Multidimensional aspects of burn wound treatment

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Part II

Partial thickness burn wounds in paediatric patients

Chapter 4

Non-silver treatment versus silver sulfadiazine in treatment of partial thickness burn wounds in children: a systematic review and meta-analysis

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ABSTRACT

The evidence for application of silver containing dressings and topicals in the treatment of partial thickness burns in pediatric patients is largely based on clinical trials involving adult patients despite the important differences between the skin of children and adults. A systematic review and meta-analysis was performed of all randomized controlled trials comparing non-silver treatment with silver containing dressings and silver topical agents in children with partial thickness burns in the acute stage. Endpoints were wound healing, grafting, infection, pain, number of dressing changes, length of hospital stay and scarring. Seven randomized controlled trials were included involving 473 participants. All trials used silver sulfadiazine as control in comparison with five different non-silver treatments. Most trials were of moderate quality with high risk of bias. Use of non-silver treatment led to shorter wound healing time (weighted mean difference -3.43 days, 95% confidence interval -4.78, -2.07), less dressing changes (weighted mean difference -19.89 dressing changes, 95% confidence interval -38.12, -.1.66) and shorter length of hospital stay (weighted mean difference -2.07 days, 95% confidence interval -2.63, -1.50) compared to silver sulfadiazine treatment, but no difference in the incidence of wound infection or grafting was found. In conclusion, non-silver treatment may be preferred over silver sulfadiazine but high-quality randomized controlled trials are needed to validly confirm the effectiveness of silver containing preparations, in particular silver containing dressings, above non-silver treatments.

INTRODUCTION

The treatment of partial thickness burns focuses on promoting rapid wound healing, preventing infection and systemic illness, decreasing pain, and minimizing long-term negative effects such as scarring and functional impairment.(1-6) Treatment modalities include silver containing topicals and other topical products, silver containing dressings, biological and (semi)synthetic dressings, enzymatic debridement, and surgical treatment.(6) Despite the wide range of treatment options, there is no consensus on the optimal treatment of partial thickness burns in children.(4-8) Yet, silver containing dressings and topical silver agents are widely used in this age group for treating partial thickness- and minor full thickness burns, and prior to grafting.(8-13) The action of silver treatments is caused by binding of the silver ions to the DNA of bacteria and bacterial spores in an aqueous environment which results in a reduced ability to replicate.(14-16) Its bactericidal properties include both gram-positive and gram-negative organisms, though resistance has been reported.(16-20)

Several reviews have evaluated the efficacy of silver treatment, but the available evidence is largely based on clinical trials involving adult patients. Various reviews found insufficient evidence that silver containing dressings and topical silver agents promote wound healing or prevent wound infection in burn patients.(8,10-12,21) These reviews as well as the majority of other reviews and clinical studies on acute burn treatment, do not specify treatment by age.

Translating this evidence to pediatric patients should be done with great caution as there are important differences between the skin of children, especially infants, and adult skin. In children, the stratum corneum (epidermis layer) and supra-papillary epidermis are respectively 30% and 20% thinner than adult skin and is yet under-keratinized compared to that of adults.(1,4,22) (23,24) Infants' skin is further characterized by a not fully developed palmar planter epidermis, decreased subcutaneous fat store, high surface hydration, high acidity, high desquamation and high keratinocyte proliferation rates. As a result, it is much more vulnerable to burn injury and subsequently more susceptible to bacterial colonization and infection due to the compromised epidermal barrier function.(25) Children also have a larger body surface area (BSA) to body weight ratio that makes them prone to hypothermia, and their metabolic systems have not yet fully developed.(1,26) Consequently, the bioavailability and absorption of an applied treatment in pediatric burn patients are greater than in adults burn patients.

We performed a systematic review of the available literature on the acute treatment of pediatric partial thickness burns, and compared outcomes after silver containing dressings and topical silver treatments versus non-silver treatments in a meta-analysis.

MATERIALS AND METHODS

Study protocol

The systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2009 Guideline.(27) The objective, inclusion and exclusion criteria, primary and secondary outcomes, and methods of synthesis were prespecified in a study protocol according to the recommendations of the Cochrane Collaboration.(28)

Search strategy

A literature search was conducted with the help of a trained medical librarian in the databases MEDLINE, EMBASE, Cochrane Library and CINAHL. The original search was conducted in October 2012, and was updated on September 2013. The search strategy combined various terms and synonyms for child(ren) and partial thickness burns. The complete search strategy is shown in supporting information 1.

Study selection

Two authors (RK and ZR) independently screened title and abstract of retrieved articles. Randomized Controlled Trials (RCT) were selected if they compared silver containing dressings and/or silver topical agents with a non-silver treatment and included pediatric patients aged 0-18 years with partial thickness burns randomized within 48 hours after injury. Studies that were not reporting on any of the primary outcomes of the review (wound healing and need for grafting) were also excluded. Full-text articles of the selected studies were obtained. Primary outcome measures were defined as time to wound healing (not predefined) and need for grafting. Secondary outcome measures were infection or colonization (predefined), number of dressing changes, pain, length of hospital stay (LOS) and scarring. If some of included patients were >18 years and age-specific results were not reported in the original publication, the authors were contacted and asked to provide additional information. If this information was not provided the study was not included. Disagreement between reviewers on study selection were resolved by discussion.

