SilverStream Clinical experience – Summary of Case Studies

Introduction

SilverStream is available in the Global market since 2011. It was 510(k) cleared by the US-FDA on Dec. 2009 and later was approved by the Israeli MOH, CDSCO (Indian FDA), Kenya, Nigeria, Philippines, S. Korea and El-Salvador MOHs, and is sold in all these countries.
Up to date, more than 50,000 patients were treated successfully worldwide with no reported adverse events.
In accordance to the approved indications for use, these patients were treated for venous ulcers, diabetic foot ulcers, pressure ulcers (bad sores), post-surgical wounds, trauma wounds and burns.

Case Studies Reported by Thomas E. Serena MD (USA 2011)

Thomas E. Serena, MD from St. Vincent Hospital, Erie, PA and KOL in wound care area in the USA, treated a series of 15 patients with SilverStream solution, **first in man**, twice weekly for two weeks using a standard syringe and a 22-gauge needle; up to 120cc of the solution was used per ulcer per day. All wound types were included in the trial. Standard dressings with no antimicrobial substances were used between treatments.

Results

The most frequently observed finding was a reduction in the loose slough covering the wound surface. This was most pronounced in patients with venous leg ulcers but was also seen in surgical wounds, pressure ulcerations and other wound types. The investigator also noted a healthier appearance to the granulation tissue in the treated wounds. One patient had bilateral venous leg ulcers. Only the ulcer on the left leg was treated with the solution while the other ulcer was cleansed with normal saline in the usual fashion for the wound center. In this patient, there was considerably less slough in the treated ulcer. One patient was discontinued due to burning on application resulting from a sensitivity to silver. Otherwise, there were no adverse events.

Conclusions

These findings suggest that further study into the effects of topical silver solution particularly in patients with venous leg ulcers is indicated. There was no testing for the presence of biofilms, but it was suggested that there might be a reduction in biofilm based on the elimination of slough or biomaterial resulting from the SilverStream solution. In addition, the visual impression of improvement in the appearance of the wound bed and promotion of wound closure also may be secondary to biofilm reduction.
The results of this case series were presented at SAWC, in Dallas, TX, April 2011 (attached).

USA Case Studies (2012)

We present here the summary of the observational study for the treatment of mildly infected or quiescent and non-progressive diabetic foot and venous leg ulcers treated with SilverStream. Retrospective data was collected from 39 consecutive wounds at 8 independent sites at the east northern belt of USA. Data was reviewed to determine the change in wound size, overall appearance and condition following either daily or weekly treatment, based on the clinical need with SilverStream over a period of 4 weeks + one week for follow-up.

Quiescent wounds were defined as wounds, which demonstrated no progression in healing and no decrease in wound size for a period of at least 1 month. The collected data was provided by each individual site.

The clinicians at each center were experienced in wound care. In this study, 39 wounds were identified from a total of 38 patients.

Wounds were irrigated with approximately 20 cc of SilverStream solution with either a bulb syringe or a hypodermic syringe with a 19-gauge needle. Typically, the solution was slowly sprayed on the wound for approximately 30 seconds. The patients also applied a dressing in which gauze was moistened with SilverStream, and was applied directly to the wound. Patients with diabetic foot ulcers also had appropriate off-loading to reduce mechanical pressure at the wound site.

Venous leg ulcer patients also had compression therapy in conjunction with a gauze dressing.

Debridement was usually performed about every 7 to 14 days, but some centers debrided more frequently in the initial stages. Patient's comments regarding their satisfaction with the wound product, as far as comfort, reduction in odor, reduction in exudate, and overall appearance of the wounds were also collected from the chart, when possible. Objective assessments by the clinicians were performed at each site, and included changes in wound size, as well as reduction in exudate and slough, and increase in wound bed vascularity, according to the attached Product Evaluation Documentation Form. All sites routinely photographed their wounds, and these photos were examined in order to document the progression of the wound once treatment began. Wounds were tracked for up to 5 weeks following initiation of treatment (4 weeks of treatment + 1 week of follow-up. Adverse events and negative changes were also reviewed.

Wound margins were traced at baseline, and after 3 and 5 weeks of treatment.

Areas of granulation and fibrous tissue were marked and measured. Changes in area and percentage of granulation versus non-granular (fibrous) tissue were recorded.

Data collection was documented at baseline and after 3 and 5 weeks (4 weeks of treatment + 1 week of follow-up). Data analysis included both subjective data from the clinician and the patient, and included their assessment of the wound appearance, as well as estimates of percentage of slough and granulation over the surface of the wound, and whether or not there had been a change in the amount of exudate. Objective measures of change in wound size were also analyzed included the change in wound size with time, and the percentage of wounds achieving closure in 4 weeks of treatment or less.

