Beck, Sarah (2014) Are silver products an effective treatment for infection of chronic wounds? [Dissertation (University of Nottingham only)] (Unpublished)

Silver products- an effective treatment for managing locally infected chronic wounds; a systematic review of the literature

Dissertation submitted for Master of Nursing Science,

School of Health Sciences

University of Nottingham

By Sarah Beck

Word Count- 15, 998

I declare that this dissertation is all my own work

Signed- Date-

Acknowledgements

I would firstly like to thank my dissertation supervisor Andy Meal, for his ongoing support during the process of carrying out this systematic review; even if at times when I may have made "fatal" mistakes.

I would also like to thank my flatmates for their support, I don't think they ever want to hear about silver dressings ever again.

I would also like to thank my Dad who gave up his time to help me proof read this review and many of my nursing essays in the past.

I would also like to thank my Mum; without her support over the years I highly doubt I would have ever been able to go to University. When I was in primary school, and my friends were outside having fun, I would be sitting inside doing 11 plus papers. I was not grateful at the time, but I am now.

I also should probably just mention my brother James… how he has helped I am not sure, he is more of a distraction; bringing round his dirty washing for me to do.

Contents

Contents of boxes flowcharts, tables and appendices

List of Boxes

List of flow diagrams

List of tables

Chapter 4

Appendices

Chapter 2

Chapter 3

Chapter 4

Chapter 6

Abstract

Aim; *T*o identify whether silver is an effective treatment for infected chronic wounds and to identify any adverse effects.

Background; Conflicting evidence exists around the effectiveness and adverse effects of silver products which has led to considerable confusion regarding this treatment in practice. With some previous systematic reviews and RCTs identifying that not enough evidence exists to recommend the use of silver products. However, a systematic review conducted by Lo et al (2008) identified that silver was an effective product for wound healing and reduction of infection levels, therefore it was important to identify if any RCTs had been published from this date to add weight to these conclusions.

Methods; A systematic review of the literature was conducted using two search strategies in order to capture both effectiveness data (RCTs), and adverse effect data (RCTs & observational studies). For effectiveness searched; databases were searched from 2008- January 2014 using Cochrane CENTRAL, MEDLINE and EMBASE- including only randomised controlled trials. Adverse effects data was extracted from from the effectiveness results, with the additional searches performed to capture observational studies. This search was conducted from 1950- January 2014 using MEDLINE, EMBASE and CINAHL databases.

Results; In total 5 RCTs and 4 observational studies were identified for inclusion in the review. It was identified that silver products are an effective treatment for infected chronic wounds, based on statistically significant results regarding wound healing and infection levels in the included controlled studies- and in combination with the results from the systematic review conducted by Lo et al (2008). Additionally, no serious adverse effects were identified.

Conclusion; This systematic review strengthens the case for the use of silver products on managing locally infected chronic wounds. However, the use of silver must be accompanied by a thorough wound assessment; a "two week challenge" is recommended before reassessing for alternative treatment options.

