The infected wound were specifically classified based on swelling, redness, tenderness, throbbing pain, localized warmth, the presence of pus either in the wound or draining from it, and red streaks spreading away from the wound.

Treatment and follow up

The study duration was 4 weeks and the follow up was carried out every 7 days. At each time point (7, 14, 21, and 28 days) wound measurements (width, length) were taken and the wound area reduction was calculated. Also other information such as wound depth, levels of exudate, pain level felt by the patient at the dressing change, and wound colour were taken or observed. Dressing changes and wound assessments were performed by a qualified nurse or clinician in each center. Dressing application and changes procedures followed the instructions for use (IFU) of each dressing. Dressing change frequency was every 3–4 days depending on the conditions of the wound following the hospitals standard protocols of care. A standard cleaning procedure, according to the hospitals standard protocols of care, using sterile saline solution was performed before the reapplication of a new dressing.

Primary end point

At each time point the following primary measurement was recorded to assess healing progression: wound width (greatest—cm) and length (greatest—cm) were measured using a wound measurement scale following the standard practices employed in each of the hospitals. The wound area reduction (cm^2) was calculated using the following formula:

$$\text{Wound Area Reduction} = (W0 - W1)/W0 \times 100\%$$

$W0$, wound area before the application of the dressing; $W1$, wound area at the time of measurement.

Secondary end points

- **Pain at dressing change**: The pain felt by the patient at each dressing change was recorded using a Numerical Rating Scale (NRS11, 0–10 level: Level 0: no pain, Level 1–3: light pain, Level 4–6: moderate pain, Level 7–10: severe pain).
- **Wound depth at dressing change**: A sterile cotton swab was inserted into the wound at the deepest point and the swab was marked at the point level to the skin surface. The distance from the tip of cotton swab to the marked point was recorded as the wound depth.
- **Degree of wound exudation**: The description of the wound exudate was assessed by the expert clinicians based on their experience and recorded at each dressing change as dry, moist, wet, saturated, or leaking according to local practice.
- **Integral removal of the dressing**: This was observed and recorded at each dressing change as either yes or no.
- **Wound healing duration**: The duration of treatment from the start to the end was recorded if the wound was healed before 30 days.

Safety evaluation

All adverse events and serious adverse events (SAE) during the study were reported in writing by logging the event into the Case Report Form. The clinical investigator evaluated the adverse events based on clinical experience and professional judgment and included date, duration, type, medical checks, severity, prognosis and the relationship to the medical devices. The consequence and severity of the adverse effects was finally evaluated by the sponsor after the trial period.

Furthermore, the study required that any SAE that occurred during the trial be reported to the sponsor, ethical committee of the medical institution and the State Food and Drug Administration department within 24 hours following the event.

Statistical analysis

Statistical analysis was performed using SPSS 19 and SAS 9.2 by the Biomedical Statistics Department of South China Medical University. Two-sided testing was conducted for all the statistic deductions. The statistical significance level (p) was less than 0.05, and the confidence interval (CI) was 95%.

The effectiveness analysis took last observation carried forward for supplementation, i.e., the last observation data would be used as the final result for the subjects with partial loss on the whole therapy process. The safety evaluation did not include the lost data.

For the primary end point, superiority validation was used and covariance analysis was taken with consideration of central effect adjustment and the influence of other possible factors. A 95% CI of the difference of wound area reduction rate between the test group and control group was used for estimation. The lower limit above 10% was considered that the end point was clinically effective.

For the secondary end points, two-sample t-test or adjusted t-test (heterogeneity of variance) was used. For enumeration data, Pearson χ^2 test was conducted. For ranked data, Wilcoxon two-sample test was conducted. Considering the covariates, covariance analysis was conducted for measurement data, logistic regression was conducted for enumeration data, and ranked logistic regression was conducted for ranked data.

The Pearson χ^2 test was conducted in safety analysis to compare the incidence rates of adverse events of the two groups, and listed the adverse events that happened in this trial.

