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Original article

Clinical outcomes of home parenteral nutrition patients using taurolidine as catheter lock: A long-term cohort study

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SUMMARY

Background & aims: Central venous access device (CVAD)-related complications, such as central-line associated bloodstream infections (CLABSIs), CVAD-related venous thromboses (CRVTs) and −occlusions frequently occur in home parenteral nutrition (HPN) patients. A preventive strategy to decrease the incidence of CLABSIs is the use of CVAD lock solutions, such as 2% taurolidine. The aim of this study was to evaluate long-term clinical outcomes of our HPN cohort while using taurolidine as lock solution. In addition, we explored risk factors associated with CVAD-related complications.

Methods: We conducted a retrospective analysis of complications (CLABSIs, CRVTs and CVAD occlusions) and adverse events in adult HPN patients while using taurolidine as lock solution. Patients with a benign underlying disease leading to intestinal failure were included between 2006 and 2017 at our tertiary referral centre for intestinal failure. Primary outcome was the effectiveness of taurolidine, as described by complication incidence rates. Secondary objectives were to assess adverse events of taurolidine, complication rates of patients who subsequently discontinued taurolidine and started using 0.9% saline alternatively, and risk factors associated with complications.

Results: In total, 270 HPN patients used taurolidine during 338521 catheter days. CLABSIs, CRVTs and CVAD occlusions occurred at a rate of 0.60 (CI95% 0.52−0.69), 0.28 (CI95% 0.23−0.34), and 0.12 (CI95% 0.08−0.16) events per 1000 catheter days, respectively. In 24 (9%) patients, mild to moderate adverse events resulted in discontinuation of 2% taurolidine. A subsequent switch to 0.9% saline resulted in an increased CLABSI rate (adjusted rate ratio 4.01 (95%CI 1.23−13.04), P = 0.02). Several risk factors were identified for CLABSIs (a lower age, nontunneled catheters, infusion frequency), CRVTs (site of vein insertion), and CVAD occlusions (type of CVAD).

Conclusion: Complication rates remained low in the long-term, and use of taurolidine was generally safe. The identified risk factors may help to create new strategies to further prevent CVAD-related complications and improve HPN care in the future.

1. Introduction

Intestinal failure (IF) patients mostly depend on life-long treatment with home parenteral nutrition (HPN) and/or fluids. This is a complex time-consuming therapeutic strategy where −preferably− expert centres train patients and/or their caregivers to manage central venous access devices (CVADs) and infusion devices at home [1]. Life-threatening CVAD-related complications frequently occur and apart from the underlying condition leading to IF, central line-associated bloodstream infections (CLABSIs) are the foremost threat to CVAD- and patient survival [2,3]. Therefore, prevention of CLABSIs is crucial to maintain venous access and to

Abbreviations: CI, confidence interval; CLABSI, central line-associated bloodstream infection; CRVT, central venous access device-related venous thrombosis; CTCAE, common terminology criteria for adverse events; CVAD, central venous access device; HPN, home parenteral nutrition; IF, intestinal failure; NA, not applicable.

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avoid hospitalizations. Both HPN-patients and –experts have independently categorized the incidence of CLABSIs as the most important outcome indicator for the quality of HPN care [4].

The key strategy to prevent CLABSIs is strict adherence to antiseptic protocols when managing CVADs. An additional preventive strategy is the use of CVAD lock solutions. Already since the 1970s, the antimicrobial agent taurolidine has been used as a local agent to treat bacterial peritonitis, yet its effectiveness to prevent CLABSIs as a CVAD lock solution was discovered only recently [5–8]. Taurolidine inhibits the microbial adhesion to the endoluminal catheter surface and destroys microbial cell membranes and toxins [9–12]. Clinical experience with taurolidine in our own tertiary IF referral centre started in 2006, when 2% taurolidine was investigated in an open-label randomized trial [6]. Here, taurolidine significantly decreased CLABSI rates, when compared to the –at that time– most often used lock solution (low-dose heparin (150 U/mL)). Later, we compared the effects of these lock solutions in a retrospective cohort study in 212 HPN-patients who had used heparin (from 2000 to 2008) or 2% taurolidine (from 2008 to 2011) [7]. The observed CLABSI incidence rates were 3.14 and 0.60 per 1000 catheter days for heparin and taurolidine, respectively. A similar difference between these lock solutions was recently confirmed in a double-blind randomised trial [8].

Despite its efficacy to prevent CLABSIs in HPN patients, there is still limited experience with taurolidine in the real-world HPN setting, and long-term clinical outcomes of CVAD-related complications and taurolidine-related adverse events are lacking. Furthermore, several potential risk factors for CVAD-related complications in HPN populations have been suggested in studies that were of limited methodological quality, and none of these studies was performed in sufficiently robust cohorts of HPN patients against a background of taurolidine as lock solution [13–20].

