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A systematic review and meta-analysis of clinical outcomes associated with nanocrystalline silver use compared to alternative silver delivery systems in the management of superficial and deep partial thickness burns

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ABSTRACT

Objective: The purpose of this systematic review and meta-analysis was to assess the clinical effectiveness of nanocrystalline silver compared to alternative silver delivery systems (silver sulphadiazine [SSD] and silver nitrate) in adults and children with superficial and deep partial thickness burns.

Methods: PubMed, EMBASE, Cochrane and other databases were searched to identify relevant randomised controlled trials and observational studies.

Results: Eight studies that assessed both nanocrystalline silver and SSD and one study that compared nanocrystalline silver vs. silver nitrate were identified. Nanocrystalline silver compared to SSD/silver nitrate was associated with a statistically significant reduction in infections (odds ratio [OR] 0.21, 95% CI 0.07–0.62, $p=0.005$), length of stay in hospital (mean difference -4.74 (95% CI -5.79 to -3.69 , $p=0.00001$) and surgical procedures (OR 0.40, 95% CI 0.28–0.56, $p=0.00001$). Three studies that reported on pain had lower pain scores with nanocrystalline silver use than with SSD/silver nitrate; a high level of heterogeneity precluded pooling estimates.

Conclusion: This comprehensive systematic review and meta-analysis of the available evidence suggest that the use of nanocrystalline silver dressings results in shorter length of stay in hospital, less pain, fewer surgical procedures and reduced infection rates compared to silver sulphadiazine/silver nitrate.

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1. Introduction

Burns are a serious health problem affecting adults and children globally [1]. In the United States alone, over 480,000

people require medical care for burns each year, leading to 40,000 hospitalisations [2]. The survival rate is a favourable 97% [2], however, burns are a cause of considerable morbidity.

Superficial burns affect the epidermal skin layer and superficial layer of dermis. Partial thickness burns may involve

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damage to deeper structures of the dermis and structures such as blood vessels and nerves [3]. Treatment of these burns is aimed at controlling infection and promoting healing with good aesthetic outcomes, and a wide variety of wound care products are currently available [3]. The process of burn management can often lead to infection resulting from local damage to the skin's protective barrier, together with suppressed immune system function [4,5]. This high risk of infection often results in delayed wound healing and longer hospital stays, in addition to higher treatment costs [5]. Patient comfort on the potentially frequent application of dressings during wear and removal is also an important consideration in managing burn wounds [6] and there has been renewed focus on how antimicrobial delivery systems impact on pain control.

The antimicrobial properties of silver have been recognised since Roman times [7]. This heavy metal has a broad spectrum of activity against bacteria, yeasts and fungi and has been used in modern day wound healing since the early 1960s when 0.5% silver nitrate aqueous solution was used as an alternative to antibiotics in the management of major burns [8]. However, rapid inactivation by protein and chloride in the burn wound meant application frequencies could be up to 12 times per day to ensure that sufficient levels of silver ions were available to reduce the bacterial load [9]. Silver sulphadiazine (SSD) was introduced in the late 1960s, and this combination of silver linked to a sulphadiazine carrier reduced the frequency of application to once/twice daily as the effective release and replenishment of bactericidal levels of ionic silver were considerably improved [10]. SSD is still considered the standard antimicrobial treatment for burn wounds in many parts of the world. However, advances in technology have led to newer silver dressings with improved forms of delivery systems, aimed at improving efficacy while minimising side effects [9]. The unique structure of the nanocrystalline silver dressing dictates activity and releases and replenishes bactericidal levels of positively charged silver ions to ensure fast and effective kill over extended time periods [11].

The management of burn wounds can take many forms. With the benefits of multiple treatment options come challenges for clinicians over which to choose. The purpose of this systematic review and meta-analysis was to assess the clinical effectiveness of nanocrystalline silver compared to two alternative silver delivery systems in adults and children with superficial and deep partial thickness burns in terms of

infection control, length of stay (LOS) in hospital, surgical procedures and pain reduction.

2. Methods

2.1. Systematic review eligibility criteria

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [12]. It was based on the planned Population, Intervention, Comparator, and Outcomes (PICO) elements outlined in Table 1.

2.2. Search strategy

Studies were identified by searches of the following electronic databases: PubMed, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), and the European Trials Register. A search strategy was used to identify studies indexed on PubMed, and this was modified for searches of the other databases to account for differences in syntax and thesaurus headings. Search terms included both free text and MeSH terms. No limits were applied for language. The searches were run to include citations from 1990 (when most of the commonly used silvers became available) to May 2015. A pearl-growing technique (i.e. searching the references of relevant papers identified in the original search) was used to identify further publications of interest.

2.3. Study selection and data extraction

Two reviewers independently assessed the full text papers of the studies identified during the abstract assessment stage for inclusion, and any differences in opinion were arbitrated by a third reviewer. Initially, five papers were fully independently data extracted by two reviewers using a standardised data extraction form and then validated by one reviewer. Since agreement between the two reviewers was high the remaining papers were independently extracted by one reviewer and

Table 1 – Inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Type of study	RCTs, retrospective and prospective comparative observational studies	Systematic reviews, conference abstracts, case series, case reports, narrative reviews, editorials, opinions; studies performed in animals
Population	Adults and children with deep partial and superficial partial thickness burns	Full thickness burns
Geographical location	Publications from any country	None
Interventions	Nanocrystalline silver (ACTICOAT), SSD, silver nitrate	Other silver dressings other than nanocrystalline silver (ACTICOAT), SSD and silver nitrate
Outcomes of interest	Infection, LOS, incidence of surgical procedures (defined as debridement & skin grafting) and pain	

LOS, length of stay [in hospital]; SSD, silver sulphadiazine; RCT, randomised controlled trial.

validated by a second reviewer; any discrepancies were resolved through discussion, with involvement of a third reviewer if necessary.