All patients were given an adequate supply of SilverStream wound irrigation solution to treat their wound(s) on a daily basis, based on their individual clinician's preferred protocol. Nearly all were instructed to irrigate the wounds on a daily basis, and to moisten the dressing with the SilverStream prior to application. The average number of applications was 4.8 times per week (SD = 1.78). In doing the analysis, wounds that had a surface area between 1 and 15 cm^2 were analyzed separately, and as part of the general pool of data, which contained wounds that measured between 1 and 52.2 cm^2.

Based on the clinical data it was found that 92% of all wounds demonstrated a decrease in surface area. The average wound size in the 1-15cm^2 group (which included both venous and pressure wounds) decreased from 6.74cm2 to 5.12cm^2 after 3 weeks, representing a 36.2% decrease, and to 2.92cm^2 representing a 60.9% decrease in wound size after 4 weeks of treatment, achieving a score higher than Sheehan criteria (Sheehan et al. *Diabetes Care*. 2003;26:1879-1882).

When all wounds were included, a decrease was seen in average wound size from 11.01cm^2 to 9.28cm^2 (- 33.2%) after 3 weeks, and to 7.37cm^2 (-50.2%) after 5 weeks was recorded. In addition, 25.6% of the wounds achieved complete closure in 4 weeks of treatment or less from the initiation of treatment.

Treatment with SilverStream resulted in an increase in granulation tissue and decrease in the percentage of non-viable (fibrous) tissue as well. At baseline, approximately 74.9% of the wound surface was described as granular, and 25.1% as fibrous in appearance. In the smaller wound group, the percentage was 76.0% granular and 24.0% fibrous. After 3 weeks of treatment, the ratio shifted to 81.7% granular and 18.3% fibrous overall and 84.3% granular to 15.7% fibrous in the smaller wound group.
After 4 weeks of treatment, the ratio shifted to 85.9% granular and 14.1% fibrous, and in the smaller wound group, the granulation tissue reached 92.3%, while the fibrous portion dropped to on 7.7%. Although stimulation of quiescent wounds was the primary objective of this study, treatment also resulted in closure of 6 wounds during the first 3 weeks (15.5%) and 10 wounds during the first 4 weeks (25.6%) of treatment.

Adverse events were virtually non-existent, with 1 patient reporting an apparent hypersensitivity of silver. In addition, 10.5 % complained of pain during the irrigation process, but this was not attributed to the solution itself, but rather the mechanical pressure to the wound surface associated with irrigation. 66.7% of the patients indicated that the application of SilverStream to their wounds produced a soothing sensation. 2.8% described a burning or itching sensation following irrigation.

In this observational study, 10/39 wounds (25.6%) exhibited signs of mild to moderate infection, including odor, purulence, local erythema, and cellulitis at baseline, and 100% of those signs of infection were resolved after 4 weeks or less of treatment without the use of concomitant oral antibiotics. Physicians reported total absence of slough and maceration in all cases, by week 3.

We can conclude that wounds treated with SilverStream improved in many respects. The data strongly supports the hypothesis that signs of infection are eliminated, fibrotic tissue was reduced, granulation tissue area was increased, and the cardinal signs of infection were eliminated in all wounds in this study. The combination of an antimicrobial, surfactant, detergent, and buffer in SilverStream has resulted in reduction in wound discharge and odor, and has led to closure in otherwise stagnant wounds.
Most patients found the solution soothing in use, and this was attributed to glycerol presence and to the menthol component presence, which has a cooling and calming effect, as well as playing a role in combating odors, and helping to disrupt slough and biofilms.
Although 25.6% of the wounds treated with SilverStream closed completely, its greatest attribute appears to be its ability to normalize conditions within the wound bed, by reducing slough, increasing granulation tissue, controlling odor, and reducing bacteria load. The investigators observed clear improvement in the overall condition of wounds treated with SilverStream, and believe that it can be used as an excellent daily wound treatment, or can be used to prepare the wound for more advanced biologic tissue grafts and skin substitutes.