Therefore, the aim of this study was to evaluate CVAD-related outcomes in our HPN patient cohort who used taurolidine as lock solution over the last decade. Secondary objectives were to report on patients having adverse events when using taurolidine, and their subsequent outcomes when starting 0.9% saline as alternative. Finally, we explored patient–, HPN– and CVAD-related risk factors associated with CVAD-related complications to provide a background for future studies on complication prevention in this vulnerable population.

2. Methods

2.1. Patients

Patients were selected from the Nijmegen IF Registry, a retrospective single-centre web-based database, comprising adult IF patients who have been under treatment at our tertiary referral centre for IF since 1976 [21]. In the present study, all adult patients (≥18 years) with a benign underlying disease leading to intestinal failure between 2006 and 2017 were included. From 2006, HPN-patients in our centre started to switch from low dose heparin to 2% taurolidine (Taurosept, Geistlich Pharma AG Wolhusen, Switzerland) as the standard CVAD lock solution as part of the mentioned single-centre study, before in 2008 all patients switched to 2% taurolidine [6]. Patients had to receive ≥1 month ≥ 2 bags per week of nutrition and/or fluids (saline and/or glucose) via a CVAD, such as a nontunnelled catheter (e.g. peripherally inserted central venous catheter), a subcutaneously tunneled central venous catheter, or a subcutaneous port system. Only newly inserted CVADs locked with taurolidine or 0.9% saline solution were included in the analyses to exclude any carry-over effect from other previously used lock solutions in the same CVAD. Patients having intra-abdominal desmoid or neuroendocrine tumours as underlying disease were included in the analyses due to the chronic nature of their disease [22]. Patients who used arteriovenous fistulae to administer parenteral nutrition were excluded for the time period they used this venous route, as these patients do not use a CVAD lock solution, and because inclusion of arteriovenous fistulae might result in an underestimation of CLABSI incidence [23].

2.2. Data collection

The following data were used from the Nijmegen IF Registry: patient characteristics (sex, age, pathophysiological mechanism of intestinal failure, underlying disease, medical history), medication (immunosuppressants, anticoagulants and opiates), CVAD characteristics (type, date of insertion and removal, reason for removal, vein used for CVAD insertion), HPN characteristics (type, number of infusions per week), and type of CVAD-related complications (CLABSIs, CVAD-related venous thromboses (CRVTs), and CVAD occlusions).

2.3. CVAD training and management

Before start of HPN-treatment, patients were trained in aseptic CVAD handling and HPN/fluid administration by specialized nurses during a training period of 1–2 weeks in our referral centre. This training has been implemented according to a standardized protocol and is in line with recent ESPEN guidelines [1]. A detailed explanation of the CVAD care protocol can be found elsewhere [7]. Patients received HPN/fluid administration via home community nurses in case a patient was unable to be trained. None of our technical procedures changed during the study period. CVAD management was performed against a background setting where almost exclusively olive oil-based parenteral nutrition formulations (Baxter International Inc. Illinois, USA) were used.

After each parenteral nutrition or fluid administration, the CVAD was flushed with 10 mL sterile physiological saline solution. Subsequently, approximately 5 mL 2% taurolidine was instilled into the CVAD until the next parenteral nutrition and/or fluid administration. Taurolidine dwell time differed per patient and depended on the number of infusions per week. Taurolidine was flushed into the patient before each infusion, in order to reduce CVAD handling and to minimize the potential risk for blood clots and/or endoluminal biofilm formation when withdrawing taurolidine.

Two type of CVADs were used foremostly: the Hickman catheter (C. R. Bard, Inc. New Jersey, USA), a subcutaneously tunneled catheter, preferably single-lumen inserted in the right-sided jugular or subclavian vein, or an implantable subcutaneous port system consisting of a metal compartment covered by a membrane, with an attached catheter. Nontunneled catheters and peripherally inserted catheters were almost exclusively used for short-term periods (days–weeks) due to a potentially increased risk for CVAD-related complications [1,24]. Usually, peripherally inserted catheters had been placed in peripheral centres before patient referral. After each CVAD insertion, a standard chest X-ray was performed to detect potential procedure-related complications and in order to ensure the correct placement and position of the CVAD tip at the junction of the superior vena cava and the right atrium.

2.4. Outcomes and definitions

Primary objective was to determine the effectiveness of taurolidine as CVAD lock solution, as described by the incidence rate of CVAD-related complications (CLABSIs, CRVTs, CVAD occlusions) over the last decade. Secondary objectives were to assess patient-reported adverse events, CVAD-related complication rates of patients who discontinued taurolidine and started using 0.9% saline

alternatively, and risk factors for CVAD-related complications in patients using taurolidine as lock solution.