2.4. Quality assessment

The methodological quality of the randomised controlled trials (RCTs) was assessed independently by two reviewers according to the Cochrane risk of bias tool and observational studies were assessed using the GRACE checklist. The Cochrane risk of bias tool addresses seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and “anything else” [13]. The GRACE checklist is an 11-item tool that assesses the quality of data and methods of observational studies [14].

2.5. Meta-analysis

The meta-analysis was performed according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology Group [15] and the quality of reporting of meta-analyses recommendations for improving the quality of meta-analyses of RCTs [16].

A standard pair-wise meta-analysis was conducted using either a fixed-effect model where there was no evidence of significant heterogeneity between studies (I^2 statistic less than 50%), or a random-effects model when heterogeneity was likely (I^2 statistic more than 50%). For dichotomous outcomes, odds ratio (OR) was reported as the summary statistic, and for

continuous outcomes, the (weighted) mean difference (MD) was reported. In the absence of suitable data to perform a meta-analysis, the available data was tabulated and discussed in a narrative review. Data were analysed separately for RCTs and observational studies. In a further analysis all data were combined to ensure that all available evidence was utilised; furthermore, combining evidence from RCTs and observational studies increases the sample size which provides more statistical power to detect differences between interventions. A similar approach has been used in previous studies in other therapy areas and the results of RCT and observational studies have been found to be largely similar especially if known confounders are controlled for in observational studies [17-19].

3. Results

3.1. Study selection and characteristics

The search of electronic databases identified 1587 potentially relevant studies, of which 1057 were screened after the removal of duplicates (Fig. 1). Following the initial screening, a total of 52 articles were retrieved for full-text assessment, of which nine studies met the inclusion criteria. Of these, eight studies assessed both nanocrystalline silver and SSD [20-27] and one study compared nanocrystalline silver vs. silver nitrate [28].

The characteristics of the studies that evaluated both nanocrystalline silver and SSD/silver nitrate are shown in Table 2. The studies were published between 1998-2010. Three

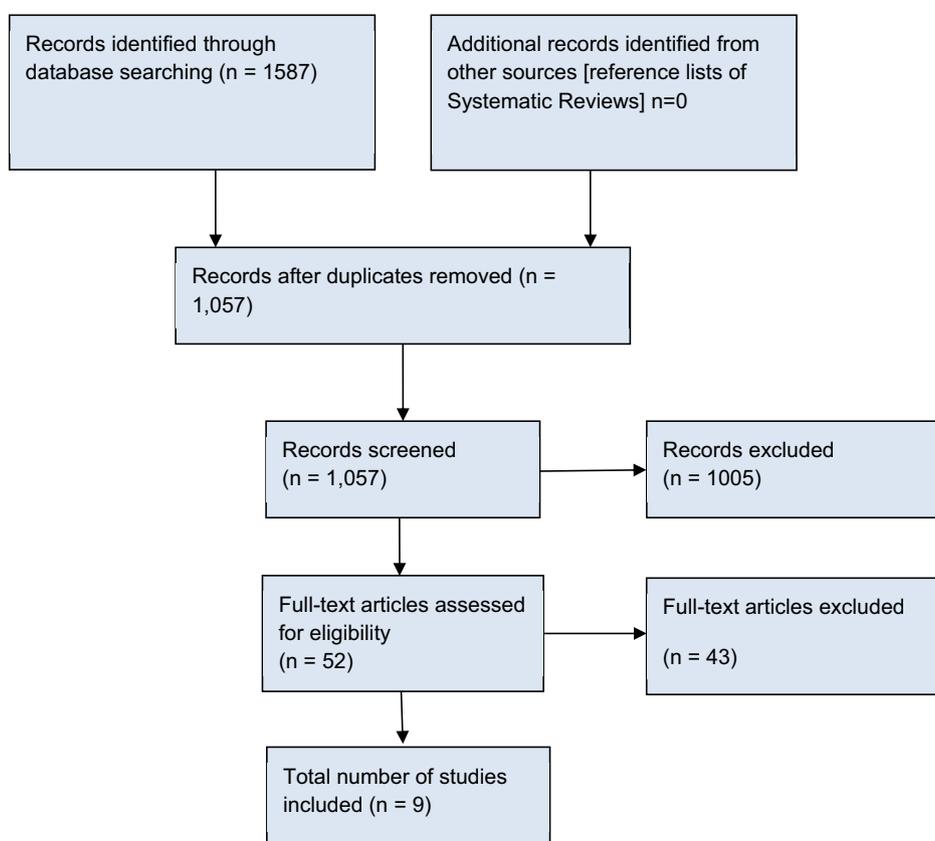


Fig. 1 – PRISMA flow diagram for studies included and excluded from the systematic review.

Table 2 – Characteristics of the nanocrystalline silver vs. SSD/silver nitrate studies.