The full data of this observational study was described in “Wound Irrigation Stimulates Quiescent and Mildly Infected Diabetic Foot Ulcers and Venous Stasis, Author Ulcers" (draft for publication) and the 5 different posters (attached), presented in the main wound-care USA conferences during 2011 & 2012 (SAWC, DFCON, APMA & Diabetic Limb Salvage)

India first case studies series (2012-2013)

In the following section, we have summarized 17 case studies where patients are treated with SilverStream solution (a summary booklet is attached).
These cases are collected from several clinical centers in India during 2012-2013.
SilverStream solution was applied for several indications including trauma cases (5 patients), diabetic foot ulcers (2 patients), pressure ulcers (2 patients), venous ulcers (4 patients) and burns (4 patients). There were additional 3 cases with different etiologies which were not summarized in this section (10 - Year Old Wound which Originated out of Minor Injury; 1 Year Old Chronic Ulcer Originated from a Shoe Bite; Foot Abscess with Chronic Infection). The case studies were conducted according to the attached Product Evaluation Protocol Form.
The physicians described several clinical parameters including wound size (cm^2), signs of infection (%), granulation tissue (%) and non-viable tissue (%) assessed at the beginning and at the end of the treatment.

<u>Venous Ulcers</u>
Four patients with venous ulcers were treated with SilverStream for 1.5 to 8 weeks, daily (2 cases) or alternate days (2 cases). The size of the wound area decreased in average from 12.8 cm^2 to 1.5 cm^2. Wound infection was present in all patients; following the treatment, no signs of infection were present.

Wound granulation tissue increased from 5% to 100% at the end of the treatment. Non-viable tissue decreased from 92.5% to 5%.

Diabetic Ulcers

Two patients with diabetic ulcers were treated with SilverStream 3 times a week for 3 weeks (1 patient) and twice a day for a week (1 patient).

The size of the wound area decreased from 15 cm^2 to 0 (complete healing) and from 15 cm^2 to 1 cm^2, respectively.

Wound infection was present in both patients at the beginning of the treatment; following the treatment with SilverStream, one patient showed no signs of infection and another patient has 10% of the initial infection intensity.

Wound granulation tissue increased from 0% to 100% in one patient and from 0% to 20% in another patient at the end of the treatment. Non-viable tissue decreased in both patients.

There were no adverse reactions.

Pressure Ulcers

Two patients with pressure ulcers were treated with SilverStream daily and twice a week for 2 and 10 weeks, respectively.

The size of the wound area decreased from 11 cm^2 to 7 cm^2, in average.

Wound infection was present in all patients; following the treatment, no signs of infection were present.

Wound granulation tissue increased from 0% to 100% in both patients.

Non-viable tissue decreased in both patients (100% to 0% and 20% to 0%, respectively).

Burns

Four patients with burns were treated with SilverStream daily or alternate days for 2 to 10 weeks.

The size of the wound area decreased from 43 cm^2 to 0 cm^2 (complete healing) at the end of the treatment.

Wound infection was present in all patients; following the treatment, no signs of infection were present.

Wound granulation tissue increased from 7.5% to 96% in average.

Non-viable tissue was reduced from 77.5% to 5% in average.

Trauma

Five patients with trauma wounds were treated with SilverStream daily or alternate days for 2 or 3 weeks.

The size of the wound area decreased from 56cm^2 to 0 cm^2 (complete healing) at the end of the treatment.

Wound infection was present in all patients; following the treatment, no signs of infection were present.

Wound granulation tissue increased from 2.5% to 94% in average.

Non-viable tissue was reduced from 80% to 2.5% in average.

India second case studies series (2016)

In the following section, we have summarized 47 case studies where patients are treated with SilverStream solution.

These cases are collected from ~20 clinical centers and private clinics throughout the India during 2016.

SilverStream solution was applied for several indications including acute wounds (8 patients), diabetic foot (14 patients), pressure (5 patients) and venous ulcers (8 patients), first and second degree burns (3 patients) and Fournier gangrene, infected necrotizing fasciitis and infected wounds with abscess (5 patients). There were another four cases with different etiologies that were not summarized in this report.

The physicians described several clinical parameters including wound area (cm^2), signs of infection (%), granulation tissue (%), non-viable tissue (%), exudate amount (%), status of wound improvement, patient feeling and other parameters measured or assessed at the beginning and at the end of the treatment.

Venous Ulcers

Eight patients with venous ulcers, mainly on lower extremities (1 patient also had diabetic foot ulcers and first and second degree burns) were treated with SilverStream solution during 2 to 10 weeks.

SilverStream was applied with syringe and/or poured on gauze, daily (1 case) or alternate day (7 cases).

The size of the wound area treated at the first treatment ranged from 5 to 20 cm^2, at average 7.1 cm^2.

At the last treatment, the wound area in 7 patients was 0 cm^2 (complete healing); 1 patient had 2 cm^2.

Wound infection was present in all patients at the beginning of the treatment; following treatment with SilverStream, none of the patients showed signs of infection.