Data extraction

Two reviewers independently extracted information from each included trial on: (1) characteristics of trial participants including number of participants, age, type of partial thickness burn, method of burn assessment, percentage total body surface area (TBSA), follow-up of the patients, and the trial's inclusion and exclusion criteria; (2) type of interventions; (3) outcome measures: time to wound healing, need for grafting, infection or colonization, number of dressing changes, pain, length of hospital stay (LOS) and scarring. When the outcomes were not reported in a form suitable for meta-analytic calculation, we derived these data from graphical representation

of the outcomes, or by estimation based on the available information in the publication (for example recalculating a standard error from an exact p-value).(29) If needed we contacted the authors for additional information. When outcomes were presented for superficial and deep partial thickness burns separately, a pooled mean difference or pooled OR was computed for that single study (fixed-effect meta-analysis) summarizing the outcome in the total group with partial thickness burns.

Risk of bias assessment

The risk of bias of the individual randomized controlled trials was assessed as 'low', 'high' or 'unknown' independently by the two reviewers according the Cochrane Collaboration's tool for assessing risk of bias.(28) Discrepancies were resolved by discussion.(28)

Meta-analysis

Meta-analysis of study outcomes was performed using Review Manager (RevMan), version 5.2 (Cochrane Collaboration, Copenhagen: The Nordic Cochrane Centre).

We performed a meta-analysis calculating a pooled mean difference (continuous outcomes) or odds ratio (OR, for binary outcomes) and its corresponding 95% confidence interval (CI) in a random effects model.

Meta-analysis of binary outcomes was based on the crude numbers in both study arms. If in a study the number of events was equal to zero for binary outcomes, all cell counts were increased by one for all the studies to enable the computation of the pooled OR. For continuous variables calculations were performed based on mean estimates and accompanying standard deviations (SD) in both groups. In case of missing SD but a known p-value, the standard deviation was obtained by calculating the z-value and standard error of the mean (SEM), a method described by Altman et al.(29)

To assess heterogeneity between studies the Cochran's chi-squared test and the I^2 statistic were used. Heterogeneity was assumed for Cochran's chi squared test P-values < 0.1 or $I^2 > 50\%$.(30)

Finally, sensitivity analysis was performed to assess the robustness of the results if heterogeneity was detected, by excluding studies with outlying results.

RESULTS

Study selection

The search identified 1128 potentially relevant studies in the literature databases, of which 593 were screened after removal of duplicates (Figure 1). A total of 156 articles were retrieved for full text assessment. Of these, 131 studies were not randomized and therefore excluded. Eighteen randomized studies were excluded because no age-specified results were reported. Authors of these studies were contacted, of whom only two replied but did not provide the requested information because the numbers of pediatric patients were insufficient to be analysed separately. The remaining seven studies with age-specific results were included.

Study and patient characteristics of the seven included studies are summarized in Table 1. The RCT's compared silver sulfadiazine (SSD) to collagenase ointment and Polymyxin (bacteriostatic)(31), Amniotic membrane(32), Biobrane® / TransCyte® (biosynthetic skin substitute dressings)(33-35) or Mepitel® (silicon coated nylon dressing).(36,37) All seven RCTs were open label and single-center studies. The study populations differed with respect to the percentage TBSA. Two studies reported on patients with a mean TBSA < 5% (33,36) and five studies on patients with a mean TBSA <15%. (31,32,34,35,37) No RCTs including silver based dressings comparing with non-silver treatment among children were found.

The time between trauma and presentation at the hospital varied from 24 hours to a maximum of 48 hours post-burn between the studies. Five studies included patients with partial thickness burns**,** whereas one study also included superficial burns(32) and another only reported on superficial partial thickness burns(34). Only two studies reported the length of follow-up.(31,32)

Risk of bias assessment

The assessed risk of bias in the included studies is presented in Table 2.(28) In general, risk of bias was considered to be high, and important information was often lacking. In three studies the method of randomization was not described. Lal et al.[33] included seven patients (9%) that were not randomized but for whom treatment choice was based on the preferences of the resident on-call. In all studies allocation concealment was unclear and none of the studies were blinded. Three studies reported incomplete outcome data(33,34,36) and in one study it was unclear in how many patients the outcomes were measured or how many participants were lost to follow-up.(37) Selective reporting was difficult to judge since authors do not present the original study protocol.