Author	Country	Study design	Sample size	Mean age (years) ± SD (range)	Mean TBSA ± SD (range), %
Muangman et al. [24]	Thailand	RCT of nanocrystalline silver vs 1% SSD in patients with partial thickness burns	50 patients Nanocrystalline silver=25; SSD=25	30	15.5
Huang et al., [23]	China	RCT of nanocrystalline silver vs SSD in patients with residual wounds post burn	166 wounds Nanocrystalline silver=83; SSD=83	36.81 ± 2.49	54.17 ± 23.41
Varas et al., [27]	USA	RCT of nanocrystalline silver vs SSD in patients with partial-thickness burns, 2 burn wounds each	14 patients (28 wounds) Nanocrystalline silver=14; SSD=14	41 (25-68)	14.6 (4.5-27)
Tredget et al., [28]	Canada	RCT of nanocrystalline silver vs 0.5% solution of silver nitrate	30 patients (60 wounds) Nanocrystalline silver=30; silver nitrate=30	35.2 ± 3.2	10.5 ± 1.5
Fong et al., [21]	Australia	A series of audits (observational study) nanocrystalline silver vs SSD in a convenience sample of people with burns	70 patients Nanocrystalline silver=19; SSD=51	NR	9
Cuttle et al., [20]	Australia	Retrospective cohort study in paediatric population with partial or full thickness burn comparing nanocrystalline silver and SSD	569 patients Nanocrystalline silver=241; SSD=328	50 months	5
Peters and Verchere, [25]	Canada	Retrospective cohort study in paediatric population with partial or full thickness burn. Nanocrystalline silver patients were managed as outpatients while SSD patients were managed as inpatients	103 patients Nanocrystalline silver=30; SSD=73	3.23 ± 3.99	6.72 ± 4.13
Tonkin and Wood, [26]	Australia	A combination of retrospective and prospective cohort study comparing SSD and nanocrystalline silver in patients with mixed burns with deep partial being most common (41%)	72 patients Nanocrystalline silver=36; SSD=36	36	9
Gravante and Montone, [22]	UK	Retrospective study for period Nov-Dec 2005 and Jan-Feb 2006 in ambulatory patients with mixed superficial and partial thickness burns. Patients were treated with many dressings, including nanocrystalline silver and SSD	347 patients	48 ± 20.5	4 ± 2 64% had superficial wounds

NR, not reported; SD, standard deviation; SSD, silver sulphadiazine; TBSA, total body surface area; RCT, randomised controlled trial.

studies were from Australia [20,21,26], two from Canada [25,28] and one each from the USA [27], UK [22], Thailand [24] and China [23]. Two studies involved paediatric patients [20,25], with the remaining studies were in adult populations [21-24,26-28]; therefore the mean age across studies ranged from 50 months-48 years. There were differences between studies in the sample sizes and in the mean total body surface area (TBSA) (Table 2). There were four RCTs [23,24,27,28] and five observational studies [20-22,25,26].

3.2. Risk of bias assessment

In the overall assessments for each RCT, as well as the assessments for the individual outcomes of interest, all of the trials were rated as having an unclear risk of bias. This was generally due to a lack of information being reported in the

methods. The majority of the observational studies were deemed to be of adequate quality.

3.3. Meta-analysis

3.3.1. Infection control

The incidence of infection was reported by three studies, including two RCTs (Muangman et al. [24] and Tredget et al. [28]) and one observational study (Fong et al. [21]). The incidence of infection with nanocrystalline silver vs. SSD/silver nitrate was 10.5% vs. 55% in Fong et al. [21]; 12% vs. 16% in Muangman et al. [24]; and 21% vs. 67% in Tredget et al. [28]. The meta-analysis of the RCTs using a fixed-effects model showed significant heterogeneity ($I^2=58\%$, $p=0.012$), and therefore a random-effects model was used for statistical analysis (Fig. 2). The results of the meta-analysed RCTs demonstrated no

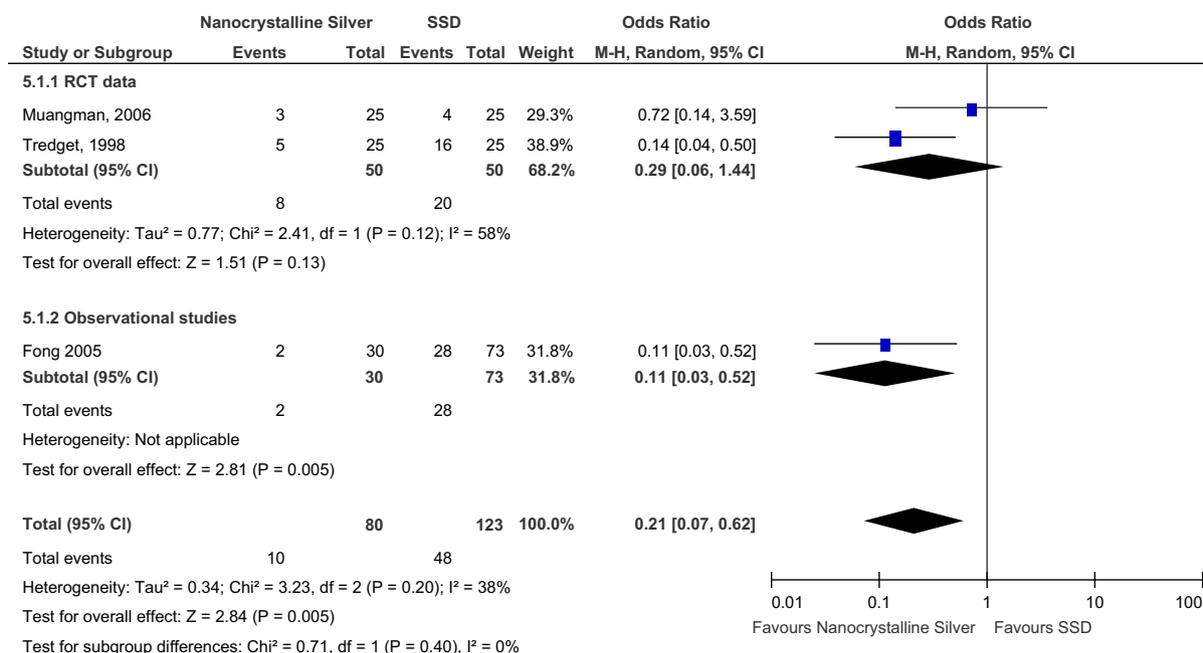


Fig. 2 – Impact of nanocrystalline silver on infection control (random effects model).