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Appendix 1

Table 1, Comparison of systematic reviews

Reference	Title	Studies included	Objectives	Adverse effects	Conclusions Made
Carter, Tingley-Kelley and Warriner (2010)	Silver treatments and silver-impregnated dressings for the healing of leg wounds and ulcers: A systematic review and meta-analysis	10 RCT's were selected for inclusion - searches conducted up to 2008	1)Conduct a systematic review of silver dressings and treatments in wounds focusing on healing outcome and parameters; and 2) attempt a meta-analysis for these parameters	- Does not look at the adverse effects of silver products	Some evidence that silver-impregnated dressings improve the short-term healing of wounds and ulcers, long term effects remain unclear. Clinical trial data with longer follow-up times are needed to address these issues.
Chambers, Dumville and Cullum (2007)	Silver treatments for leg ulcers: a systematic review	9 RCT's were selected for inclusion	To determine the quantity and quality of current research on the effectiveness of silver based dressings and topical agents for the treatment of leg ulcers. Involves RCT's looking at the effects of silver-based dressings and topical agents for leg ulcer healing.	-Does not look at the adverse effects of silver products	Studies provided inconsistent evidence regarding the effects of silver-based dressings and topical agents on wound healing. Studies generally provided poor evidence due to a lack of statistical power, poor study designs, and incomplete reporting. Concludes that the current evidence base on the use of silver-based products is limited- both the quantity and quality of available evidence. Highlights the need for more rigorous research to be carried out before the routine use of silver on leg ulcers is justified.
Lo et al (2008)	The effectiveness of silver-releasing dressings in the management of non-healing chronic wounds: a meta-analysis	8 RCT's and meta-analysis performed on the data from 1399 participants.	The purpose of the study was to examine the efficacy of silver-releasing dressings in the management of non-healing chronic wounds.	-Does comment on the adverse effects found in the RCT's it reviewed	Found that silver dressings significantly improved wound healing, reduced odour and pain related symptoms, decreased wound exudates and had prolonged dressing wear time when compared with alternative wound care approaches. In all studies indicated an improved quality of life using silver dressings in wound management with no associated severe adverse effects.
Vermeulen et al (2007)	Topical silver for treating infected wounds	Only 3 RCT's were found in total for inclusion in the review. With a total of 847 participants	To evaluate the effects on wound healing of topical silver and silver dressings in the treatment of contaminated and infected acute or chronic wounds.	-Does comment on the adverse effects found in the randomised control trials it reviewed. (see review)	Only three trials with a short follow-up duration were found. There was insufficient evidence to recommend the use of silver containing dressings or topical agents for the treatment of infected or contaminated chronic wounds.

Appendix 2

Effectiveness Search Strategies

Medline using OVID format using Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE. 2 search strategies; sensitivity-maximizing version and a sensitivity- and precision-maximizing version (Higgins and Green, 2008) (It is recommended that searches for trials for inclusion in Cochrane reviews begin with the sensitivity-maximizing version in combination with a highly sensitive subject search. If this retrieves an unmanageable number of references the sensitivity- and precision-maximizing version should be used instead)

Medline search strategy, OVID format, sensitivity- maximising version (2008)

#1 randomized controlled trial.pt.

#2 controlled clinical trial.pt.

#3 randomized.ab.

#4 placebo.ab.

#5 drug therapy.fs.

#6 randomly.ab.

#7 trial.ab.

#8 groups.ab.

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 exp animals/ not humans.sh.

#11 #9 not #10

#12 silver.mp. or silver compounds/ or silver nitrate/ or silver sulfadiazine/

#13 infection.mp. or wound infection/

#14 chronic.mp. or chronic disease/

#15 wound.mp. or wound healing/ or skin ulcer/

#16 #11 and #12 and # 13 and #14 and #15

#17 limit #16 to yr= 2008- 2014

Medline search strategy, OVID format, sensitivity- and precision-maximizing version (2008)

#1 randomized controlled trial.pt.

#2 controlled clinical trial.pt.

#3 randomized.ab.

#4 placebo.ab.

#5 clinical trials as topic.sh.

#6 randomly.ab.

#7 trial.ti

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 exp animals/ not humans.sh.

#10 #8 not #9

#11 silver.mp. or silver compounds/ or silver nitrate/ or silver sulfadiazine/

#12 infection.mp. or wound infection/

#13 chronic.mp. or chronic disease/

#14 wound.mp. or wound healing/ or skin ulcer/

#15 #10 and #11 and # 12 and #13 and #14

#16 limit #15 to yr= 2008- 2014

EMBASE search strategy, OVID format filter from Wong et al, 2006

#1 random:.tw.

#2 placebo:.mp.

#3 double-blind:.tw.