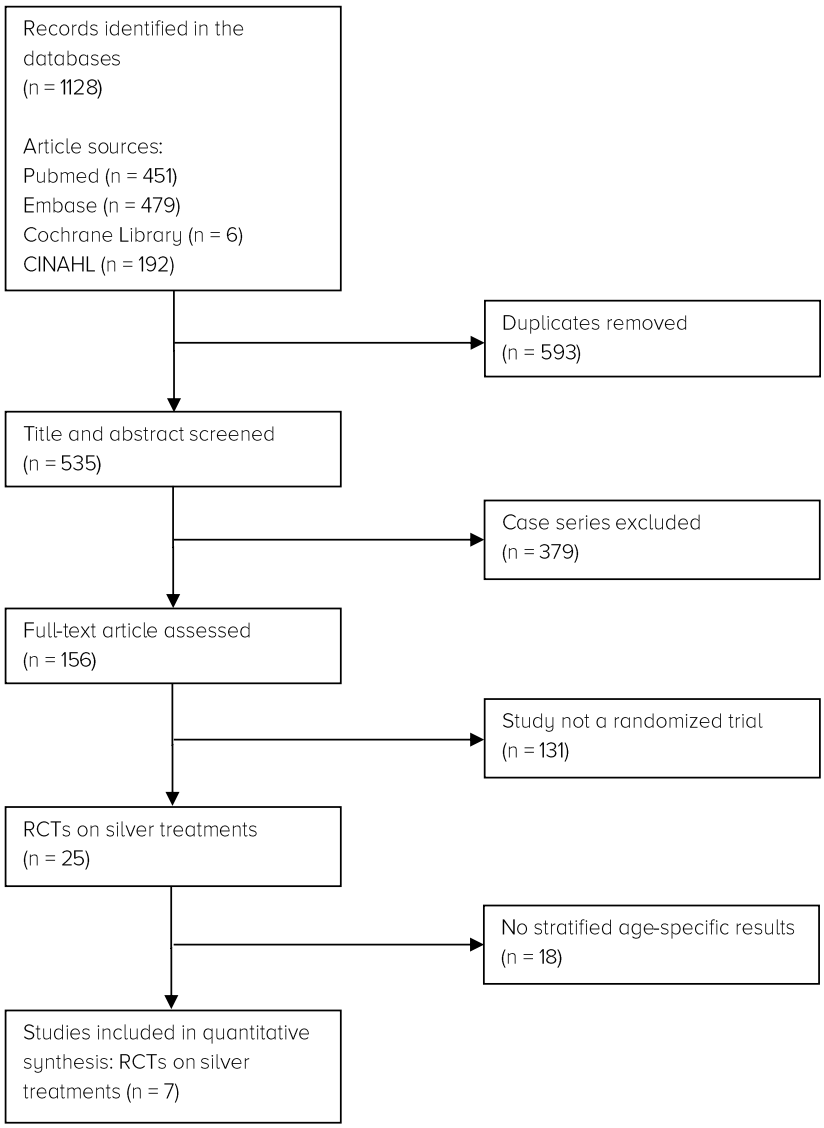

Figure 1. Flow chart of study selection.

Table 1. Characteristics of included trials.

Study	Participants	Age in years (Mean (SD))	Study design (Country)	Intervention (I)	Controle (C)	follow-up in months (mean (SD))
Ostlie et al. 2012	100 patients with partial thickness burns TBSA: I = 9.4% (SD = 6.1) C = 9.9% (SD = 6.8) Assessment: Clinical	2 months – 18 yr. I = 4.8 (NR) C = 5.1 (NR)	Open label, single center RCT (USA)	Collagenase Santyl Ointment (CO) + Polymixin (n = 50)	SSD (n = 50)	I = 8.0 (8.9) C = 5.8 (7.5)
Mostaque et al. 2011	102 patients with partial thickness burns TBSA < 15% Assessment: Clinical	1 day - 12 yr. I = 3.6 (2.3) C = 4.0 (2.4)	Open label, single center RCT (Bangladesh)	Amniotic membrane (AM) (n = 51)	SSD (n = 51)	Up to 6 months, no data provided
Kumar et al. 2004	33 patients (58 wound sides) with partial thickness burns TBSA: average 5% Assessment: LDI	Average age: 3.6 yr.	Open label, single center RCT (Australia)	Biobrane® (n = 17) TransCyte® (n = 20)	Silvazine® (n = 21)	NR
Barret et al. 2000	20 patients with partial thickness burns TBSA: 8.9% (SD = 4.9) Assessment: Clinical	NR	Open label, single center RCT (USA)	Biobrane® (n = 10)	SSD (n = 10)	NR
Lal et al. 2000	79 patients with superficial partial thickness burns TBSA: I = 11.5 (SD = 0.9) C = 11.8 (SD = 1.1) Assessment: Clinical	I = 2.8 (SEM = 0.5) C = 3.4 (SEM = 0.6)	Open label, single center RCT (USA)	Biobrane® (n = 34)	SSD (n = 45)	NR

Table 1. Continued.

Study	Participants	Age in years (Mean (SD))	Study design (Country)	Intervention (I)	Controle (C)	follow-up in months (mean (SD))
Gotschall et al. 1998	63 patients with partial thickness burns TBSA: I = 6.8% (SD = 3.4) C = 5.1% (SD = 2.2) Assessment: Clinical	NR	Open label, single center RCT (USA)	Mepitel® (n = 33)	SSD (n = 30)	NR
Bugmann et al. 1998	76 with partial thickness burns TBSA: I = 2.3 (SD = 2.0) C = 1.9 (SD = 2.1) Assessment: Clinical	I = 3.29 (3.1) C = 3.43 (3.7)	Open label, single center RCT (Switzerland)	Mepitel® (n = 41)	SSD (n = 35)	NR

I: intervention, C: control, SD: standard deviation, SEM: standard error of the mean, SSD: Silver sulfadiazine, LDI: Laser Doppler Imaging, LOS: length of stay, NR: Not reported, PBD: post-burn day, RCT: Randomized Controlled Trial, TBSA: total body surface area.