CI, confidence interval; df, degree of freedom; I², test of heterogeneity; M-H, Mantel-Haenszel; OR, odds ratio; SSD, silver sulphadiazine; RCT, randomised controlled trial. The forest plot shows the odds ratio (OR) calculated by the random effects model. Squares represent individual study effects and diamonds represent the summary effect from the meta-analysis. Horizontal bars represent 95% CIs and the vertical line in the OR plot is at 1, corresponding to the null hypothesis of no effect.

statistically significant difference between nanocrystalline silver and SSD/silver nitrate in the incidence of infection (OR 0.29, 95% CI 0.06-1.44, $p=0.13$). Results of the observational study by Fong et al. [21] showed a statistically significant reduction in infection rates with nanocrystalline silver compared to SSD (OR 0.11, 95% CI 0.03-0.52, $p=0.005$).

When both RCT and observational data were pooled together there was a statistically significant reduction in infections with nanocrystalline silver compared to SSD/silver nitrate (OR 0.21, 95% CI 0.07-0.62, $p=0.005$), with a moderate level of statistical heterogeneity ($I^2=38%$, $p=0.2$, $\chi^2=3.23$, $DF=2$) (Fig. 2). The meta-analysis showed that the incidence of infection was 13% with nanocrystalline silver and 39% with SSD/silver nitrate; the SSD/silver nitrate group had a 3-fold risk of developing infection when compared with nanocrystalline silver. These results suggest that treatment with nanocrystalline silver significantly reduces the risk of infection when compared with SSD/silver nitrate.

3.3.2. Length of stay

In total six studies i.e. one RCT and five observational studies reported LOS. The results of the RCT by Huang et al. [23] demonstrated a statistically significant decrease in LOS in patients treated with nanocrystalline silver vs. SSD (fixed effect model mean difference (MD) -3.37 , 95% CI -5.18 to -1.56 , $p=0.0003$) (Fig. 3). The observational study by Peters and Verchere [25], in which patients treated with nanocrystalline silver were seen as outpatients while those treated with SSD were seen as inpatients, was excluded from the meta-analysis as it contributed to high statistical heterogeneity. The meta-analysis (fixed effects model) of the remaining observational

studies [20,21,26] showed a statistically significant reduction in LOS with nanocrystalline silver vs. SSD (MD -5.44 , 95% CI -6.73 to -4.15 , $p=0.00001$), with a moderate level of statistical heterogeneity ($I^2=35%$) (Fig. 3).

The results from the RCTs and observational studies were pooled together (excluding the study by Peters and Verchere [25]), and the results maintained statistical significance in favour of nanocrystalline silver: the MD was -4.74 (95% CI -5.79 to -3.69 , $p=0.00001$), with a moderate level of statistical heterogeneity ($I^2=47%$, $p=0.09$, $\chi^2=9.5$, $DF=5$) (Fig. 3). Overall, the results of the RCT and observational studies were in agreement with a similar effect size, supporting the notion that using nanocrystalline silver significantly reduces LOS in patients with superficial and deep partial thickness burns.

3.3.3. Surgical procedures/skin grafting

The incidence of surgical procedures was reported by five studies, including one RCT and four observational studies. The results from the RCT demonstrated no statistical benefit of nanocrystalline silver over SSD (OR 0.60, 95% CI 0.15, 2.47, $p=0.48$) [24]. Data from the observational studies [20,21,25,26] showed a statistically significant reduction in surgical procedures with nanocrystalline silver vs. SSD (OR 0.39, 95% CI 0.27-0.55, $p=0.0001$), with evidence of a moderate level of statistical heterogeneity ($I^2=35%$, $p=0.20$, $\chi^2=4.6$, $DF=3$) (Fig. 4).

When data from the RCTs and observational studies were pooled together the results maintained statistical significance in favour of nanocrystalline silver (OR 0.40, 95% CI 0.28-0.56, $p=0.00001$), with a low level of statistical heterogeneity ($I^2=19%$, $p=0.29$, $\chi^2=4.96$, $DF=4$). The overall incidence of