#4 #1 or #2 or #3

#5 silver.mp. or silver chloride/ or silver derivative/ or silver dressing/ or silver impregnation/ or silver nanoparticle/ or silver nitrate/ or sulfadiazine silver/

#6 exp infection/ or infection.mp. or wound infection/

#7 chronic.mp. or chronic wound/

#8 exp wound/ or wound.mp. or wound care/ or wound complication/ or wound healing/

#9 #5 and #6 and #7 and #8

#10 #4 and #9

#11 limit #10 to yr= 2008- 2014

CENTRAL- Cochrane Central Register of Controlled trials

#1 chronic

#2 silver

#3 wound

#4 infection

#5 #1 and #2 and #3 and #4

Appendix 3

Adverse effects search strategies

Medline using OVID format (1946 to jan wk 3 2014) searches on 29/01/2014

[RCT filter used to exclude RCT's]

MEDLINE OVID format, sensitivity- maximising version (2008)

#1 randomized controlled trial.pt.

#2 controlled clinical trial.pt.

#3 randomized.ab.

#4 placebo.ab.

#5 drug therapy.fs.

#6 randomly.ab.

#7 trial.ab.

#8 group.ab.

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 exp animals/ not humans.sh.

#11 9 not 10

#12 silver.mp. or silver compounds/ or silver nitrate/ or silver sulfadiazine/

#13 infection.mp. or wound infection/

#14 chronic.mp. or chronic disease/

#15 wound.mp. or wound healing/ or skin ulcer/

#16 (#12 and #13 and#14 and #15) not 11

Medline search strategy, OVID format, sensitivity- and precision-maximizing version (2008)

#1 randomized controlled trial.pt.

#2 controlled clinical trial.pt.

#3 randomized.ab.

#4 placebo.ab.

#5 clinical trials as topic.sh.

#6 randomly.ab.

#7 trial.ti.

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 exp animals/ not humans.sh.

#10 #8 not #9

#11 silver.mp. or silver compounds/ or silver nitrate/ or silver sulfadiazine/

#12 infection.mp. or wound infection/

#13 chronic.mp. or chronic disease/

#14 wound.mp. or wound healing/ or skin ulcer/

#15 (#11 and #12 and #13 and #14) not #10

#16 review.ab.

#17 #15 not #16

EMBASE search strategy, OVID format filter from Wong et al, 2006- used to exclude RCT's

#1 random:.tw.

#2 placebo:.mp.

#3 double-blind:.tw.

#4 #1 or #2 or #3

#5 silver.mp. or silver chloride/ or silver derivative/ or silver dressing/ or silver impregnation/ or silver nanoparticle/ or silver nitrate/ or sulfadiazine silver/

#6 exp infection/ or infection.mp. or wound infection/

#7 chronic.mp. or chronic wound/

#8 exp wound/ or wound.mp. or wound care/ or wound complication/ or wound healing/

#9 #5 and #6 and #7 and #8

#10 #9 not #4

#11 review.ab.

#12 #10 not #11

CINAHL

S1 (MH "Leg Ulcer") OR (MH "Venous Ulcer") OR (MH "Pressure Ulcer") OR (MH "Foot Ulcer") OR "wound”

S2 (MH "Silver") OR (MH "Ionic Silver Dressings") OR (MH "Silver Compounds") OR (MH "Silver Nitrate") OR (MH "Silver Sulfadiazine") OR "silver"

S3 (MH “Infection”) or (MH “wound infection”) or (MH “chronic wound”) OR “infection”

S4 (MH “Case Control Studies”) OR (MH “Case Studies”) OR (MH “Matched Case Control”) OR (MH “One-Shot Case Study”) OR (MH “Case Management”)

S5 ((MH "Infection") or (MH "wound infection") or (MH "chronic wound") OR "infection") AND (S1 AND S2 AND S3 AND S4)

Appendix 4

Data Extraction Form, Outcomes 1&2 (Adapted from Cochrane Wounds group, data extraction form)

Date of Extraction	
Authors	
Bibliographic details of study	
Country of study	
No. of participants at start of study	
Notes/ short description	