RESULTS

A total of 90 patients were enrolled into the study, 45 in each group. There have been 11 patients who did not turn up for the dressing change or withdrew from the study. The result was that the total patient number reduced to 42

Table 2. Demographic data and baseline wound characteristics

Item		Group		
		Test Group	Control Group	Total
Gender	Male	26(57.8%)	23(51.1%)	49(54.4%)
	Female	19(42.2%)	22(48.9%)	41(45.6%)
Age (Years)		61.22 ± 15.12	63.20 ± 18.65	
Duration of wound		44.18 ± 66.44	53.76 ± 94.00	
Surrounding skin	Edema	20(44.4%)	18(40.0%)	38(42.2%)
	Hyperplasia of epidermis	6(13.3%)	3(6.7%)	9(10.0%)
	Tissue hardening	15(33.3%)	15(33.3%)	30(33.3%)
	Pigmentation	20(44.4%)	18(40.0%)	38(42.2%)
	Infected or allergic	19(42.2%)	22(48.9%)	41(45.6%)
Wound type	Pressure ulcer	3(6.7%)	3(6.7%)	6(6.7%)
	Lower limb vascular ulcer	12(26.7%)	13(28.9%)	25(27.8%)
	Diabetic foot ulcers	8(17.8%)	8(17.8%)	16(17.8%)
	Chronic infected wound	21(46.7%)	15(33.3%)	36(40.0%)
	Chronic ulcerative wound	1(2.2%)	6(13.3%)	7(7.8%)
Wound size	Length (cm)	4.18 ± 3.04	5.10 ± 4.57	
	Width (cm)	2.56 ± 2.18	3.20 ± 3.00	
	Area (cm^2)	15.66 ± 28.01	19.74 ± 28.70	
	Depth (cm)	1.43 ± 1.39	1.13 ± 1.33	
Wound infected		35(77.8%)	34(75.6%)	69(76.7%)
Wound color	Pink	9(20.0%)	5(11.1%)	14(15.6%)
	Red	8(17.8%)	10(22.2%)	18(20.0%)
	Yellow	6(13.3%)	6(13.3%)	12(13.3%)
	Black	1(2.2%)	5(11.1%)	6(6.7%)
	Mix color	21(46.7%)	19(42.2%)	40(44.4%)
Complication		8(17.8%)	7(15.6%)	15(16.7%)
Pain level		4.51 ± 2.39	4.53 ± 2.14	
Pain description	Painless	3(6.7%)	0(0.0%)	3(3.3%)
	Mild pain	13(28.9%)	14(31.1%)	27(30.0%)
	Moderate pain	20(44.4%)	24(53.3%)	44(48.9%)
	Severe pain	9(20.0%)	7(15.6%)	16(17.8%)
Degree of wound exudation	Dry	4(8.9%)	4(8.9%)	8(8.9%)
	Wet	3(6.7%)	8(17.8%)	11(12.2%)
	Moisturized	15(33.3%)	14(31.1%)	29(32.2%)
	Saturated	16(35.6%)	10(22.2%)	26(28.9%)
	Leaked	7(15.6%)	9(20.0%)	16(17.8%)

in the test group and 37 in the control group. The dropout and withdrawal numbers between groups were statistically insignificant ($p = 0.108$).

The average age of the test group was 61.22 ± 15.12 and the control group 63.20 ± 18.65. Mean wound duration at the time of the enrollment was 44.18 ± 66.44 days for the test group and 53.76 ± 94.00 days for the control group. There was no statistical difference ($p < 0.05$) in the condition of the skin surrounding the wound, wound type and wound color between the two groups. The gender distribution in the two groups was not statistically significant ($\chi^2 = 0.403$, $p = 0.525$). There was no statistical difference ($p < 0.05$) between the two groups in the baseline data of primary and secondary end points before treatment. Demographic data and baseline wound characteristics are given in Table 2.

Although it was not one of study endpoints, the distribution of the wound locations are summarized in Table 3.

Primary end point

There was a decrease in wound area in both the test and control groups at the 4 week treatment point compared to the baseline. The wound area at the end of the treatment

Table 3. Distribution of wound locations

Location	Percentage (%)
Back	3
Lower limb	30
Foot	42
Buttock	9
Abdomen	12
Lap	3

(4 weeks) period in the test group was $5.40 \pm 12.00\,cm^2$ and in the control group was $13.18 \pm 19.64\,cm^2$. The wound area reduction was greater in the test group ($65.97 \pm 4.48\%$) than the control group ($39.95 \pm 4.48\%$) and was found to be statistically significant ($p < 0.001$).

At weeks 2 and 3, the wound area reduction in the test group was greater than that of the control. This was found to be statistically significant ($p < 0.033$). At week 1, no statistical significance ($p < 0.05$) was reported in the wound area reduction between the two groups (Figure 1).

Secondary end points

Figure 2 demonstrates that there was less pain following dressing removal in the test group compared to the control group at the week 4 time point; average pain level in the test group was 1.12 ± 0.23 and in the control group 2.30 ± 0.23 ($p < 0.001$). The difference in pain level was statistically significant ($p < 0.05$) at weeks 2 and 3.