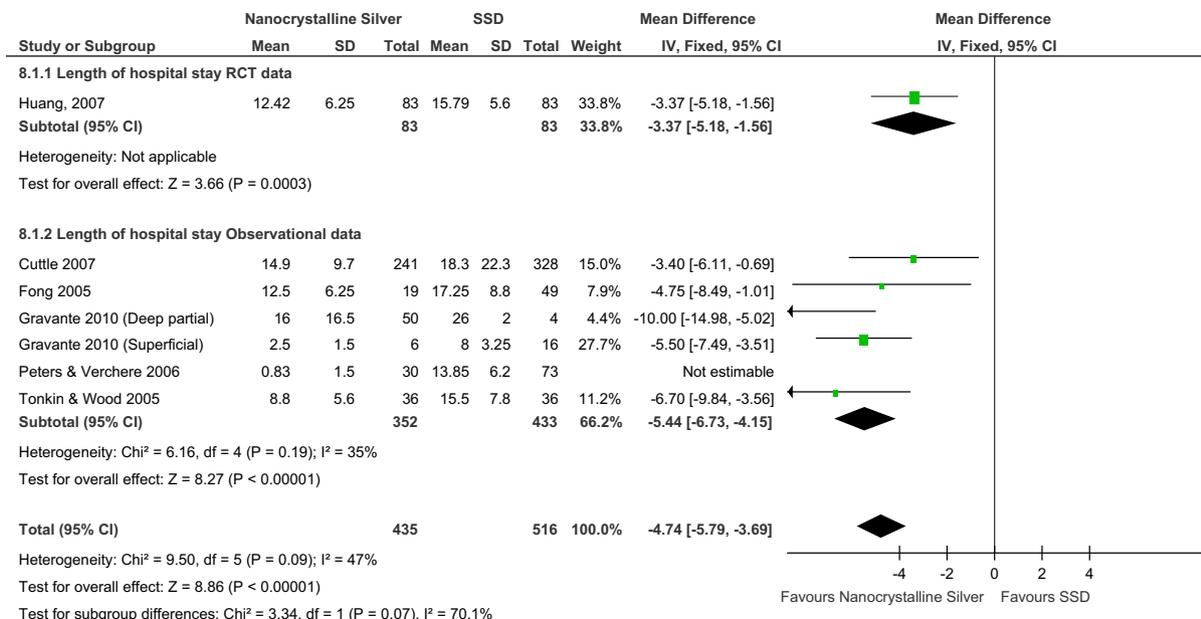


Fig. 3 – Impact of nanocrystalline silver on length of stay (fixed effects model)^a. CI, confidence interval; df, degree of freedom; I², test of heterogeneity; IV, inverse of variance; SD, standard deviation; SSD, silver sulphadiazine; RCT, randomised controlled trial.^a The study by Peters and Verchere [25] was excluded from the meta-analysis because it contributed to a high level of statistical heterogeneity.

surgical procedures was 16% with nanocrystalline silver compared to 33% with SSD, i.e. a 2.1 fold increase with SSD. We believe the difference between nanocrystalline silver and SSD with surgical procedures may be based on reduced time for epithelialisation.

3.3.4. Pain reduction

Three RCTs reported on pain, however the results from the meta-analysis showed a high level of statistical heterogeneity, and therefore the results from the individual studies are described narratively. All of the studies reported lower pain

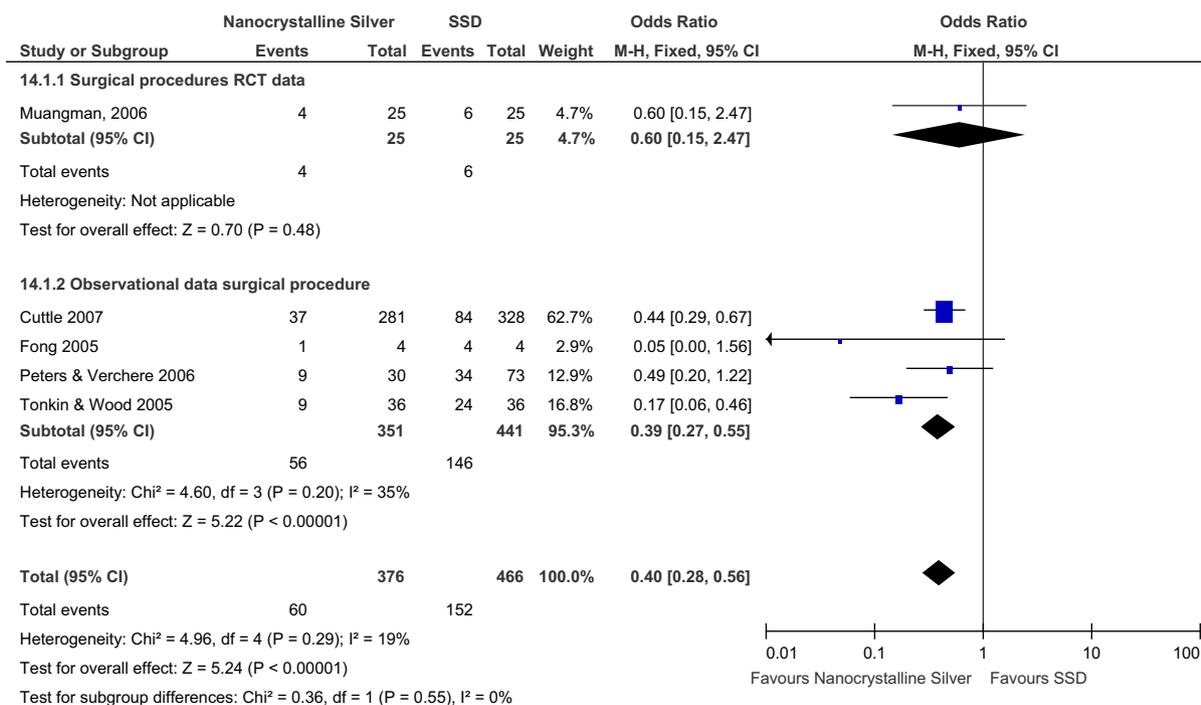


Fig. 4 – Impact of nanocrystalline silver on the incidence of surgical procedures (fixed effects model). CI, confidence interval; df, degree of freedom; I², test of heterogeneity; M-H, Mantel-Haenszel; OR, odds ratio; SSD, silver sulphadiazine; RCT, randomised controlled trial.

scores with nanocrystalline silver than with SSD/silver nitrate. The mean scores (SD) on a 10-point scale (0=no pain, 10=severe pain) ranged from 4 (0.6) vs. 5 (0.7) in Muangman et al. [24]; and 3.2 (2.68) vs. 7.9 (2.65) ($p < 0.0001$) in Varas et al. [27]. Using a 5-point scale, Tredget et al. [28] reported mean scores of 2.6 (standard error [SE]: 0.4) vs. 3.9 (0.5) ($p < 0.05$). Therefore, there appears to be a trend that nanocrystalline silver is associated with less pain than SSD/silver nitrate. However, this should be interpreted with caution because, in addition to the inherent problems of assessing pain due to its subjective nature, the studies did not report on analgesic use (and whether it differed between groups), the sample sizes from each study were small (Table 1), and the high level of heterogeneity between studies precluded us from pooling estimates. Therefore, additional, well-designed, large studies are needed to clarify the effect of nanocrystalline silver on pain.