Wound granulation tissue was increased more than 8 times in average (from 12.9 to 100%) at the end of the treatment. In all cases, the amount of exudate decreased.

Non-viable tissue treated with SilverStream decreased from 88.6% to 1.4% in average.

All patients described SilverStream application as soothing. There were no adverse reactions.

In all cases, the condition of the wound significantly improved and the physicians were very satisfied with SilverStream solution, describing it as a great product.

Diabetic foot ulcers

Fourteen patients with diabetic foot ulcers (1 patient had also second degree burn) were treated with SilverStream solution during 3 to 10 weeks.

SilverStream was applied with syringe and/or poured on gauze, daily (7 cases), alternate day (6 cases) and every 3rd day (1 case).

The size of the wound area treated at the first treatment ranged from 2 to 500 cm^2, at average 53 cm^2.

At the last treatment, the wound area in all patients was significantly smaller; the average wound area was 8 cm^2, almost a 7-fold reduction.

Wound infection was present in 13 patients at the beginning of the treatment; at the end of the treatment none of the patients showed signs of infection.

Wound granulation tissue was increased almost 3 times in average (from 20 to 57%) at the end of the treatment. In all cases, the amount of exudate decreased.
Non-viable tissue in the wounds treated with SilverStream decreased from 75.7% to 1.7%.
Ten patients described SilverStream application as soothing; one patient felt no sensation (the feeling in 3 patients were not reported).
There were no adverse reactions.
In all cases, the condition of the wound significantly improved and the physicians described SilverStream as (major comments):

- Very effective in improving granulation tissue.
- Very good and effective product.
- Capable to eradicate malodor.

Pressure ulcer

Five patients with pressure ulcers were treated with SilverStream solution during 1 to 12 weeks.
SilverStream was applied with syringe and poured on gauze, daily (5 cases) or alternate day (2 cases).
The size of the wound area treated at the first treatment ranged from 8 to 150 cm^2, at average 51 cm^2.
Measured at the last treatment, the wound area in all patients decreased significantly; the average wound area was 18cm^2, almost a 3-fold reduction.
Wound infection was present in all patients at the beginning of the treatment; 100% of these signs were resolved at the end of the treatment.
Wound granulation tissue was increased more than 3 times in average (from 20 to 71%) at the end of the treatment. In all cases, the amount of exudate decreased.
Non-viable tissue treated with SilverStream decreased from 83% to 30%.
Three patients described SilverStream application as soothing; one patient complained for discomfort and one patient felt pain and discomfort.
There were no adverse reactions.
In all cases, the condition of the wound significantly improved and the physicians described SilverStream as (major comments):

- Highly effective in generating granulation tissue.
- Reduce bad odor, helps in reducing slough.
- Very effective against bioburden.

First and Second Degree Burns

Three patients with first and second-degree burns were treated in Victoria Hospital (Bangalore) with SilverStream solution during 2 to 4 weeks.
The SilverStream was applied with syringe and/or poured on gauze, daily (1 case), alternate day (1 case) and every 5 days (1 case).
The size of the wound area decreased from 40 cm^2 to 21 cm^2 (the wound area size was reported on only 1 case).
Wound infection was present in all 3 patients at the beginning of the treatment.

100% of these signs were resolved after the treatment (the infection status was not reported in one patient).
All patients described SilverStream application as soothing. There were no adverse reactions.
In all cases, the condition of the wound significantly approved and the physicians were satisfied with SilverStream application, describing it to be "very effective".

Fournier gangrene, infected necrotizing fasciitis and infected wounds with abscess

Five patients with Fournier gangrene infected necrotizing fasciitis and/or infected wounds with abscess were treated with SilverStream solution during 1 to 4 weeks.
SilverStream was applied with syringe and poured on gauze and applied on wound, daily (1 case), alternate day (3 cases) and every 3 days (1 case).
The size of the wound area treated at the first treatment ranged from 25 to 500 cm^2, at average 173.6 cm^2. At the last treatment, the wound area decreased to 138 cm^2, at average.
Wound granulation tissue increased almost 3 times in average (from 32 to 87%) at the end of the treatment.
Wound infection was present in all 5 patients at the beginning of the treatment; at the end of the treatment none of the patients showed signs of infection.
Non-viable tissue treated with SilverStream decreased from 75% to 10% in average. In all cases, the amount of exudate decreased. There were no adverse reactions.
In all cases, the condition of the wound improved and the physicians described SilverStream to be:

- Effective both in acute and chronic wound specially with extensive slough and necrotic tissue.
- Effective in chronic wounds where bacteria are resistant to majority of antibiotics.