Table 2. Risk of bias assessed according to the criteria as described by Higgins et al.[27]

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ostlie et al 2012	-	?	+	?	-	?	+
Mostaque et al 2011	-	?	+	+	-	+	-
Kumar et al 2004	-	?	+	+	+	?	-
Barret et al 2000	?	?	+	?	-	?	-
Lal et al 2000	+	+	+	+	+	?	-
Gotschall et al 1998	?	?	+	+	?	?	+
Bugman et al 1998	?	?	+	?	+	+	-

?: unclear, +: high risk of bias, -: low risk of bias.

META-ANALYSIS: PRIMARY OUTCOMES

Time to wound healing

Wound healing was clinically assessed in five studies,[31,33-36] and by Laser Doppler Imaging (LDI) in combination with clinical judgment in one study.(33) Wound healing was defined as >90% re-epithelialisation(33), as complete closure(36), as covering of the moist and red granulation tissue with pale epidermis(32), or was not defined (31,34,35,37).

All six studies (419 patients in total) that reported wound healing, found significantly longer healing times for burns treated with SSD compared to burns treated with other non-silver dressings (Amniotic Membrane(32), Biobrane®(33-35), TransCyte®(33) or Mepitel®(36,37)). (Table 3). In a meta-analysis, the weighted mean difference (WMD) in healing time between non-silver treatments and SSD was -3.43 days (95% CI -4.78, -2.07, $p < 0.0001$) (Figure 2). Statistical heterogeneity was detected ($I^2 = 78\%$, $p = 0.0002$).

The study of Gotschall al. was a clear outlier for this outcome. After exclusion of this study in a sensitivity analysis, no significant changes in the direction and magnitude of the estimates were seen (WMD -3.26 days, 95% CI: -4.53, -.2.00, p = 0.0005).

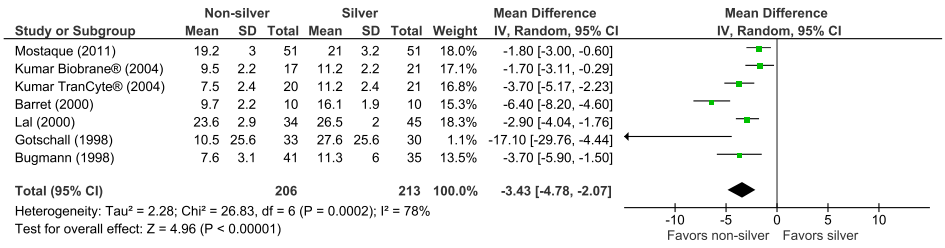

Figure 2. Forest plot for time to wound healing.

Need for grafting

Five of the seven studies reported on the need for wound grafting.(31,33-36) In none of the individual studies a statistically significant difference in the need for grafting was found between SSD and non-silver treatment (Table 3). The meta-analysis also showed no significant difference in the need for grafting between patients that were treated with SSD and those treated with non-silver (Odds Ratio [OR] 0.71, 95% CI: 0.40, 1.24, p = 0.23), and this trend was consistent in the sensitivity analysis (Figure 3). No statistical heterogeneity between the studies was detected (I^2 = 0%, p = 0.79).

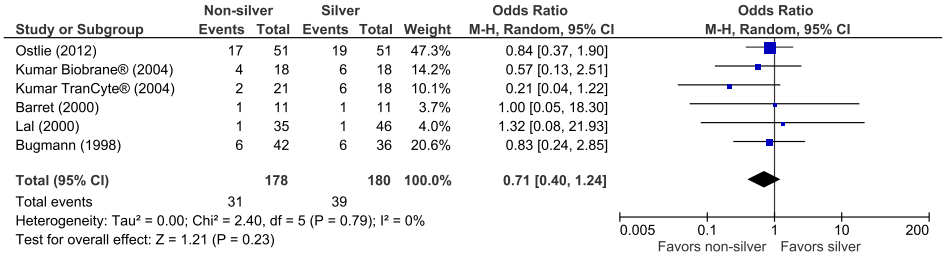

Figure 3. Forest plot for wound grafting.

Meta-analysis: Secondary outcomes

Infection/colonization

Six of the seven studies reported infection rate, although four studies neither provided a definition of infection, nor taken swabs to determine wound colonization. Kumar et al. took wound swab and defined infection as loss of product due to an inflammatory response, while only results on infection were reported.(33) Gotschall et al. stated no definition of infection

but wound swabs were taken, while no results on colonization were reported.(37) In the separate studies, no statistically significant differences in infection rate were found between the treatment groups (Table 3). The meta-analysis also did not show a significant difference in wound infection between patients that were treated with SSD vs. those treated with non-silver. (OR: 0.87, 95% CI: 0.37, 2.04, p = 0.76). Statistical heterogeneity was not detected (I^2 = 21%, p = 0.27) (Figure 4).