4. Discussion

The systematic review and meta-analysis presented provides evidence that the use of nanocrystalline silver dressings results in shorter LOS, less pain, fewer surgical procedures and reduced infection rates compared to SSD/silver nitrate. Although the meta-analysis of RCTs did not show a statistical benefit in infection reduction between nanocrystalline silver and SSD, the lower incidence of infections associated with nanocrystalline silver use may be due to a number of factors. Firstly, treatment with SSD cream results in a moist uneven macerated eschar with loose edges, which may promote bacterial proliferation and ingress into devitalised tissue [26,29,30]. Nanocrystalline silver, through superior bactericidal activity, modulates the inflammatory response helping to reduce eschar formation and provide better solutions for exudate control. The sustained release of interventional concentrations of positively charged silver ions leads to fewer dressing changes and thus reduced exposure of the wound to external pathogens [31]. A number of *in vitro* studies have demonstrated the effectiveness of nanocrystalline silver as an antimicrobial wound cover compared to other dressings [32-40], which can be attributed to the amount of silver released [33,37].

Nanocrystalline silver, through hard, fast and effective kill, helps modulate the ever-present inflammatory response, which may aid healing and lead to improved long term aesthetic outcomes [41-45]. In addition, the reduced infection incidence and anti-inflammatory properties may result in fewer surgical procedures and a shorter LOS. Fewer surgical procedures and a shorter LOS may in turn also lead to a reduced risk of nosocomial infection [46]. By ensuring a more rapid bacterial kill and being used as a first line therapy nanocrystalline silver modulates the inflammatory response thus potentially reducing burn wound conversion to a deeper wound. This clinical benefit could potentially lead to less grafting and hence fewer surgical procedures. This has been demonstrated in a paediatric population by Cuttle et al. [20] who also saw additional economic benefits in terms of reductions in overall scar management materials. Furthermore, nanocrystalline silver has been shown to have a faster time to re-epithelialisation than standard of care treatment

regimens [47]. The rate of re-epithelialisation across mesh skin grafts is increased with exposure to silver. The reduced pain compared to SSD/silver nitrate may be due to fewer dressing-changes with nanocrystalline silver [21,46,48]. Certainly the frequent applications of silver sulphadiazine have been shown to be associated with pain, even when specialist nurses are present and appropriate analgesic use is in place. The cleansing and removal properties of the cream and pseudoeschar contribute to the discomfort experienced by the patient [49].

The current systematic review and meta-analysis has a number of strengths. We performed a comprehensive systematic review by searching a large number of databases and using a "pearl-growing" technique, whereby the references of relevant papers identified in the original search were searched to identify further publications of interest. The identified studies were assessed for quality, which can be helpful when interpreting the results. In addition, when conducting a meta-analysis it is important to consider the clinical and methodological differences between studies, which can be measured statistically i.e. the presence of statistical heterogeneity. In our analysis we used the most appropriate methods to deal with statistical heterogeneity [50], either using a random-effects model, a method that involves an assumption that the effects being estimated in the different studies are not identical [50]; identifying and removing the source of the heterogeneity (i.e. the publication by Peters and Verchere [25] in the LOS outcome); or describing the results narratively when the level of heterogeneity was still high with the random-effects model, as was the case for the pain outcome.

The results of this analysis are generally in-line with another systematic review and meta-analysis conducted in 2009 by Gravante et al., which assessed RCTs in burn patients comparing nanocrystalline silver versus SSD or silver nitrate [46]. Compared with SSD/silver nitrate, nanocrystalline silver was associated with a significant lower incidence of infections (9.5% vs. 27.8%, odds ratio: 0.14, 95% CI 0.06-0.35; $[\text{chi}]^2$ test, $p < 0.001$) and decreased pain values (Hedges' G: -1.44 , 95% CI: $-1.86/-1.01$; $p < 0.0001$), while there were contrasting results for LOS. The meta-analysis by Gravante, however, did not report on the level of statistical heterogeneity and only used a fixed-effects model. From a systematic review and meta-analysis of RCTs, Wasiak et al. reported that nanocrystalline silver healed burns more quickly than SSD, however there was no statistical difference in the number of infections, pain, LOS and need for surgery [3].

Whereas the analyses from Gravante et al. and from Wasiak et al. included only RCTs, which were limited in number and quality [3,46], this systematic review and meta-analysis also included observational studies, which had greater numbers of patients. While potential biases are likely to be greater for observational studies compared with RCTs, observational studies can be incredibly useful because they provide insights into real-world situations, including having diverse populations. Meta-analyses based on well-designed observational studies generally produce estimates of effect similar to those from meta-analyses based on RCTs [17,51].

The majority of the observational studies identified in this systematic review were deemed to be of adequate quality, and the results of RCTs and of observational studies were largely in agreement, strengthening confidence in the validity of the

results. When the data were combined from both RCT and observational studies, there was low to moderate evidence of statistical heterogeneity, suggesting that the pooling of the results was acceptable. Overall, the inclusion of observational studies in this analysis appears to be a valid approach, providing more comprehensive and generalisable, real-world evidence, which is especially useful in the field of burns clinical research where there is a lack of large RCTs.