The definition of a CLABSI was based on the current Centers for Disease Control and Prevention (CDC) guidelines for surveillance of bloodstream infections [25,26]. A CLABSI episode required the following conditions [1]: presence of a systemic infection or sepsis (such as fever, hypotension and/or chills) [2], a recognized pathogen cultured from one or more blood cultures [3], the cultured pathogen is not related to an infection at another site, and [4] in case of a cultured common commensal (e.g coagulase-negative *Staphylococcus* species), at least two positive blood cultures had to be positive from the CVAD and/or peripheral vein. A symptomatic CRVT was defined as a vascular thrombosis of a vein along the tract or the tip of the CVAD. A diagnosis was based on clinical symptoms suggestive for a CRVT (e.g. edema, venous distension and swelling) with or without the use of a diagnostic modality (e.g. duplex ultrasound or a computed tomography scan). A CVAD occlusion was defined as a complete obstruction of the CVAD lumen (e.g. failure to flush or aspirate, or the inability to infuse into the CVAD). Use of anticoagulants was defined as >50% of catheter days on anti thrombotic drugs. Use of immunosuppressants was defined as >50% of catheter days on systemic non-chemotherapeutic drugs that suppress or reduce the strength of the body's immune system. Use of opiates was defined as >50% of catheter days on drugs containing opium or its derivatives.

2.5. Adverse events

Patient-reported adverse events resulting in discontinuation of the use of 2% taurolidine were graded independently by two investigators (YW and MG) according to the common terminology criteria for adverse events (CTCAE version 4.0) [27]. A third investigator judged in case consensus was lacking (GW). The CTCAE categorizes the severity of an adverse event in grades from 1 to 5 with a clinical description per grade. In general, grade 1 is mild (asymptomatic or mild symptoms), grade 2 is moderate (minimal, local or noninvasive intervention indicated), grade 3 is severe (medically significant, but not immediately life-threatening), grade 4 is life-threatening, and grade 5 is death related to the adverse event. If possible, patients with an adverse event switched first to another taurolidine-containing solution (1.35% taurolidine with 4% citrate; TauroLock, TauroPharm GmbH Waldbüttelbrunn, Germany). In case of repeated adverse events, the use of taurolidine was discontinued and generally 0.9% saline solution was subsequently used.

2.6. Ethical statement

The research ethics committee of the Radboudumc in Nijmegen, the Netherlands, approved the use of the Nijmegen IF Registry (reference number 2015-1890). Formal informed consent was waived by the ethical committee as no identifying patient data were collected and all data were anonymously entered in the database. This study was conducted in accordance with good clinical practice guidelines and the code of conduct for medical research [28]. The STROBE guidelines were followed to report this study [29].

2.7. Statistical analysis

Baseline characteristics were summarized using descriptive statistical methods. Continuous variables were presented as means with standard deviations or medians and interquartile ranges (IQR) if not normally distributed. CVAD-related complication rates were expressed as the number of complications per 1000 catheter days with 95% confidence intervals (CI). Time-to-event endpoints were calculated with Kaplan–Meier analyses in patients who started HPN between 2006 and 2017. Adverse events were summarized using descriptive statistical methods. Comparisons between taurolidine and saline CVADs were made with the use of a random effect Poisson regression analysis with patient as level and catheter days as offset (after correction for statistically significant different baseline characteristics, or a change of $\geq$10% on unadjusted estimates by a covariate). Risk factors for CVAD-related complications were identified with the use of random effect Poisson regression analysis. Potential risk factors included sex, age at start CVAD, pathological mechanism of intestinal failure, diabetes, CVAD training, HPN experience, type of CVAD, vein used for CVAD insertion, type (nutrition or fluids) and frequency of parenteral support, and use of anticoagulants, immunosuppressants or opiates. Risk factors which showed in the univariable Poisson regression analysis a P value of $\leq$0.10 were included in the final multivariable Poisson regression analysis. Missing data were excluded from analyses. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS statistical software package version 22.0 (SPSS Inc., Chicago, IL), or R software version 3.2.4 (The R Foundation for Statistical Computing) for the Poisson regression analyses.

3. Results

3.1. Demographics

Between 2006 and 2017, a total of 757 newly inserted CVADs were locked with taurolidine for 338521 catheter days in 270 HPN patients. Baseline characteristics of both patients and CVADs are shown in Table 1. In total, 244 (90%) patients or caregivers were trained to administer HPN, and 26 (10%) received HPN via home community nurses. The median number of CVADs per patient was two (range 1–19), and the median CVAD survival was 206 days (range 1–4058). The latter varied for tunneled catheters, subcutaneous port systems, nontunneled catheters and peripherally inserted catheters from 206 days (range 1–4058), to 399 (range 5–3112), 9 (range 2–218), and 70 days (range 5–645), respectively. Reasons for CVAD removal are shown in Appendix Table 1.

