

Research Article

Exit Site Care in Peritoneal Dialysis: Silver as a Possible Strategy?

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Abstract

Peritoneal dialysis (PD) is a well-tolerated home renal replacement therapy for patients with end-stage renal disease. One of the critical points for the success of a PD program is the care of the peritoneal catheter and the exit site. A target for the incidence of infections/year should not exceed 0.40. The aim of the study was to observe whether our exit-site cleansing and dressing method, which involves the application of silver-releasing dressing may be associated with a reduction in the incidence of exit-site infections compared to the data reported in the literature.

The data of 51 patients attending the Peritoneal Dialysis DH of the AOU Federico II in Naples in the period between July 2021 and September 2023 were analyzed.

Overall, 27670 catheter days were analyzed with an average incidence of 0.23 infections/year/patient. The average incidence (0.23) is lower than the target suggested by the ISPD (0.4 infections/year/patient) and the average estimated in the USA (0.5-0.6 infections/year/patient). The average incidence from 2021 to 2023, equal to 0.23 episodes/year/patient, is therefore lower than the incidence of 2014-2015 (0.38 episodes/year/patient), a two-year period in which we did not use dressings with silver Exit-Pad.

The use of Exit-Pad silver ion-releasing dressings Ag may further hinder the development of such infections by reducing the failure of peritoneal treatment and the transition to hemodialysis.

Introduction

Peritoneal dialysis (PD) is a well-tolerated home renal replacement therapy for patients with end-stage renal disease. Although technological innovations and improvements in clinical practice in PD have significantly reduced adverse outcomes related to PD, infections, including peritonitis and exit-site / tunnel infections, still remain very frequent complications [1].

One of the critical points for the success of a Peritoneal Dialysis program, therefore, is the care of the peritoneal catheter and the exit site; in fact, approximately 20% of patients on Peritoneal Dialysis are permanently transferred to hemodialysis due to problems related to the catheter and/or the exit site [2].

Exit-site infections have been estimated at between 0.1

and 1.2 episodes per year, based on prophylactic strategies, geographical variations, and sample size. In the USA, an incidence of 0.53-0.6 episodes per year has been estimated [3]. However, a new target for the incidence of infections/year should not exceed 0.40 [4].

Possible risk factors are associated with poor exit-site care, failure to use prophylactic methods, poor immobilization of the catheter, history of injuries caused by catheter traction, swimming, presence of pets during exchanges, and mechanical stresses on the exit site [3].

The most commonly isolated organisms reported for exit site infections were, in descending order of frequency, *diphtheroids* (20.5%), *S. aureus* (13.6%), *Pseudomonas aeruginosa* (13.6%) and *fungus* (9.1%) [4].

Daily application of mupirocin to the exit site has been

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shown to be a cost-effective strategy to decrease the risk of exit site infection from *S. aureus* [5-7]. However, in contrast to previous findings of superior benefit compared to standard care, Obata and colleagues in a systematic review and meta-analysis of RCTs demonstrated that it was uncertain whether the application of mupirocin ointment prevents exit site infection [8].

An alternative topical antibacterial prophylactic agent is gentamicin. Daily application of gentamicin to the exit site was shown to be highly effective in preventing exit site infection caused by *Pseudomonas* species, and as effective as topical mupirocin in reducing *S. aureus* exit site infections [9]. However, its use has been restricted by limited availability and concerns of a change in the microbiologic profile of organisms responsible for the catheter-related infection, gentamicin resistance [10,11], and development of other atypical infections [12]. Alternating between mupirocin and gentamicin exit site application has been discouraged due to the observed increase in the risk of fungal peritonitis compared with gentamicin alone [13].

A Cochrane systematic review and meta-analysis reported very low certainty evidence that various dressing systems (chlorhexidine, povidone-iodine, sodium hypochlorite gauze + fixomull, blister film) may make little or no difference to exit site infection rates [14].

Although past studies have not demonstrated a real advantage in using a silver ring device (designed by Grosse-Siestrup in 1992) mounted on the PD catheter and positioned on the exit site at skin level in preventing infections [15,16], in recent studies it has emerged that the correct use of an advanced dressing that has a controlled antibacterial action, such as the Exit-Pad silver ion-releasing one Ag, could be a further valid tool to prevent exit-site infections [17].

Furthermore, the Exit-Pad silver dressing stimulates the healing of a new exit site and avoids maceration by absorbing secretions and keeping the sinus dry [18].

The aim of the study was to observe whether our exit-site cleansing and dressing method, which involves the application of silver-releasing dressings, is associated with a reduction in the incidence of exit-site infections compared to the data reported in the literature.