Study eligibility

Study characteristics	**Eligibility criteria**	**Eligibility criteria met?** Yes No Unclear	**Location in text or source**
Date of study	2008 onwards	☐ ☐ ☐	
Type of study	Randomised Controlled Trial	☐ ☐ ☐	
Participants	Adults with an infected or heavily colonised chronic wounds	☐ ☐ ☐	
Type of intervention	Use of silver products	☐ ☐ ☐	
Type of comparison	Compared to control/ standard treatment	☐ ☐ ☐	
Type of outcome measures	-A measure of healing rate/ reduction of infection i.e. time to complete wound healing, changes in wound area, resolution of infection/exudate/ inflammation -Adverse effects	☐ ☐ ☐ ☐ ☐ ☐	
INCLUDE ☐		☐ EXCLUDE	
Reason for exclusion			

Do not proceed if study is excluded from the review

Trial Characteristics

	Description as stated in report/ paper
Aim of study (e.g. efficacy, equivalence etc.)	
Study Design	
Method of Randomisation	
Start date	
End date	
Duration of participation (from recruitment to follow-up)	
Ethical approval needed/ obtained for the study	Yes ☐ No ☐ Unclear ☐

Participants/ population

	Description (include comparative information for each intervention or comparison group if available)
Population description (from which study participants are drawn)	
Setting (including location and social context)	
Inclusion/ Exclusion criteria	
Method of recruitment of participants (phone, mail, clinic patients)	
Informed consent obtained	Yes ☐ No ☐ Unclear ☐

Baseline imbalances	
Withdrawals and exclusions, with reasons	
Patient Characteristics; i.e. Age Sex Race/ Ethnicity Severity of illness Co-morbidities Socio-demographic factors	
Wound Characteristics; i.e. Type of wound Recurrent wound? Duration of wound Wound area	

Study Intervention details

	Description as stated in report/ paper
Groups involved in intervention	
No. randomised to groups	
Theoretical basis (include key references)	
Silver product used	
Controls/ comparison treatment	
Treatment protocol	
Care setting	
Care providers	

Co-interventions	
Duration of intervention	
Economic information	

Analysis

	Description as stated in report/ paper
What population analysis was performed at baseline?	
What wound analysis was performed at baseline?	
What infection analysis was performed?	

OUTCOME 1- Outcomes in study extracted related to the effectiveness of silver

	Description as stated in report/ paper
Definition of outcome(s)	
Timing of assessment (s)	
Person measuring/ reporting outcome	
Assumed risk estimate (e.g. baseline population risk noted in background)	
Length of follow-up	
Statistics used to assess outcome	
Results of outcome(s)	

OUTCOME 2- Adverse Effects- (information to be extracted as suggested by The Centre of Reviews and Dissemination, 2009)

	Description as stated in report/ paper
Report of side-effects of treatment in paper?	
Side-effects of treatment	
Frequency, severity and seriousness of the event(s)	
Method of monitoring of adverse effects (e.g. reported at follow-up/ patient diary)	
Withdrawals from treatment due to adverse effects	

Quality assessment for outcome 2- (Questions from Loke, Price and Herxheimer, 2008)
On conduct:

- Are definitions of reported adverse effects given?
- Were the methods used for reporting adverse effects reported?

On reporting:

- Were any patients excluded from the adverse effects analysis?
- Does the report provide numerical data by intervention group?
- Which categories of adverse effects were reported by the investigators?

Author's conclusions

	Description as stated in report/ paper
Limitations of study	
Implication of study	

References to other relevant studies	

Comments on the Quality of the RCT (use CASP assessment framework)