3.2. CVAD-related complications

The patient's underlying diseases and CVAD characteristics in relation to unadjusted complication rates are shown in Table 2. In total, 203 CLABSIs occurred in 163 CVADs of 105 patients, resulting in 0.60 CLABSIs/1000 catheter days (CI95% 0.52–0.69). The cumulative proportion of CLABSI-free patients after ten years was 56% (Appendix Fig. 1A). In 131 CVADs (104 tunneled catheters, 20 subcutaneous port systems, 6 nontunneled catheters and 1 peripherally inserted catheter), a CLABSI was the reason for CVAD removal. The microorganisms causing CLABSIs are shown in Appendix Table 2. In total, 137 monobacterial bloodstream infections occurred, of which 101 (74%) were caused by Gram-positive bacteria. The most commonly isolated microorganisms were *Staphylococcus* species, such as *Staphylococcus epidermidis* (n = 34) and *Staphylococcus aureus* (n = 41). In 36 (18%) cases, a polybacterial bloodstream infection occurred, in 12 (6%) an isolated fungemia and in the remaining 18 (9%) cases mixed bloodstream infections of bacteria and fungi occurred.

Ninety-five CRVTs occurred in 91 CVADs of 67 patients, resulting in 0.28 CRVTs/1000 catheter days (CI95% 0.23–0.34). The cumulative proportion of CRVT-free patients was 66% after ten years (Appendix Fig. 1B). In 53 CVADs (41 tunneled catheters and 12

Table 1
Baseline patient– and central venous access device characteristics of patients using taurolidine and saline locks.

	Taurolidine	Saline	P value
Patient characteristics	n = 270	n = 10	
Female — no. of patients (%)	193 (72)	10 (100)	0.16
Pathological mechanism — no. (%)			
Short bowel syndrome	117 (43)	3 (30)	0.33
Gastrointestinal motility disorder	95 (35)	7 (70)	
Mechanical obstruction	13 (5)	0 (0)	
Extensive small bowel mucosal disease	19 (7)	0 (0)	
Intestinal fistula	16 (6)	0 (0)	
Other	10 (4)	0 (0)	
Medical history — no. of patients (%)			
Diabetes	23 (9)	0 (0)	0.61
CVAD characteristics	**n = 757**	**n = 27**	
Age at start CVAD — mean years (±SD)	52 (16)	49 (10)	0.29
HPN experience at start CVAD — median years (IQR)	1.5 (0.1–4.0)	5.3 (1.9–7.3)	0.006
Type of venous access device — no. of CVADs (%)			
Tunneled catheter	543 (72)	17 (63)	0.68
Subcutaneous port system	160 (21)	8 (30)	
Nontunneled catheter	46 (6)	2 (7)	
Peripherally inserted catheter	8 (1)	0 (0)	
Site of insertion — no. of CVADs (%)			
Jugular vein	435 (58)	12 (44)	0.001
Subclavian vein	155 (21)	3 (11)	
Femoral vein	94 (12)	10 (37)	
Other	19 (3)	2 (7)	
Unknown	54 (7)	0 (0)	
Type of infusion — no. of CVADs (%)			
Nutrition	640 (85)	23 (85)	0.74
Fluids	88 (12)	4 (15)	
Unknown	29 (4)	0 (0)	
Infusions — no. per week			
2	18 (2)	0 (0)	0.60
3	32 (4)	2 (7)	
4	48 (6)	3 (11)	
5	56 (7)	0 (0)	
6	42 (6)	1 (4)	
7	533 (70)	21 (78)	
Unknown	28 (4)	0 (0)	
Drugs — no. of CVADs (%)			
Anticoagulants[a]	441 (58)	15 (56)	0.89
Unknown	12 (2)	0 (0)	
Immunosuppressants[b]	154 (20)	4 (15)	0.80
Unknown	11 (2)	0 (0)	
Opiates[c]	307 (41)	5 (19)	0.02
Unknown	18 (2)	0 (0)	

CVAD; central venous access device, HPN; home parenteral nutrition, IQR; inter-quartile range, SD; standard deviation.
Note that patients may have had multiple (taurolidine or saline) CVADs and may have been included in both the taurolidine and saline group. Only patients with newly inserted CVADs with taurolidine and/or saline were included. Age at start CVAD was compared using the independent *t*-test. HPN experience was compared using the Mann–Whitney-*U* test. All other characteristics were compared using the Chi-square test.
[a] Anticoagulants comprise anti thrombotic drugs, such as acetylsalicylic acid, phenprocoumon, and warfarin.
[b] Immunosuppressants comprise systemic non-chemotherapeutic drugs that suppress or reduce the strength of the body's immune system, for example, adalimumab, methotrexate, or prednisolone.
[c] Opiates comprise drugs containing opium or its derivatives, such as codeine, tramadol, or oxycodone.

subcutaneous port systems), a CRVT was the reason for CVAD removal.

In total, 99 CVAD occlusions occurred in 31 CVADs of 27 patients, resulting in 0.12 CVAD occlusions/1000 catheter days (CI95% 0.08–0.16). The cumulative proportion of CVAD occlusion-free patients after ten years was 85% (Appendix Fig. 1C). In 10 CVADs (5 tunneled catheters, 4 subcutaneous port systems, and 1 peripherally inserted catheter), a CVAD occlusion was the reason for CVAD removal.