Methods

To deal with bacterial resistance close attention has been paid to Ag-based compounds which, in contrast to many antibiotics do not give significant rise to microorganism resistance [19].

In a case-control study to evaluate the beneficial effects of silver dressing on the healing of wounds with ulcers and on the control of infections in burn patients, silver dressing rapidly, easily, and safely resisted wound bacteria, promotes wound healing, and shortens recovery time [20].

From data collected in the literature, in the Peritoneal Dialysis DH of the AOU Federico II, exit-site medications with Exit-Pad silver ion-releasing one Ag began in 2016. From July 2021 we began collecting data on the incidence of exit-site infections.

We therefore enrolled 51 patients belonging to the Peritoneal Dialysis DH of the AOU Federico II of Naples in the period between July 2021 and September 2023. Some patients are present for more than a year but are included in the total count only once.

This study was conducted in accordance with the standards of the *International Conference on Harmonization-Good Clinical Practice* and with the *Declaration of Helsinki*.

The study was approved by the Institutional Ethical Committee of Federico II Hospital (Protocol n. 93/2023).

No sponsor was involved in the study design, recruitment, and data analysis phases.

Patients were included in the study only after signing the Informed Consent. This consent could be withdrawn at any time during the study and for any reason and had no effect on the clinical management of the participants.

For all the patients followed, a dressing protocol was used which included cleansing the exit site every other day and every time they used the shower with a sequence that included: hydrogen peroxide solution, povidone-iodine and Amuchina 0.05%; followed by application of a silver-releasing dressing on the catheter emergency (Exit-Pad Ag). Sterile gauze and skin emergency kits were used to complete the dressing. Each patient was asked to pay attention to the hygiene practices to be respected (hand cleansing, use of a mask to cover the nose and mouth, doors and windows closed, absence of pets in the room) and to check whether at the exit site and in the surrounding area there were any signs of redness, edema or discharge. Furthermore, each patient applied an ostomy bag to the area surrounding the exit site during the shower. For each patient in whom signs of redness, edema, or secretion were found, a culture swab was performed in the emergency of the catheter and empirical topical therapy was instituted; following a positive culture, antibiotic therapy was initiated according to the susceptibility test.

As further proof of the possible usefulness of the Exit Pad Ag, the incidence rates obtained were then compared with the incidence rates of exit-site infections of the 62 patients followed at the Peritoneal Dialysis DH of the AOU Federico II in the two-year period 2014-2015, during which the same cleansing and dressing protocol, but without the use of Exit Pad Ag.

Patients experiencing one of the following conditions were allowed to leave the study: 1) use of other dressing

techniques; 2) pregnancy; 3) switch to hemodialysis; 4) renal transplant.

Inclusion criteria

The inclusion criteria for this study were:

- Adult subjects (> 18 years)
- Implantation of the Tenckhoff-type catheter for at least 3 months
- Signing of the Informed Consent

Socio-demographic data (sex, age, smoking, weight, height, dialysis age, residual urinary volume, kt/v, and laboratory tests) (Table 1) and details of the clinical and pharmacological history were collected at the beginning of the study.

The characteristics of the dialysate and the state of the exit site, in relation to the ISPD 2005 classification⁹ (Table 2), were assessed at every single visit (every month).

Statistic analysis

Baseline characteristics were summarized as number (percentage) or mean \pm standard deviation. All analyses were performed using Microsoft Excel ver. 2016.

Results

Table 3 shows the data for the two-year period 2014-2015 with the relative incidences of exit-site infection (episodes/year). 2 cases of refractory infection resolved after 2 months

Table 1: Socio-demographic data.

N° Patients	51
Woman/Man	28/23
Smoking (yes/no)	20/31
Average age (years)	57.5 \pm 7.3
Dialysis age (months)	55.2 \pm 21.4
Dialysis method (APD/CAPD)	22/29
Residual urinary volume (ml/24h)	1200 \pm 350
KT/V	2.1 \pm 0.73
nPCR (g/kg/day)	0.8 \pm 0.2
Total protein (g/dl)	6.6 \pm 0.6
Albuminemia (g/dl)	3.7 \pm 0.3
Total cholesterol (mg/dl)	159.2 \pm 34.7
Triglyceridemia (mg/dl)	153.8 \pm 78.6
Hb (g/dl)	11.4 \pm 1.4
Vit. D (ng/ml)	16 \pm 6
Calcemia (mg/dl)	9 \pm 0.8
Phosphoremia (mg/dl)	5.5 \pm 1.1

Table 2: Exit-site scores.

	0 points	1 point	2 points
Edema	No	< 0.5 cm	> 0.5 cm
Crust	No	< 0.5 cm	> 0.5 cm
Redness	No	< 0.5 cm	> 0.5 cm
Ache	No	Mild	Severe
Secretion	No	Serous	Purulent

of therapy and 1 case of refractory infection resolved after 2 months of therapy.