Extractor's comments on the following;
-Internal validity

- *Selection bias*

- *Performance bias*

- *Measurement bias*

- *Attrition bias/ exclusion bias*

-External validity (Generalizability)-

Appendix 5

Table 2- Characteristics of RCTs included in the review

Author and Title	Study objectives	Participants	Intervention (treatment and duration)	Outcome measures
Beele et al (2010)	Observe performance of an ionic silver alginate/ carboxymethyl cellulose dressing on wounds that are critically colonised and report whether the dressing can be used to manage and reduce an "at risk" wound from becoming infected.	36 from the Netherlands and Belgium VLU and PU	Use of an ionic silver alginate/ carboxymethyl cellulose dressing vs control for 4 weeks -no co-interventions stated	-Measures of wound healing -Measures of infection levels
Harding et al (2012)	Compare the wound healing of 2 silver dressings against venous leg ulcers at risk of infection. Primary objective was to show the non-inferiority of Aquacel ®Ag to ®Urgotul silver.	281 from UK, Germany, France, Denmark and Poland VLU	Use of both silver products for 4 weeks then non-silver product used in each group for 4 weeks. -compression therapy	-Measures of wound healing -Measures of infection levels
Lazareth et al (2012)	Assess the ability of a silver lipidocolloid contact layer to promote the healing process of VLU presenting inflammatory signs suggesting heavy bacterial colonisation and delayed healing, in comparison with the same wound dressing not impregnated with silver salts.	102 from France VLU	Use of silver product vs control for 4 weeks. Then both groups were treated with the same treatment as the control. -compression therapy & secondary dressing of Tetra medical applied	-Measures of wound healing -Measures of infection levels
Miller et al (2010)	Compare the clinical effectiveness of cadexomer iodine and nanocrystalline silver. The nul hypothesis was posed, that there is no expected differences in healing rates.	281 from Australia LU	Use of iodine vs nanocrystalline silver products for 12 weeks -compression therapy	-Measures of wound healing
Woo et al (2012)	Aims to evaluate if topical silver dressings that consist of alginate powder is effective in managing chronic wounds that exhibit signs of critical colonisation and promote wound healing	34 from Canada A range of chronic leg ulcers and foot ulcers.	Use of silver alginate powder dressing vs control for 4 weeks -Appropriate plantar pressure redistribution devices were used for some patients.	-Measures of wound healing -Measures of infection levels

VLU- Venous leg ulcer
PU- Pressure ulcer
LU- Leg ulcer

Appendix 6

Characteristics of observational studies included in the review

Study authors and Date	Trial characteristics	Study Aims/ objectives	Participants	Intervention	Study conclusions/ outcomes
Bhattacharyya and Bradley (2006)	Single case study	The report presents the difficulties encountered when managing a wound colonised with MRSA, which was successfully treated with nanocrystalline silver.	1 patient, London hospital Lewisham	Treatment of a patient's chronic knee wound with nanocrystaline silver releasing dressing.	They speculate that the use of nanocrystaline silver may have reduced bacterial loading at the wound site and thereby decreased the stimulus for autoimmune reaction in patients with psoriasis.
Coutts and Sibbald (2005)	Single centre, open-label case series	Evaluate the clinical improvement in chronic wounds over a 4 week period, whilst undergoing treatment with silver containing hydrofiber dressing.	30 participants, Canada Wounds included: -4 diabetic neuropathic foot ulcers -13 venous stasis ulcers -4 pressure ulcers -9 miscellaneous wounds	4 week application of silver containing hydrofiber dressing to chronic wounds.	Majority of wounds decreased in size (70%) with decrease exudate, decreased purulence and resolution of surface slough (75%). There was also an increased quantity of granulation tissue. A de-sloughing action was also seen in pts. with pre-existing slough at baseline (54% had peri-wound maceration at baseline, 85% of these resolved).
Richards and Chadwick (2011)	A single centre, open, non-randomised case series.	Evaluate the effectiveness of Mepilex Ag in the management of signs and symptoms of wound infection in a number of diabetic foot ulcers (DFU).	15 participants. Inpatients and outpatients of a specialist podiatry clinic who presented with active DFU's with local signs of infection	Each participant was treated according to local clinical practice and evaluated over a 4 week period during the wound management with Mepilex Ag.	-Erythema, oedema and heat (infection related symptoms) were reduced by the end of the study when compared with the baseline -Exudate levels were also reduced at end of study when compared to baseline. With 93.3% (14/15) of DFU producing mild or no exudate. -Pain scores reduced over the course of the study. -Trend of a decline in wound size was noted over the course of the study -100% of investigators rated the treatment as "good" or "very good". -only 1 AE
Truchetet et al (2012)	Prospective observational study	To describe the motivations for using a silicone, silver-releasing dressing and the type of wounds treated with this dressing, and to evaluate the short-term impact on wound characteristics.	794 participants Adult patients in the community. A range of wound types, chronic& acute- evaluated independently at baseline.	Use of a silicone, silver releasing dressing (Mepilex Ag) on wounds.	The primary rationale for prescription of a silver dressing was treatment of possible wound infection.