When combining all CVAD-related complications, a total of 337 complications occurred in 257 CVADs of 131 patients, resulting in 1.00 CVAD-related complication/1000 catheter days (CI95% 0.89–1.11). In 195 CVADs (150 tunneled catheters, 36 subcutaneous port systems, 6 nontunneled catheters and 2 peripherally inserted catheters), a CLABSI, CRVT or CVAD occlusion was the reason for CVAD removal. The cumulative proportion of CVAD-related complication-free patients after ten years was 38% (Appendix Fig. 1D).

3.3. Adverse events

In 24 (9%) patients an adverse events resulted in discontinuation of the use of 2% taurolidine (Fig. 1). The median time to an adverse event was 596 days (IQR 281–1853). Only one patient experienced directly an adverse reaction (grade 2) at start of taurolidine use. Fourteen (58%) patients experienced symptoms directly after instillation of taurolidine, nine (38%) at start of infusion of nutrition/fluids, and two (8%) during the infusion time of nutrition/fluids. Symptoms varied from mild to severe complaints, but no life-threatening events occurred. Two of three patients with a grade 3 adverse event had a moderate anaphylactic-like reaction.

Table 2
Patient's underlying diseases and venous access device characteristics in relation to (unadjusted) catheter-related complication rates.[a]

Patient or CVAD characteristic	CLABSI rate (95%CI)[b]	CRVT rate (95%CI)[b]	CVAD occlusion rate (95%CI)[b]
All Patients	0.60 (0.52–0.69)	0.28 (0.23–0.34)	0.12 (0.08–0.16)
Female	0.61 (0.52–0.72)	0.28 (0.22–0.35)	0.13 (0.09–0.18)
Male	0.57 (0.43–0.73)	0.28 (0.18–0.40)	0.09 (0.04–0.16)
Short bowel syndrome	0.44 (0.35–0.55)	0.29 (0.21–0.37)	0.14 (0.09–0.20)
Crohn's disease	0.36 (0.23–0.53)	0.26 (0.15–0.41)	0.18 (0.09–0.31)
Mesenteric infarction	0.37 (0.24–0.54)	0.28 (0.17–0.43)	0.16 (0.08–0.27)
Surgical complications	0.50 (0.23–0.92)	0.31 (0.11–0.67)	0.25 (0.08–0.58)
Radiation enteritis	0.43 (0.15–0.93)	0.43 (0.15–0.93)	0 (0–0)
Other	0.79 (0.49–1.19)	0.28 (0.12–0.53)	0 (0–0)
Intestinal dysmotility	0.83 (0.67–1.00)	0.25 (0.17–0.35)	0.09 (0.05–0.16)
Primary/idiopathic	0.83 (0.64–1.05)	0.24 (0.15–0.37)	0.11 (0.05–0.20)
Secondary	0.82 (0.58–1.12)	0.27 (0.15–0.46)	0.07 (0.02–0.18)
Intestinal fistulae	1.71 (0.92–2.87)	0.14 (0.01–0.63)	0.29 (0.05–0.88)
Iatrogenic	3.16 (1.58–5.54)	0.32 (0.02–1.39)	0.63 (0.10–1.95)
Non-iatrogenic	0.52 (0.09–1.61)	0 (0–0)	0 (0–0)
Extensive small bowel mucosal disease	0.32 (0.11–0.68)	0.32 (0.11–0.68)	0 (0–0)
Mechanical obstruction	0.45 (0.16–0.97)	0.36 (0.11–0.84)	0 (0–0)
Diabetes	1.20 (0.78–1.75)	0.40 (0.18–0.74)	0.20 (0.06–0.46)
No diabetes	0.56 (0.48–0.65)	0.27 (0.22–0.33)	0.11 (0.08–0.15)
Type of CVAD			
Tunneled catheter	0.70 (0.60–0.81)	0.31 (0.24–0.38)	0.06 (0.03–0.10)
Subcutaneous port system	0.30 (0.21–0.42)	0.21 (0.13–0.31)	0.22 (0.14–0.32)
Nontunneled catheter	6.56 (2.61–13.30)	1.09 (0.06–4.81)	2.19 (0.36–6.75)
Peripherally inserted catheter	1.44 (0.24–4.43)	0.72 (0.04–3.16)	0.72 (0.04–3.16)
Site of insertion			
Jugular vein	0.61 (0.51–0.72)	0.25 (0.19–0.32)	0.07 (0.04–0.11)
Subclavian vein	0.56 (0.41–0.75)	0.28 (0.17–0.41)	0.13 (0.07–0.23)
Femoral vein	0.82 (0.51–1.25)	0.65 (0.37–1.04)	0.13 (0.03–0.34)
Type of infusion			
Nutrition	0.59 (0.51–0.69)	0.28 (0.22–0.35)	0.12 (0.09–0.17)
Fluids	0.51 (0.33–0.74)	0.17 (0.08–0.31)	0.06 (0.02–0.16)

CI; confidence interval, CLABSI; central line-associated bloodstream infection, CRVT; CVAD-related venous thrombosis, CVAD; central venous access device.
[a] Note that patient's underlying diseases and their complication rates were unadjusted for possible confounders.
[b] Complication rates are expressed as events per 1000 catheter days.