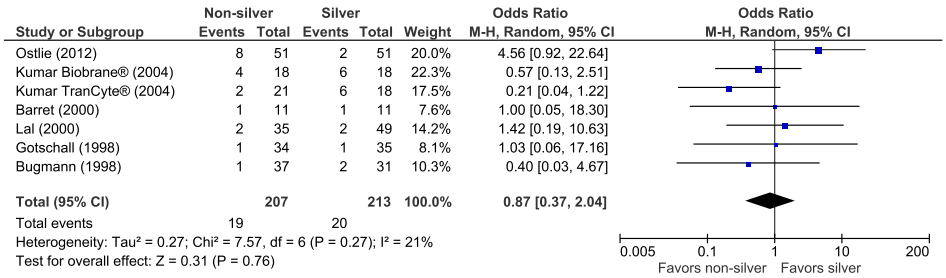

Figure 4. Forest plot for infection.

Dressings change

Four studies reported on this outcome. Gotschall et al. reported that the time required for dressings change was shorter when Mepitel® was used than with SSD.(37) Three studies reported a reduced number of dressing changes with Amniotic Membrane, Biobrane®, TransCyte® and Mepitel® treated burns compared with SSD.(32,33,36,37) (Table 3) The meta-analysis of these three studies showed that significantly less dressings changes were needed in patients treated with non-silver vs. those treated with SSD (Weighted mean difference [WMD] -19.89 dressing changes, 95% CI: -38.12, -.1.66, p = 0.03). Statistical heterogeneity between the studies was detected (I^2 = 99%, p < 0.00001) (Figure 5).

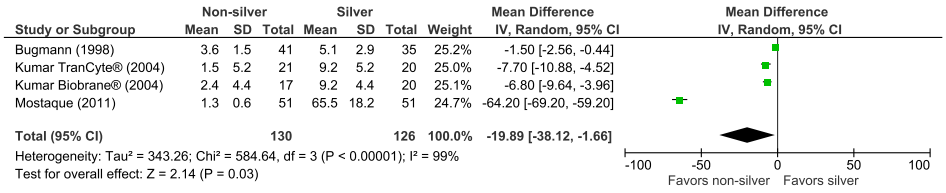

Figure 5. Forest plot for number of dressing changes.

The study of Mostaque et al. was a clear outlier for this outcome. After exclusion of this study in a sensitivity analysis, the meta-analysis showed a smaller but still significant difference in dressing changes favoring non-silver treatment. (WMD -5.15, 95% CI: -9.63, -.0.68, p = 0.02).

Pain

Four studies reported on pain, but this was not measured in a uniform manner, so no meta-analysis was performed for this outcome (Table 3). Gotschall et al. presented an overall significant pain reduction with Mepitel® compared to SSD(37) and in another study Biobrane® was found to significantly reduce pain at the first- and second day after admission compared to SSD.(35) Amniotic Membrane also led to significantly lower pain scores during and in between dressings changes compared to treatment with SSD.(32) Kumar et al. reported that patients who were treated with Biobrane® required significantly less pain medication compared to patients treated with Silvazine®(33) (Table 3).

Length of hospital stay (LOS)

Four studies reported LOS, three of which reported significantly reduced LOS after treatment with Amniotic Membrane and Biobrane® compared to SSD. (32,34,35) Ostlie et al. found no difference in LOS between Collagenase Ointment and Polymyxin and SSD treated burn wounds.(31) Our meta-analysis showed the weighted was -2.07 days (95% CI -2.63, -1.50, p < 0.00001) shorter in non-silver treatments compared to SSD (Figure 6). No statistical heterogeneity between the studies was detected (I^2 = 35%, p = 0.20).

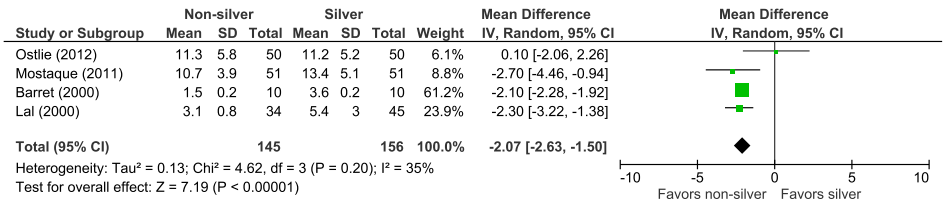

Figure 6. Forest plot for number of Length of hospital stay (LOS).

Scar formation

None of the selected studies reported on scar formation.

Table 3. Outcome results.