Acute wounds

Eight patients with acute wounds on extremities (lower extremities 7 patients; upper extremity 1 patient), were treated with SilverStream solution during 1 to 8 weeks.
The SilverStream was applied with syringe and/or poured on gauze, daily (5 cases) or alternate day (2 cases). The majority of wounds were previously treated with standard dressings such as betadine, saline or hydrogen peroxide.
The size of the wound area treated at the first treatment ranged from 3 to 372 cm^2, with the average of 99 cm^2. Measured at the last treatment, the wound area in all patients was significantly smaller; the average wound area was 56 cm^2, the decrease of ~ 45%.
Wound infection was present in all patients at the beginning of the treatment; following the treatment with SilverStream, 7 out of 8 patients showed no signs of infection.
The wound granulation tissue was increased almost 3 times in average (from 28 to 78%) at the end of the treatment. In all cases, the amount of exudate decreased. The non-viable treated tissue decreased from 68.3% to 11.6%.
Six patients described SilverStream application as soothing; one patient felt discomfort (the feeling of 1 patient was not reported).

There were no adverse reactions.
In all cases, the condition of the wound significantly improved and the physicians described SilverStream as (major comments):

- Highly effective in removing slough
- Enables fast recovery
- Easy to use and cost-effective

Israel Case Studies

Erysipelas is a bacterial skin infection involving the upper dermis that characteristically extends into the superficial cutaneous lymphatics. Historically, Erysipelas occurred on the face, but cases today most often involve the legs.

Objective
Ulceration prevention of calves due to the bacterial infection of dermis and hypodermis, using SilverStream treatment, in order to shorten the hospitalization and to discharge the patients without wounds was conducted at Hadassah University hospital, Jerusalem, Israel.

Method
8 patients admitted to dermatology department with Bullous Erysipelas, were treated with intravenous antibiotics and with topical SilverStream solution once a day.

Results
In 8 of the patients there was an erosive skin presentation at admission, which was resolved in 5-21 days, with no formation of chronic ulcers and no other side effects. After discharge from hospitalization, the patients were supervised by the wound care clinic for 2 more months, with no new development of infection or ulcers.

Conclusions
SilverStream is an effective solution for chronic ulcers preventing in case of Bullous Erysipelas. The solution is time saving and cost effective.

The full data of this observational study was presented at EWMA 2017 conference, the European largest and most known conference of wound care (poster is attached).

Prospective Clinical Study in Diabetic Foot Ulcers

A prospective comparative study was conducted at MKCG Medical College, Berhampur, Odisha, India. A total of 100 patients having diabetic foot ulcer were studied and consent for various procedures were obtained from them. Data regarding granulation tissue formation, pus culture and sensitivity report, skin graft acceptance and hospital stay were analyzed in tabular manner.

Materials and Method

In study group, 2 mL of silver nitrate solution was taken in a syringe after cleaning the wound with distilled water, drying it with sterile gauze and then the silver nitrate solution (SilverStream) was sprinkled over the wound surface. After this, the wound was covered with gauze soaked with silver nitrate solution (SilverStream), whereas in control group dressing was done by 50% w/v povidone-iodine solution. Dressings were done and followed every alternate day for 14 days. Size of ulcers was measured weekly. Wound culture was done on day 1 and on day 14, observed side effect (local and systemic) were documented.

The results obtained were statistically evaluated and compared on following points.

1. Effect of silver nitrate solution on bacterial load in the wound.
2. Rate of granulation tissue formation.
3. No. of days required for healing.
4. Skin graft uptake.
5. Side effect of topical silver nitrate dressing.

Variables were compared using the chi-square t-test and 'p' value was obtained and found to be significant.

Results

Among 100 study subjects, 50 were taken as control group and 50 as study group. The granulation tissue formation on 14th day was 95% in study group and 82% in control group. Successful skin graft uptake was 94% in study group and 80% in control group. Hospital stay in study group was 25.6 ± 3.4 days and 35.3 ± 7.2 days. Pus culture sensitivity test on day 14 was positive in 6 cases in study group and 12 cases in control group. The results are summarized in the following table:

Parameter	Control (Povidone)	Study (SilverStream)
Granulation tissue on 14th day	82%	95%
Skin graft uptake rate	80%	94%
Hospital stay	**35.3±7.2 days**	**25.6±3.4 days**
Positive pus culture	12 patients	6 patients

This study was published in J. Evid. Based Med. Healthc., pISSN-2349-2562, e-ISSN-2349-2570/ Vol. 4/Issue 73/Sept. 11, 2017 (attached).

References

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