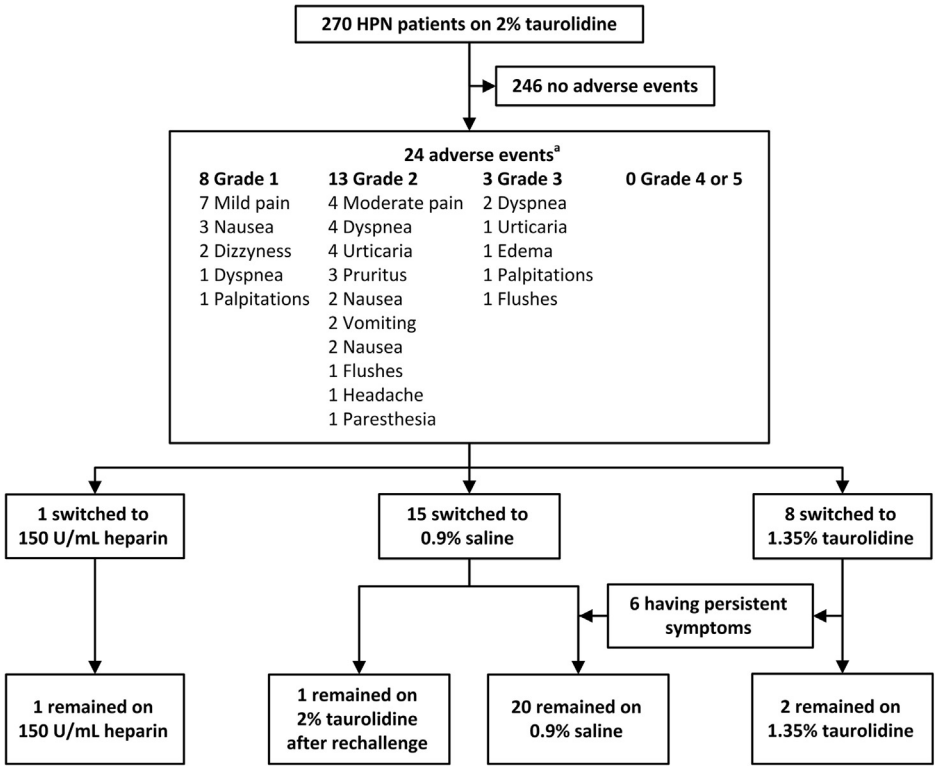

Fig. 1. Patient-reported adverse events for 2% taurolidine. CTCAE; common terminology criteria for adverse events, HPN; home parenteral nutrition. [a] Patients may have had multiple complaints. Patient-reported adverse events which resulted in discontinuation of the use of 2% taurolidine were graded according to the CTCAE version 4.0.(26) Grade 1 is mild (asymptomatic or mild symptoms), grade 2 is moderate (minimal, local or noninvasive intervention indicated), grade 3 is severe (medically significant, not immediately life-threatening), grade 4 is life-threatening, and grade 5 is death related to the adverse event.

3.4. CVAD-related complication rates in patients switching to 0.9% saline

Of the 20 patients who eventually switched to 0.9% saline, ten had one or more newly inserted CVADs locked with 0.9% saline during follow-up. Baseline characteristics of these patients are shown in Table 1. When comparing CVAD-related complication rates of patients on saline with the overall taurolidine population, CLABSI rates were increased by approximately four fold, after adjustment for possible baseline confounders (P = 0.02) (Table 3). Similar observations were made when CVAD-related complication rates were compared within the patients themselves, before and after the switch from taurolidine to saline (Appendix Tables 3 and 4).

3.5. Risk factors associated with CVAD-related complications

In Table 4, results of the multivariable Poisson regression analysis for CVAD-related complications risk factors are shown. A lower age at CVAD start, insertion of nontunneled catheters, and a higher infusion frequency per week were independently associated with a higher risk for CLABSIs.

Risk factor analysis for CRVTs showed that insertion of a CVAD in a left vein (either jugular, subclavian or femoral) was independently associated with a higher risk for CRVTs, when compared with veins on the right side of the body.

Only the type of CVAD was univariably associated with a risk for CVAD occlusions. When compared with tunneled catheters, both subcutaneous port systems and nontunneled catheters showed a higher risk for CVAD occlusions. Nontunneled catheters were associated with a higher risk for CVAD occlusions as well, when compared with subcutaneous port systems.