Study	**Wound healing** Definition. Mean (SD)	**Need for grafting** Number (%)	**Infection** Method. Definition Infection number (%)	**Number of dressings change** Mean (SD)	**Pain**		**LOS (mean (SD))**
Ostlie et al. 2012	NR	I = 16 / 50 (32%) C = 18 / 50 (36%)	Clinical judgment. No definition. No swab taken. I: 7 (14%) C: 1 (2%)	NR	NR		In days I = 11.3 (5.8) C = 11.2 (5.2)
Mostaque et al. 2011	Number of days until the moist and red granulation tissue is covered with pale epidermis. Superficial partial thickness burns I = 13.3 (1.0) C = 14.2 (1.0) Deep partial thickness burns I = 21.6 (1.4) C = 23.7 (1.5)	NR	NR	I = 1.3 (0.6) C = 65.5 (18.2)	During application Painless[3] I = 43 (84.3%) C = 11 (21.6%) Painful I = 8 (15.7%) C = 40 (78.4)	In-between application No pain I = 17 (33.3%) C = 6 (11.8%) Some pain I = 34 (66.7%) C = 12 (23.5) Persistent pain I = 0 (0%) C = 33 (64.7%)	In days I = 10.7 (3.9) C = 13.4 (5.1)
Kumar et al. 2004	Number of days until >90% reepithelialization. I Biobrane® = 9.5 (NR) I TransCyte® = 7.5 (NR) C: 11.2 (NR)	I Biobrane® = 3 / 17 (17%) I TransCyte® = 1 / 20 (5%) C = 5 / 17 (24%)	Clinical judgment. Loss of product due to an inflammatory response and exudate. Swab taken. I Biobrane® = 3 / 17 (5.6%) I TransCyte® = 1 / 20 (1,9%) C = 5 / 17 (9.3%)	I Biobrane® = 2.4 (NR) I TransCyte® = 1.5 (NR) C = 9.2 (NR)	Less pain medication with non-silver treatment than with Silvazine® (p = 0.0001)		NR
Barret et al. 2000	In days. (Wound healing not defined) I = 9.7 (SEM = 0.7) C = 16.1 (SEM = 0.6)	I = 0/ 10 (0%) C = 0/ 10 (0%)	Clinical judgment. Definition not reported. No Swab taken. I: 0/ 10 (0%) C: 0/ 10 (0%)	NR	Pain at second day[4] I = 2.6 (SEM = 0.3) C = 3.8 (SEM = 0.4)	Pain medication (doses/ person/ day) I: 2.6 (SEM = 0.3) C: 3.8 (SEM = 0.4)	In days I = 1,5 (SEM = 0.2) C = 3,6 (SEM = 0.2)

Table 3. Continued.

Study	Wound healing Definition. Mean (SD)	Need for grafting Number (%)	Infection Method. Definition Infection number (%)	Number of dressings change Mean (SD)	Pain	LOS (mean (SD))
Lal et al. 2000	In days. (Wound healing not defined) Data derived from graphical representation	I = 0 / 34 (0%) C = 0 / 45 (0%)	Clinical judgment. Definition not reported. No Swab taken. I: 1 / 34 (2,9%) C: 1 / 48 (2.2)	NR	NR	< 3 yrs old[6] I = 0.5 (SEM = 0.08) C = 0.2 (SEM = 0.08) p < 0.05 3 - 17 yrs old I = 0.4 (SEM = 0.02) C = 0.2 (SEM = 0.02)
Gotschall et al. 1998	In days. (Wound healing not defined) I = 10.5[1] (NR) C = 27.6[1] (NR)	NR	Clinical judgment. Definition not reported. Swab taken. I: 0 / 30 (0%) C: 0 / 33 (0%)	I = 22 minutes[2] C = 31 minutes[2]	I = 3.8 (NR)[5] C = 4.6 (NR)	NR
Bugmann et al. 1998	Number of days until complete closure I = 7.6 (3.1) C = 11.3 (6.0)	I = 5 / 41 (12.2%) C = 5 / 35 (14.3%)	Clinical judgment. Definition not reported. No Swab taken. I: 0 / 36 (0%) C: 1 / 30 (3.3%)	I = 3.6 (1.5) C = 5.1 (2.9)	NR	NR

I: intervention, C: control, NR: not reported, SEM: Standard Error of the Mean. [1] Median, [2] Mean time required for dressings change, [3] Number of patients (%), [4] Mean score on Visual Analog Scale (VAS) and faces scale with grading zero to four, [5] Mean score on objective pain scale, [6] Days/ % TBSA burned (no exact data was given; values derived from the diagram).

DISCUSSION

This study is the first systematic review and meta-analysis of RCT's comparing the outcomes of non-silver treatments with SSD that focuses only on pediatric patients with partial-thickness burns. In our meta-analysis we found that wounds treated with non-silver treatments healed more rapidly, required less dressing changes and shorter LOS than SSD. In addition, there are indications that non-silver treatments cause less pain than SSD treatments in burn wounds. However, there is no evidence to support the use SSD in treatments for prevention of wound infection and lesser grafting in pediatric patients with partial-thickness burns. Unfortunately, none of the included studies reported results on scar formation which is one of the most important outcomes in burn patients.

The methodological quality of the included RCTs was moderate and the risk of bias was high. In general, bias cannot be avoided when writing a review due to language bias and publication bias. We were unable to assess the extent hereof, but the 'file drawer problem' should not be underestimated, since there is a tendency that significant results are published more readily than non-significant results, leading to overestimation of the true treatment effect. Another limitation of this review was that the available information on study results was limited. Although authors were requested to provide us with missing data, none of the authors provided the requested information.