Table 4 shows the data from July 2021 to September 2023 with the related incidences of exit-site infection (episodes/year). 2 cases of refractory infection resolved after 2 months of therapy for one patient and after surgical externalization of the cuff for the second patient. 1 refractory infection resolved after 3 months of therapy.

The average incidence (0.23) is lower than the target suggested by the ISPD (0.4 infections/year/patient) and the average estimated in the USA (0.5-0.6 infections/year/patient).

The average incidence from 2021 to 2023, equal to 0.24 episodes/year/patient, is therefore lower than the incidence of 2014-2015 (0.38 episodes/year/patient), a two-year period in which we did not use dressings with silver Exit-Pad.

Discussion

Peritoneal dialysis is an effective renal replacement therapy technique that offers numerous potential advantages to patients undergoing this treatment compared to hemodialysis, including a simpler technique, greater feasibility of use in remote communities, generally lower costs, less need for trained personnel, fewer management challenges during natural disasters, possibly better survival in the early years, greater ability to travel, fewer dietary restrictions, better preservation of residual renal function, greater satisfaction with treatment, better quality of life, outcomes better after subsequent kidney transplant, delayed need for vascular access (especially in children), reduced need for erythropoiesis-stimulating agents, and lower risk of blood-borne viral infections and SARS-CoV-2 infection [21].

For these numerous advantages listed, it is therefore important to prolong dialysis treatment using DP for as long as possible. One of the critical points for the success of a Peritoneal Dialysis program is the care of the peritoneal catheter and the exit site; in fact, approximately 20% of patients on Peritoneal Dialysis are permanently transferred to hemodialysis due to problems related to the catheter and/or the exit site [2]. Adequate hygiene standards and the use of appropriate dressings can help reduce the risk of developing such infections.

Therefore, numerous strategies have been implemented to reduce the risk of infections, using different dressing systems and types of topical antibiotics, but to date, no unanimous opinions have been found on their use and effectiveness.

In recent years, various techniques have been studied in the surgical field to accelerate wound healing and reduce the risk of infections by combating antibiotic resistance.

Table 3: Results of infections between 2014-2015.

Year	N° Patients	Catheter days	N° Infections	Incidence (episodes/year)	Refractory Infections	Recurrent Infections	Repeated Infections
2014	54	17340	16	0.34	2	0	0
2015	61	21600	25	0.42	1	0	0
overall	62	33940	41	0.38	3	0	0

Table 4: Results of infections between July 2021 and September 2023.

Year	N° Patients	Catheter days	N° Infections	Incidence (episodes/year)	Refractory Infections	Recurrent Infections	Repeated Infections
2021	31	5153	3	0.21	1	0	0
2022	40	12534	8	0.23	2	0	0
2023	41	9983	7	0.26	1	0	0
overall	51	27670	18	0.24	4	0	0

In particular, in a study conducted on burn patients, it was shown that: 1) Silver per se, as a metal, can hardly be absorbed by bacteria, but it can be ionized into the active form by wound secretions to bind cell membrane and proteins; 2) by interacting with sulfhydryl groups in the respiratory enzymes of microorganisms such as bacteria, silver is able to undermine the functions of these enzymes and some DNAs; 3) Silver preferentially inhibits the replication of bacterial DNAs by binding their bases [20,22]. As such, it has been hypothesized that Ag(I) has the ability to act in a multimodal manner where if a resistance mechanism is developed, the metal ion can still elicit its antibacterial effect in other ways [23].

Treatment of either *Staphylococcus aureus* or *E. coli* with 0.2 ppm silver nitrate led to the observation by transmission electron microscopy (TEM) that the cytoplasm of both shrank and separated from the 'cell wall' [24]. This degradation and the subsequent liberation of cellular contents into the extracellular space resulted in cell death.

Destabilization and increased permeability of the cell membrane were observed in *E. coli* treated with silver nitrate, resulting from increased ROS generation [25]. Co-administration of silver and existing antibiotics increased the efficacy of the antibiotic towards the bacteria. This effect was rationalized as resulting from the synergistic effect of silver ions increasing cell permeability, allowing easier passage of the antibiotic [22].

Some evidence exists to suggest that the binding of silver to nucleic acids may be important in its toxicity to bacteria—when *P. aeruginosa* was treated with sublethal SSD, ~15% of silver ions were associated with DNA or RNA [26].

Meanwhile, treatment of either *S. aureus* or *E. coli* with silver nanoparticles led to condensation of the DNA and inhibition of replication [27].