The average wound depth decreased in both the test and control groups during the study period. After 4 weeks treatment, the wound depth was significantly lower in the test group (0.30 ± 0.48 cm) than the control group (0.54 ± 0.86 cm) ($p = 0.025$). The difference was not statistically significant ($p > 0.05$) at weeks 1, 2, and 3. The wound depth at different time points in the two groups is shown in Figure 3. It can be seen that the decrease rate of wound depth in test group was faster than the control group.

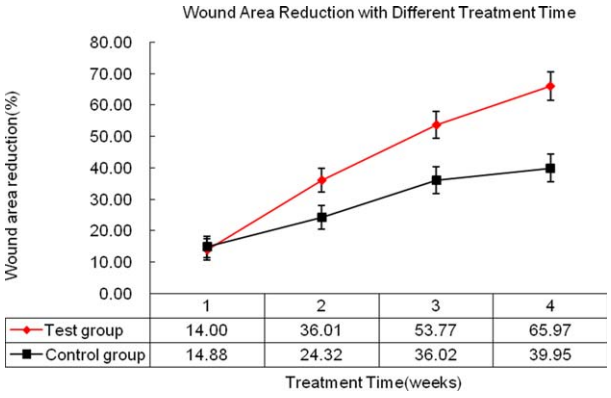

Figure 1. The change in wound area reduction (%) over a 4 week treatment period between the test group (chitosan) and the control group (gauze). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

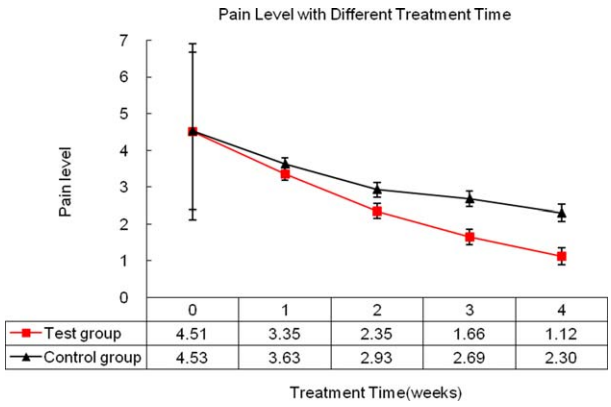

Figure 2. A comparison of pain levels (1 mild–10 severe) between test group (chitosan) and control group (gauze). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The level of exudate was assessed by the clinicians based on their experience and recorded as dry, moist, wet, saturated and leak during the study. The test product, when compared to the control, demonstrated superiority in the management of the wound exudate. The number of wounds with "saturated" exudate for the test group dropped from 12 to 2 after 4 weeks' treatment, while the control group from 12 to 6, which indicated an improved in wound conditions in the test group. The mean exudate score at week 4 was significantly ($p = 0.008$) lower in the test group (40.51) when compared to the control group (50.49). At weeks 1, 2, and 3 there was no difference between the two groups. Table 4 compares the patient number of wound exudate between the test group and control group. The high percentage of "saturated" wounds in the control group were attributed to the natural low absorbency of the gauze dressing, further exaggerated by the presence of vaseline in the control dressing.

In both the test and control groups the dressings remained integral following dressing change or at dressing removal. There was no significance difference between the two groups.

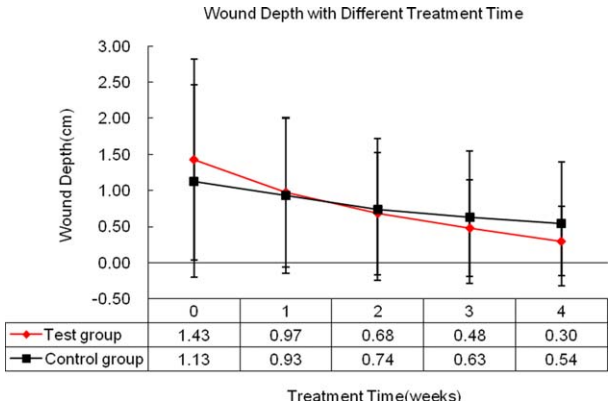

Figure 3. Wound depth between Test Group (chitosan) and Control Group (gauze). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 4. Patient number and score of wound exudate level between Test Group and Control Group