This current systematic review and other (systematic) reviews highlight the paucity of high quality evidence from RCTs regarding the effect of different treatments for burns, with trial reporting and trial conduct being of poor or unclear quality [3,31,52]. Using a comprehensive database search, we could only identify four RCTs comparing nanocrystalline silver with SSD/silver nitrate, with sample sizes ranging from 14 patients (28 wounds) to 166 wounds. Furthermore, the quality of the evidence provided by these studies was low and limited, which may potentially bias the results. For example burn depth estimates were unreported or there was no formal or direct assessment of burn wound depth, which may have erroneously led to the inclusion of some studies that were a mixture of various burn depths. In addition, there was a failure to report on randomisation techniques and allocation concealment, subjective outcome assessment, lack of blinding at outcome assessment and poor reporting of withdrawals and adverse events data. Another limitation was that the definition of surgical intervention was not consistent across studies, with the definitions including grafting, surgery, and debridement and grafting, which potentially makes the meta-analysis results from this outcome less reliable.

Overall, clinical research for burns care has been hampered by a number of challenges [52,53], which include: the heterogeneity of the patient population due to the complex nature of burns, including different burns sizes and depths; the diverse range of burn care interventions and associated confounding variables; differences in the timing and selection of various outcome measures; a lack of appropriate, standardised measurement tools to assess, for example, the extent of the injury, the impact of the injury on the given individual, and the outcome post injury; and resource constraints of undertaking clinical research. SSD may be thought of as an older product in terms of its availability to the burn community but it is still a widely used treatment in burn wound care on a global basis. To be effective frequent applications are required due to the relatively poor delivery of silver from the cream base. Nanocrystalline dressings have been developed to optimise silver delivery over extended time periods with one goal of freeing up resources associated with frequent dressing changes to do other things in a very challenging clinical environment. It is hoped that a future direction of clinical research conducted in the burn community will provide essential evidence comparing the more modern burn wound dressings containing antiseptics.

5. Conclusions

There is a need for better-reported, high-quality trials to help clinicians make informed decisions on the best options for patients with deep partial and superficial partial

thickness burns. However, this comprehensive systematic review and meta-analysis of the available evidence from both RCTs and observational studies suggest that the use of nanocrystalline silver dressings results in shorter length of stay in hospital, less pain, fewer surgical procedures and reduced infection rates compared to silver sulphadiazine/silver nitrate.

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Authors' contributions

All authors of this paper have directly participated in the analysis, interpretation of the data and have read and fully approved the final version here submitted.

Conflict of interest

LN and PT are employees of Smith & Nephew. CDR provides consultancy support to Smith and Nephew. LB has no conflict of interest.

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REFERENCES

- [1] World Health Organization. Burns. Fact sheet no. 365. Available from: <http://www.who.int/mediacentre/factsheets/fs365/en/>. [Accessed April 2016].
- [2] American Burn Association. Burn incidence and treatment in the United States. Available from: http://www.ameriburn.org/resources_factsheet.php. [Accessed April 2016].
- [3] Wasiak J, Cleland H, Campbell F, Spinks A. Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev* 2013;3:CD002106.
- [4] Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. *Clin Microbiol Rev* 2006;19:403-34.
- [5] Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, Natesan S, et al. Burn wound healing and treatment: review and advancements. *Crit Care* 2015;19:243.
- [6] Norman AT, Judkins KC. Pain in the patient with burns. *Contin Educ Anaesth Crit Care Pain* 2004;4:57-61.
- [7] White RJ. An historical view of the use of silver in wound management. *Brit J Nurs* 2001;10:3-8.
- [8] Polk Jr. HC. Treatment of severe burns with aqueous silver nitrate (0.5 percent). *Ann Surg* 1966;164:753-70.
- [9] Murphy PS, Evans GR. Advances in wound healing: a review of current wound healing products. *Plast Surg Int* 2012;2012:190436.
- [10] Gillett AP. Antibiotic prophylaxis and therapy in burns. *J Hosp Infect* 1985;6(Suppl. B):59-66.
- [11] Nadworny PL, Burrell RE. A review of assessment techniques for silver technology in wound care. *J Wound Technol* 2008; 2:6-22.