Appendix 7

Study authors and date	No. of partici-pants	Trial duration (weeks)	Type of silver product	Wound type	Results related to this outcome
Beele et al (2010)	36	4	Silver alginate/ carboxymethyl-cellulose dressing	PU, VLU	-Greater improvement in wound healing in test treatment -Greater reduction in levels of wound infection in test treatment.
Lazareth et al (2008)	102	8	Urgotul ®silver (silver lipidocolloid)	VLU	-Greater improvement in wound healing in test treatment -Greater reduction in levels of wound infection in test treatment at week 4.
Meaume et al (2005)	99	4	Silver releasing hydro-alginate	VLU, PU	-mASEPSIS score did not differ significantly between groups in first 2 wks of treatment -4 wk closure rate was statistically significant in silver test group (p=0.024)
Munter et al (2006)	619	4	Silver-releasing foam	Ulcers of varying ateologies	-Statistically significant (p<0.05) difference in wound area reduction in favour of silver test group. -Decreased odour, reduced exudates, improved pain
Verdú et al (2004)	125	6	Charcoal silver dressing	PU with wound infection	-Test group had a statistically significant (p=0.003) positive effect on bacterial management when compared to control. -Study authors state healing time was reduced for test group.
Woo et al (2010)	34	4	Silver alginate powder (arglaes powder)	A range of chronic leg and foot ulcers	-Greater rate of wound healing in silver test treatment group -Greater reduction of infection levels in the silver test treatment group
Randomised studies without clear controls					
Harding et al (2012)	281	8	Aquacel ®Ag vs Urgotul ®silver	VLU	-Both dressings were effective at promoting healing and reducing infection levels.
Miller et al (2010)	281	12	Nanocrystaline (Acticoat, acticoat absorbant, acticoat 7)	Leg ulcer	-Greater healing rate in first two weeks of treatment than the iodine treatment. -More effective in wounds that were older, larger and had more exudate

Appendix 8

Study authors and date	Country of Study	Patient characteristics	Wound characteristics	Care setting
Beele et al (2010)	Netherlands and Belgium	-pop predominantly women -mean age 73.4 silver, 73.5 control group -BMI; 30.5 and 27.1 in silver and control -Diabetes; 33.3% silver, 22.2% control -Hypertension; 33.3% silver, 27.5% control	PU & VLU -History of leg ulcer; 50% silver, 33.3% control -History of PU; 11.1% silver, 22.2% control	Not stated, however does state the patient was "visited weekly" therefore may be in community setting.
Lazareth et al (2008)	France	-pop predominantly women -mean age; 74 -mean BMI; 28.9kg/m² -18.6% were diabetics -32.4% had history of venous thrombosis	VLU -79.4% were viewed as stagnated by the investigators -leg ulcers were present for 11 months on average and were recurrent	-71% of patients were outpatients, recruited from hospital dermatology and vascular medicine.
Woo et al (2010)	Canada	-Study sample predominantly male -Mean age; 55.29 silver, and 56.9 in control group	A range of chronic wounds present for over a month. -most ulcers located below the ankle	Wound care clinic
Harding et al (2012)	UK, Germany, France, Denmark and Poland	-pop predominantly women in both treatment groups -Mean age; 68.72 in Aquacel ®Ag group and 71.21 in Urgotul ®silver group.	VLU, ABPI= 0.8 or greater, duration less than 12 months, 5-40cm² -majority of ulcers were classified as deteriorating or had shown no progress in wound healing	Participants home or in clinic
Miller et al (2010)	Australia	-58.6% of participants were female -Mean age; 79.67	Leg ulcers, ABPI= 0.6 or above -Majority of wounds were diagnosed as being venous in origin -Most wounds were located on the lower leg	Community district nursing patients, care provided in patients' homes or in clinic