4. Discussion

This is by far the largest study to date describing the long-term clinical outcomes of HPN patients while using taurolidine as CVAD lock solution. Overall, CVAD-related complication rates remained low and patient-reported adverse events were generally mild to moderate. In addition, several risk factors for CVAD-related complications were found that might spark ideas for preventive strategies.

CLABSIs remain a major threat and may seriously affect the continuity of HPN treatment. The CLABSI rate of 0.60 is relative low in the range of reported reference data (0.25–2.99 CLABSIs per 1000 catheter days) [2,19,30]. The broad range of CLABSI incidence rates in the literature suggests that multiple factors impact on CLABSI outcomes in clinical practice, including underlying conditions of patient populations, clinical experience and practice (e.g. use of different aseptic protocols, materials, and type of CVAD, nutrition and/or lock solution). Different criteria and definitions influence study outcomes as well, which eventually hampers comparisons between studies [31]. Looking at previous outcomes from our own centre, CLABSI rates during the first years of taurolidine use were identical to the overall rate in the present study, suggesting a sustained preventive effect of taurolidine in this regard [7].

In our population, a lower age was associated with a higher risk for CLABSIs. Similar results have been previously found by others, although a recently published large cohort study suggested the opposite [18,32,33]. It may be that younger patients are less compliant when managing CVADs or possibly distracted due to a more active lifestyle. Interestingly, from a caregivers' point of view, Lambe et al. observed in pediatric patients on taurolidine that a lower age of *parents* was a risk factor for CLABSIs as well. A reason for the increase in CLABSI rate found in nontunneled catheters may be extraluminal contamination of the nontunneled catheter, migration of pathogens, and subsequent CLABSIs [24]. Also, a large proportion of patients received their nontunneled catheters while being admitted to the intensive care unit. Thus, patients were likely more fragile. Noteworthy, in contrast to previous studies, we did not find any evidence for an increased risk for CLABSIs in subcutaneous port systems, when compared with tunneled catheters [14,33,34]. Finally, the number of infusions per week was an independent risk factor for CLABSIs, which has been previously shown [14,16,33]. Obviously, an increase in CVAD manipulations increases the risk for contamination of pathogens on the catheter hub, colonization, and subsequent catheter infection. These results exemplify the importance of aseptic catheter care and the necessity to minimize CVAD manipulations at all times.

It remains often difficult to differentiate between CRVTs on one side, and CVAD occlusions (either due to PN components or thrombosis) on another. It is crucial to discriminate, however, since treatment strategies differ between CRVTs (anticoagulants) and CVAD occlusions (flushing, use of sodium hydroxide solution). The reported CRVT incidence ranges from 0.08 to 0.20 per 1000 catheter days, which is lower than the CRVT rate of 0.28 found in the present study [35]. Differences in population characteristics (e.g. number of hypercoagulable patients) or CVADs protocols (e.g. CVAD placement technique) may explain these results [36]. Interestingly, there was a clear association between the site of CVAD insertion and risk for CRVTs. CVADs inserted on the right side (either jugular or subclavian) had a lower risk for CRVTs, when compared with veins on the left side (either jugular, subclavian or femoral). There was, however, no difference in CRVT risk between femoral veins. Similar left-versus-right differences have been reported in other patient populations, but not in HPN patients [37–41]. A likely reason for these differences is the anatomical variation between the venous

Table 3
Incidence of catheter-related complications in patients using taurolidine or saline locks.

	Taurolidine (n = 270)			Saline (n = 10)			Adjusted rate ratio (95%CI)	P value
	Events	Catheter days	Rate (95%CI)	Events	Catheter days	Rate (95%CI)		
CLABSIs	203	338521	0.60 (0.52–0.69)	13	8225	1.58 (0.87–2.60)	4.01[a] (1.23–13.04)	0.02
CRVTs	95	338521	0.28 (0.23–0.34)	2	8225	0.24 (0.04–0.75)	0.95[b] (0.23–4.02)	0.95
CVAD occlusions	39	338521	0.12 (0.08–0.16)	1	8225	0.12 (0.01–0.53)	0.89[c] (0.07–11.06)	0.93

CI; confidence interval, CLABSI; central line-associated bloodstream infection, CRVT; CVAD-related venous thrombosis, CVAD; central venous access device, HPN; home parenteral nutrition.
Note that patients may have had multiple (taurolidine or saline) CVADs. Only newly inserted catheters locked with either taurolidine or saline were included in the analyses to exclude any carry-over effect from previously used lock solutions.
Complication rates are expressed as events per 1000 catheter days. Taurolidine and saline catheters were compared using Poisson regression analysis, in which was corrected at patient level and for possible baseline confounders:
[a] HPN experience, vein used for CVAD insertion, infusion frequency, and use of opiates.
[b] Use of anticoagulants, HPN experience, vein used for CVAD insertion, type of infusion components, and use of opiates.
[c] HPN experience, vein used for CVAD insertion, type of venous access, and use of opiates.