It has been observed that silver interacts with proteins and amino acids, inhibiting their function, reducing bacterial growth, the expression of toxins, and the formation of biofilms [28,29].

Based on this evidence, the Peritoneal Dialysis clinic of

the AOU Federico II has decided since 2016 to adopt silver-based dressings to be applied on the exit site to reduce the risk of infection.

Recently, silver-based dressings have been increasingly used in various fields to prevent infections. In a study by J Li, silver ion dressing was used for patients with severe burns in the maintenance of central venous catheters inserted through wounds with reduced rates of central venous catheter-related infections and extended catheter days [30]. Takayuki Suzuki demonstrated that patients who were treated with a device-based silver-mixed port had a significantly lower totally implantable venous access ports (TIVAP)-related infection rate than patients without silver-mixed devices [31]. Martin Oliverius used a new silver dressing, StopBac, to prevent surgical site infections (SSI) in 32 patients after abdominal surgery confirming its suitability for both surgical wounds in patients after major abdominal surgery and for potentially infected surgical wounds [32].

Katia Monteverdi analyzed the macroscopic effect of the silver-based dressing on the cannulation site of the A-V fistula with "button hole" in hemodialysis patients. The macrophotographic analysis revealed a reduction in the signs of local inflammation at the cannulation site using a bandage containing silver, probably due to the reduction in the bacterial load [33].

An advanced dressing that has a controlled antibacterial action, such as the Exit-Pad silver ion-releasing one Ag, has been used in hemodialysis recently. Several studies have demonstrated the effectiveness of applying Exit-Pad Ag to the CVC in reducing the incidence of inflammation and related skin damage [34,35]. The Exit-Pad Ag has also been shown to have a role in the reduction of erythema and crusts and in the improvement of clinical signs on frankly infected exit sites, even in the absence of systemic antibiotic therapy [36,37] furthermore, no phenomena of allergic reaction or intolerance to the product were found [36].

Furthermore, although past studies have not demonstrated a real advantage in using a silver ring device (designed by Grosse-Siestrup in 1992) mounted on the PD catheter and positioned on the exit site at the skin level in

preventing infections [15,16], in recent studies it has emerged that the correct use of the Exit-Pad Ag could be a further valid tool to prevent exit-site infections [17], to improve the skin emergency in those patients who present an inflammatory symptomatology, but who, not having a positive result on the culture swab, are not undergoing antibiotic therapy [38] and, by ensuring the maintenance of the correct moist gradient in the lesion bed, to promote faster tissue repair and allows the resolution of some cases of exit-site infections, with a favorable cost-benefit, also allowing for greater patient well-being [39]. In another study, Bonesso Cristina presents a clinical case of a patient on Peritoneal Dialysis with recurrent and difficult-to-treat exit-site infections. The application of the Exit-Pad Ag antiseptic silver ion dressing favored the healing of the Tenckoff catheter emergency and made it possible to avoid the removal and replacement of the peritoneal catheter [40].

Furthermore, the Exit-Pad silver dressing stimulates the healing of a new exit site and avoids maceration by absorbing secretions and keeping the sinus dry [18].

From the analysis of the results collected dal 2021 in this observational evaluation conducted by the Nephrology Center of the AOU Federico II of Naples, an average incidence of 0.23 infections/year/patient emerged. Both the average incidence and the incidences calculated for each year proved to be lower than the new target of 0.4 suggested by the ISPD [3]. The average incidence of infections recorded at our Center (0.23 infections/year/patient) however, was found to be lower than the data estimated in the USA (0.53-0.6 episodes per year) [4].

Furthermore, our average incidence from 2021 to 2023 was still lower than the incidence of the two-year period 2014-2015 in which the same exit-site cleansing and dressing method was applied, without however using the Exit-Pad Ag.

In accordance with the literature and with data from our center, it has therefore emerged that the correct use of an advanced dressing that has a controlled antibacterial action, such as the Exit-Pad Ag, is associated with an annual rate being lower than the target value (0.4).

A limitation of this study, which may become the subject of future work, is that it does not have a control group in the two-year period 2021-2023 that did not use silver dressings for the exit site.

Conclusion

This study, being purely descriptive, does not allow us to draw conclusions from an inferential point of view. In fact, due to the limited sample size and the number of events lower than expected, we cannot extend the results from the sample to the population. However, the present exploratory results allow us to lay the foundations for the design of a

prospective study aimed at confirming the differences found with adequate power and size.

Anyway, although the use of adequate hygiene standards helps to prevent any exit-site infections, the use of the Exit-site Pad Ag is associated with an incidence rate lower than the target value, helping to improve the effectiveness of PD and reducing the transition to hemodialysis.

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