	0		1		2		3		4	
Weeks	Test Group	Control Group	Test Group	Control Group	Test Group	Control Group	Test Group	Control Group	Test Group	Control Group
Leak	7	9	0	3	0	1	0	0	0	0
Saturated	16	10	12	12	9	9	3	7	2	6
Wet	15	14	19	10	13	11	11	10	7	8
Moist	3	8	10	15	19	17	21	21	18	21
Dry	4	4	4	5	4	7	10	7	18	10
Average score	47.37	43.63	46.16	44.84	46.28	44.72	42.78	48.22	40.51	50.49

The mean wound duration of the test group was 27.31 ± 5.37 days and 27.09 ± 6.44 days in the control group. It was not possible to determine a statistical significance between the test and control groups in the duration of treatment. This is due to the short duration of the study which was not long enough to allow a higher proportion of chronic wounds to heal completely. However, during the study, 11 wounds had healed (nine in the test group and two in the control group) before the end of the 30 days follow up period.

Use on infected wounds

For the infected wounds, a healing rate was analyzed. It was found that the infected wounds at the start of the study in the test group achieved an improvement in healing when compared to the control group. Eight out of 35 patients in test group achieved complete healing before the end of the 4 week follow-up period, while only 1 out of 34 in control group achieved the complete healing. Another 7 out of 35 patients in test group achieved a healing rate of 80% or above, whilst only 3 out of 34 occurred in the control group. In total 43% of the infected wounds in the test group achieved a healing rate of 80% or above (23% complete healing), while this was only 11.7% in the control group (2.9% complete healing).

Safety

Both the test and control groups had no adverse events or severe adverse events reported during the study.

DISCUSSION

This open multicenter comparative prospective randomized clinical study was conducted to evaluate the safety and efficacy of a next generation chitosan wound dressing, in facilitating the healing of nonhealing in a diverse range of chronic wounds. It study involved 90 patients from three medical centers in China.

The new chitosan wound dressing reported on in this study is an advanced wound dressing made from acylated chitosan fibre. Acylated chitosan is a chitosan derivative, which gels on absorbing wound fluid and is considered to be very suitable for the treatment of chronic wounds with a high exudates level[21] as the study has demonstrated.

This new chitosan wound dressing has been shown to have a high absorbency ability demonstrated by its ability to absorb wound exudate, when compared to the vaseline gauze dressing; a fundamental requirement for advanced wound dressings. Research has shown that the chitosan dressing has a typical absorbency level of $20\,g/100\,cm^2$.[22]

Furthermore, the study has demonstrated that the new chitosan wound dressing, when compared to the control dressing, resulted in a reduced wound area and depth following 4 weeks of treatment. This highlights that the chitosan wound dressing promoted wound healing at a more advanced rate than that of the control vaseline gauze dressing.

In addition, the ability of the chitosan dressing to manage the exudate in the wound was superior to the control group. This could be attributed to the structure of the new chitosan dressing. The chitosan wound dressing is a nonwoven pad composed of chemically modified chitosan fiber. The chemically modified chitosan has a large quantity of amino groups and carboxyl groups which are hydrophilic groups and therefore are able to absorb large amounts of liquid. Furthermore, the hydroxyl groups in the chitosan chain are able to sequester the liquid to help maintain the moisture level within the wound bed, i.e., it has a gelling property.

The gelling property of the chitosan wound dressing helps to reduce pain for the patient at dressing changes. A number of studies have reported comparable or faster healing with wound dressings that gel compared to nongelling dressings such as gauze.[23,24]

The healing rate in infected wounds of chitosan test group (43%) was found to be significantly higher than the control group (11.7%). This result indicates that the chitosan wound dressing enhances wound healing to a far greater degree than traditional vaseline gauze. This may be due to that the fact that chitosan may have inherent bacteriostatic ability as has been reported in a number of studies.[25,26]

Additionally the study has demonstrated that the chitosan dressing did not result in any adverse events, or severe adverse events, over the whole duration of the study.

CONCLUSION

Chitosan has some unique properties which makes it an ideal material for use in enhancing wound healing. A unique characteristic of the new chitosan dressing is that it has been chemically modified for enhanced gelling and

absorbency so it can be used specifically in the treatment of heavily exudating chronic wounds.

Overall, within this recent study, the new chitosan wound dressing was found to be superior to the control dressing for the management of chronic wounds. The superiority of the chitosan dressing when compared to the vaseline gauze dressing was demonstrated with wound area reduction, wound depth, pain level on dressing removal and the management of wound exudate. In particular, the study highlighted further the safety of the new next generation chitosan wound dressing for clinical applications highlighting that the new chitosan wound dressing is both safe and can be effectively used for the management of chronic wounds.

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