- [12] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- [13] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- [14] Dreyer NA, Velentgas P, Westrich K, Dubois R. The GRACE checklist for rating the quality of observational studies of comparative effectiveness: a tale of hope and caution. *J Manag Care Spec Pharm* 2014;20:301-8.
- [15] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.
- [16] Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet* 1999; 354:1896-900.
- [17] Anglemeyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev* 2014;4:MR000034.
- [18] Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. *J Clin Oncol* 2005;23:8606-12.
- [19] Shrier I, Boivin JF, Steele RJ, Platt RW, Furlan A, Kakuma R, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *Am J Epidemiol* 2007;166:1203-9.
- [20] Cuttle L, Naidu S, Mill J, Hoskins W, Das K, Kimble RM. A retrospective cohort study of Acticoat versus Silvazine in a paediatric population. *Burns* 2007;33:701-7.
- [21] Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: comparative patient care audits. *Burns* 2005;31:562-7.
- [22] Gravante G, Montone A. A retrospective analysis of ambulatory burn patients: focus on wound dressings and healing times. *Ann R Coll Surg Engl* 2010;92:118-23.
- [23] Huang Y, Li X, Liao Z, Zhang G, Liu Q, Tang J, et al. A randomized comparative trial between Acticoat and SD-Ag in the treatment of residual burn wounds, including safety analysis. *Burns* 2007;33:161-6.
- [24] Muangman P, Chuntrasakul C, Silthram S, Suvanchote S, Benjathanung R, Kittidacha S, et al. Comparison of efficacy of 1% silver sulfadiazine and Acticoat for treatment of partial-thickness burn wounds. *J Med Assoc Thai* 2006;89:953-8.
- [25] Peters DA, Verchere C. Healing at home: comparing cohorts of children with medium-sized burns treated as outpatients with in-hospital applied Acticoat to those children treated as inpatients with silver sulfadiazine. *J Burn Care Res* 2006;27:198-201.
- [26] Tonkin C, Wood F. Nanocrystalline silver reduces the need for antibiotic therapy in burn wounds. *Prim Intent* 2005; 13:163-8.
- [27] Varas RP, O'Keeffe T, Namias N, Pizano LR, Quintana OD, Herrero Tellachea M, et al. A prospective, randomized trial of Acticoat versus silver sulfadiazine in the treatment of partial-thickness burns: which method is less painful? *J Burn Care Rehabil* 2005;26:344-7.
- [28] Tredget EE, Shankowsky HA, Groeneveld A, Burrell R. A matched-pair, randomized study evaluating the efficacy and safety of Acticoat silver-coated dressing for the treatment of burn wounds. *J Burn Care Rehabil* 1998;19:531-7.
- [29] de Gracia CG. An open study comparing topical silver sulfadiazine and topical silver sulfadiazine-cerium nitrate in the treatment of moderate and severe burns. *Burns* 2001; 27:67-74.
- [30] Ross DA, Phipps AJ, Clarke JA. The use of cerium nitrate-silver sulphadiazine as a topical burns dressing. *Br J Plast Surg* 1993;46:582-4.
- [31] Khundkar R, Malic C, Burge T. Use of Acticoat dressings in burns: what is the evidence? *Burns* 2010;36:751-8.
- [32] Aramwit P, Muangman P, Namviriyachote N, Srichana T. In vitro evaluation of the antimicrobial effectiveness and moisture binding properties of wound dressings. *Int J Mol Sci* 2010;11:2864-74.
- [33] Castellano JJ, Shafii SM, Ko F, Donate G, Wright TE, Mannari RJ, et al. Comparative evaluation of silver-containing antimicrobial dressings and drugs. *Int Wound J* 2007; 4:114-22.
- [34] Cavanagh MH, Burrell RE, Nadworny PL. Evaluating antimicrobial efficacy of new commercially available silver dressings. *Int Wound J* 2010;7:394-405.
- [35] Edwards-Jones V. Antimicrobial and barrier effects of silver against methicillin-resistant staphylococcus aureus. *J Wound Care* 2006;15:285-90.
- [36] Gallant-Behm CL, Yin HQ, Liu S, Heggors JP, Langford RE, Olson ME, et al. Comparison of in vitro disc diffusion and time kill-kinetic assays for the evaluation of antimicrobial wound dressing efficacy. *Wound Repair Regen* 2005; 13:412-21.
- [37] Lin YH, Hsu WS, Chung WY, Ko TH, Lin JH. Silver-based wound dressings reduce bacterial burden and promote wound healing. *Int Wound J* 2016;13(4):505-11.
- [38] Thomas S, McCubbin P. A comparison of the antimicrobial effects of four silver-containing dressings on three organisms. *J Wound Care* 2003;12:101-7.
- [39] Wright JB, Lam K, Hansen D, Burrell RE. Efficacy of topical silver against fungal burn wound pathogens. *Am J Infect Control* 1999;27:344-50.
- [40] Yin HQ, Langford R, Burrell RE. Comparative evaluation of the antimicrobial activity of ACTICOAT antimicrobial barrier dressing. *J Burn Care Rehabil* 1999;20:195-200.
- [41] Bhol KC, Alroy J, Schechter PJ. Anti-inflammatory effect of topical nanocrystalline silver cream on allergic contact dermatitis in a guinea pig model. *Clin Exp Dermatol* 2004;29:282-7.
- [42] Bhol KC, Schechter PJ. Topical nanocrystalline silver cream suppresses inflammatory cytokines and induces apoptosis of inflammatory cells in a murine model of allergic contact dermatitis. *Br J Dermatol* 2005;152:1235-42.
- [43] Hartmann CA, Rode H, Kramer B. ACTICOAT™ stimulates inflammation, but does not delay healing, in acute full-thickness excisional wounds. *Int Wound J* 2016;13(6): 1344-8.
- [44] Nadworny PL, Wang J, Tredget EE, Burrell RE. Anti-inflammatory activity of nanocrystalline silver in a porcine contact dermatitis model. *Nanomedicine* 2008; 4:241-51.
- [45] Nadworny PL, Wang J, Tredget EE, Burrell RE. Anti-inflammatory activity of nanocrystalline silver-derived solutions in porcine contact dermatitis. *J Inflamm (Lond)* 2010;7:13.
- [46] Gravante G, Caruso R, Sorge R, Nicoli F, Gentile P, Cervelli V. Nanocrystalline silver: a systematic review of randomized trials conducted on burned patients and an evidence-based assessment of potential advantages over older silver formulations. *Ann Plast Surg* 2009;63:201-5.
- [47] Demling R, DeSanti M. The rate of re-epithelialization across meshed skin grafts is increased with exposure to silver. *Burns* 2002;28(3):264-6.
- [48] Muangman P, Pundee C, Opananon S, Muangman S. A prospective, randomized trial of silver containing hydrofiber

- dressing versus 1% silver sulfadiazine for the treatment of partial thickness burns. *Int Wound J* 2010;7:271-6.
- [49] Black JS, Drake DB. A prospective randomized trial comparing silver sulfadiazine cream with a water-soluble polyantimicrobial gel in partial-thickness burn wounds. *Plast Surg Nurs* 2015;35(1):46-9.
- [50] Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [updated March 2011]. In: Higgins JPT, Green S, editors. *The Cochrane Collaboration*; 2011 Available from: www.cochranehandbook.org. [Accessed June 2016].
- [51] Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342:1887-92.
- [52] Danilla S, Wasiak J, Searle S, Arriagada C, Pedreros C, Cleland H, et al. Methodological quality of randomised controlled trials in burns care. A systematic review. *Burns* 2009;35:956-61.
- [53] Wood FM. Burn care: the challenges of research. *Burn Trauma* 2013;1:105-8.