For some study outcomes (wound healing time and number of dressing changes) statistical heterogeneity between studies was detected. This statistical heterogeneity might reflect underlying clinical heterogeneity with respect to age range, percentage TBSA, type of included burn wounds or different non-silver treatments. However, different non-silver treatments were pooled in our meta-analysis because all the individual studies had similar outcome in respect to wound healing, grafting, infection and pain compared to SSD.

Our finding that non-silver treatment is associated with more rapid wound healing compared to SSD is in line with several other literature reviews on this topic in pediatric patients. Dorsett-Martin reported inconclusive results after analysis of comparative studies from 1997-2007, though for TransCyte®, Biobrane®, beta-clucan collagen and Mepitel® often superior results were reported compared to SSD with respect to healing times and pain reduction in peediatric patients.(38) Mandal et al. reported on the basis of scanty prospective comparative studies that Biobrane® seemed to be more effective with regard to wound healing, pain control and LOS than conservative treatment, including SSD in pediatric patients.(39) A recent Cochrane review, based mainly on adult patients, found also that SSD was consistently associated with poorer healing outcomes.(8) Finally, a similar systematic review of 7 RCT's comparing silver-dressings and topical silver to

non-silver dressings found a longer healing time for partial thickness burns when silver-dressings were compared to non-silver treatment in adults [WMD 3.96 days; 95% CI 2.41, 5.5].(10) A mean difference of 3.4 days in healing time, as found in our meta-analysis, between wounds that are treated with non-silver treatment versus SSD, could be of a great important. Hospital stay, in particular dressing changes, could be traumatic for a child. Furthermore, hospital admission of a child requires that at least one parent has to stay in the hospital during that time.

Regarding wound infection and grafting, our findings are also in agreement with other studies. Different reviews conclude that there is insufficient evidence that SSD prevent wound infection. (21) (8,10,12) This despite the fact that several vitro studies have shown that silver has an antimicrobial activity against a wide range of gram positive and gram negative microorganisms, including resistant forms such as MRSA and VRE, and fungi and anaerobes. (17,18,40) Some studies found that organisms do not develop resistance to silver, but recent studies suggest that resistance does occur. (19,20) However, in vitro studies of the antimicrobial efficacy of SSD do not necessarily reflect their performance in a wound due to the complexity of the wound environment.

There have been conflicting studies regarding the workings of silver on wound healing in adults. A review by Atiyeh et al. concluded that silver-based products used as a topical antimicrobial strategy in treatment of superficial partial thickness wounds should be avoided if possible because of the cytotoxicity of silver to the wound bed.(9) In a study by Burd et al. it was found that five silver-based preparations in a tissue explant culture model, in which the epidermal cell proliferation was evaluated, resulted in a significant delay of reepithelialisation. (41) It was also found that SSD in animal models (pig and mice) lead to strong inhibition of wound reepithelialisation on the 7 Post Burn Day.(42) Another study by Poon et al. supported these findings and found that silver is cytotoxic on keratinocytes and fibroblasts in vitro models by using MTT and BrdU assays.(43) Lee et al. also found that SSD in collagen sponge was cytotoxic to fibroblasts and caused a significant impairment in the wound healing process and a decrease in wound tear strength.(42) Conversely, different studies found some silver preparation not to be toxic and suggested that silver promotes wound healing.(44,45)

It should be noted that we only found RCTs that compared SSD with non-silver treatments in our search of the literature, despite the fact that our search strategy designed to compare all silver containing dressings and/or silver topical agents with a non-silver treatment. Meanwhile, “next generation” silver containing preparations are widely used in the treatment of partial thickness burns.(9) In particular, silver containing dressings have potential advantages over SSD. These dressings contain a silver releasing compound or a sustained release of nanocrystalline silver which is covering the outer layer of the dressing, impregnated within

the structure of the dressing or as a combination of these.(3) The dressing usually consist of activated charcoal, hydrofiber, polymer film, polyacrylate matrix, nylon fabric that has been silver-plated or high-density polyethylene mesh.(9) These silver containing dressing, depending on the type of dressing, are designed to require less dressing changes, easier to apply on the wound, allow a better autolytic debridement and at the same time sustenance moist wound environment to promote wound healing, and provide sustained release of silver ion into the wound compared to SSD.(46) Various studies in adults suggests that burn wounds that are treated with nanocrystalline silver had a shorter healing time, lower incidence of infection, decreased pain level, less wound dressings and costs compared to older silver formulations such as silver nitrate or SSD.(47) On the other hand a recent Cochrane review found only a shorter haling time and less dressing changes for silver containing dressing compared to SSD in partial thickness burns. Overall there is evidence that silver containing dressing is preferable to SDD in terms of wound healing. Therefore, future studies could focus on comparison of silver containing dressing with non-silver treatments.

Some recommendations for future studies follow from this review. We would like to emphasize the importance of presenting age-specific study results as the skin of adults and children are different and may, therefore, react differently to treatment. Consequently, inclusion of patients of all ages or presenting results as if patients form one homogenous group, may mask underlying effect heterogeneity. In addition, studies on burn patients should focus on adequate randomization methods, allocation concealment and blinding of outcome assessment, and most importantly, the presentation of complete outcome data. Uniform outcome measurements should be chosen, e.g. for measuring pain, and uniform and clear definitions of wound healing and infection should be used. LDI is an accurate and reliable way to estimate wound healing in burn patients by evaluation of the differences in perfusion of the microvascular blood flow of the wound. (48,49) Lastly, future studies could focus more on comparison of silver containing dressing with non-silver treatments.

CONCLUSION

Our systematic review and meta-analysis suggests that non-silver treatment may be preferred over SSD in terms of wound healing time, dressing changes, pain and LOS, while no treatment differences were found regarding infection and grafting rates. However, we emphasize the lack of high-quality RCTs that are needed to validly confirm the effectiveness of non-silver treatments above silver containing preparations, in particular silver containing dressings, in pediatric patients with partial thickness burns.

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Appendix A. The search strategy.

For Pubmed

(("child"[mesh] OR "child"[all fields] OR "children"[all fields] NOT "child"[au]) OR "schoolchild"[all fields] OR "schoolchildren"[all fields] OR "infant"[all fields] OR "infants"[all fields] OR "adolescent"[all fields] OR "adolescents"[all fields] OR "pediatric"[all fields] OR "paediatric"[all fields] OR "neonatal"[all fields] OR "neonate"[all fields] OR "neonates"[all fields] OR "youth"[all fields] OR "youths"[all fields] OR "baby"[all fields] OR "babies"[all fields] OR "toddler"[all fields] OR "toddlers"[all fields] OR" teen"[all fields] OR "teens"[all fields] OR "newborn"[all fields] OR "newborns"[all fields]OR "puberty"[all fields] OR "suckling"[all fields] OR "sucklings"[all fields] OR "juvenile"[all fields]) AND ("burns"[MesH] OR "burns"[all fields] OR "burn"[all fields] OR "burned"[all fields] OR "burnt"[all fields] OR "burning"[all fields] OR "burnings"[all fields]) AND ("silver sulphadiazine"[all fields] OR "SSD"[all fields] OR "Flammazine"[all fields] OR "Flamazine"[all fields] OR "Silver Sulfadiazine"[MESH] OR "Sulfadiazine"[all fields] OR "Sulfafdiazine"[all fields] OR "Dermazin"[all fields] OR "Sicazine"[all fields] OR "Thermazene"[all fields] OR "silverderma"[all fields] OR "Sulfargen"[all fields] OR "Brandiazin"[all fields] OR "Silvadene"[all fields] OR "sulfazin"[all fields] OR "silver"[all fields])

For Embase

((exp child/ OR "child".mp. OR "children".mp. NOT "child".au.) OR "schoolchild".mp. OR "schoolchildren".mp. OR "infant".mp. OR "infants".mp. OR "adolescent".mp. OR "adolescents".mp. OR "pediatric".mp. OR "paediatric".mp. OR "neonatal".mp. OR "neonate".mp. OR "neonates".mp. OR "youth".mp. OR "youths".mp. OR "baby".mp. OR "babies".mp. OR "toddler".mp. OR "toddlers".mp. OR "teen".mp. OR "teens".mp. OR "newborn".mp. OR "newborns".mp.OR "puberty".mp. OR "suckling".mp. OR "sucklings".mp. OR "juvenile".mp.) AND ("exp burn/" OR "burns".mp. OR "burn".mp. OR "burned".mp. OR "burnt".mp. OR "burning".mp. OR "burnings".mp.) AND ("silver sulphadiazine".mp. OR "SSD".mp. OR "Flammazine".mp. OR "Flamazine".mp. OR "exp sulfadiazine silver/" OR "Sulfadiazine".mp. OR "Sulfafdiazine".mp. OR "Dermazin".mp. OR "Sicazine".mp. OR "Thermazene".mp. OR "silverderma".mp. OR "Sulfargen".mp. OR "Brandiazin".mp. OR "Silvadene".mp. OR "sulfazin".mp. OR "silver".mp.)

For CINAHL

((MH child+) OR (TX child*) OR (TX schoolchild*) OR (TX infant*) OR (TX adolescent*) OR (TX pediatric*) OR (TX paediatric*) OR (TX neonatal*) OR (TX neonate*) OR (TX youth*) OR (TX baby*) OR (TX babie*) OR (TX toddler*) OR (TX teen*) OR (TX newborn*) OR (TX pubert*) OR (TX suckling*) OR (TX juvenil*)) AND ((MH burns+) OR (TX burn*)) AND ((MH silver sulphadiazine) OR (TX SSD) OR (TX Flammazine*) OR (TX Flamazin) OR (TX Sulfadiazine) OR (TX Sulfafdiazine) OR (TX Dermazin) OR (TX Sicazine) OR (TX Thermazene) OR (TX silverderma*) OR (TX Sulfargen) OR (TX Brandiazin) OR (TX Silvadene) OR (TX sulfazin*) OR (TX silver*))

For Cochrane

(silver or silversulphadiazine or Flammazine) and (child or schoolchild or infant or adolescent or pediatric or paediatric or neonatal or neonate or suckling) and burn