Table 4
Multivariable Poisson regression analysis of factors associated with CVAD-related complications in patients on taurolidine.

Variable		Rate ratio (CI 95%)	P value
CLABSI			
Age at start catheter	Years	0.97 (0.95–0.99)	0.004
Diabetes	Yes	*Reference*	
	No	0.41 (0.16–1.05)	0.06
Type of CVAD	Tunneled catheter	*Reference*	
	Subcutaneous port system	0.68 (0.40–1.15)	0.15
	Nontunneled catheter	2.76 (1.12–6.74)	0.03
	Subcutaneous port system	*Reference*	
	Nontunneled catheter	4.03 (1.47–11.03)	0.007
Infusion frequency	Days per week	1.66 (1.28–2.15)	<0.001
CRVT			
Site of vein insertion (two categories)	Right vein	*Reference*	
	Left vein	3.27 (1.96–5.47)	<0.001
Site of vein insertion (six categories)	Right jugular vein	*Reference*	
	Left jugular vein	3.74 (1.97–7.11)	<0.001
	Left subclavian vein	3.10 (1.39–6.95)	0.006
	Left femoral vein	3.76 (1.40–10.07)	0.008
	Right subclavian vein	0.80 (0.26–2.44)	0.70
	Right femoral vein	1.54 (0.51–4.64)	0.44
	Right subclavian vein	*Reference*	
	Left jugular vein	4.30 (1.43–12.89)	0.009
	Left subclavian vein	3.80 (1.16–12.44)	0.03
	Left femoral vein	4.50 (1.21–16.83)	0.03
	Right femoral vein	1.66 (0.40–6.89)	0.48
	Right femoral vein	*Reference*	
	Left jugular vein	1.52 (0.49–4.68)	0.47
	Left subclavian vein	1.23 (0.36–4.20)	0.75
	Left femoral vein	1.69 (0.51–5.61)	0.40
	Left jugular vein	*Reference*	
	Left subclavian vein	0.84 (0.40–1.79)	0.59
	Left femoral vein	0.97 (0.37–2.60)	0.96
	Left subclavian vein	*Reference*	
	Left femoral vein	1.18 (0.38–3.60)	0.78
Type of CVAD	Tunneled catheter	*Reference*	
	Subcutaneous port system	0.61 (0.32–1.19)	0.15
	Nontunneled catheter	3.71 (0.49–28.22)	0.21
	Subcutaneous port system	*Reference*	
	Nontunneled catheter	4.00 (0.39–41.20)	0.24
Infusion frequency	Days per week	1.21 (0.99–1.48)	0.06
CVAD occlusion[a]			
Type of CVAD	Tunneled catheter	*Reference*	
	Subcutaneous port system	3.34 (1.39–8.01)	<0.001
	Nontunneled catheter	18.46 (3.52–96.71)	<0.001
	Subcutaneous port system	*Reference*	
	Nontunneled catheter	5.52 (1.04–29.34)	0.04

CI; confidence interval, CLABSI; central line-associated bloodstream infection, CRVT; CVAD-related venous thrombosis, CVAD; central venous access device, HPN; home parenteral nutrition, NA; not applicable.
Risk factors were analyzed using a Poisson regression analysis. Potential risk factors for CVAD-related complications in the univariable Poisson regression model included sex, pathological mechanism of intestinal failure, diabetes, age at start CVAD, CVAD training, HPN experience (years from HPN start until start CVAD), vein used for CVAD insertion, type (HPN or fluids) and frequency of infusion, and use of anticoagulants, immunosuppressants or opiates. Only variables with a P value of ≤0.10 in the univariable Poisson regression analysis were included in the final multivariable Poisson regression analysis and are presented in the table.
[a] Type of CVAD was the only univariable covariate with a P value of ≤0.10.

systems of the left and right upper limbs. Although we cannot rule out that the order of CVAD insertion (preferably first right, then left) may have affected results, the results seem consistent between all veins, and previous studies [37–41].

The CVAD occlusion rate of 0.12 per 1000 catheter days was comparable to other HPN patient populations (0.09–0.14) [18,19]. To our knowledge, this is the first study to report an association between the type of CVAD and CVAD occlusions. More specifically, subcutaneous ports were associated with a higher risk for CVAD occlusions when compared with tunneled catheters, possibly due to stasis of infusion components in the metal compartment. A reason for an increased risk of CVAD occlusions in nontunneled catheters may be the material itself, which is less flexible and has a smaller diameter of the catheter lumen. However, other –non measured– factors may play a role as well, such as the composition and amount of lipid infusions or the different type of valves used in these catheters [24,42]. In addition, catheter management of non-tunneled catheters (e.g. continuous HPN/fluid infusion, no flushing) during hospital admission may have influenced outcomes as well.

To date, a small number of studies have reported –mild to moderate– adverse events of taurolidine, such as dysgeusia, paresthesia, pain at infusion, nausea and vomiting [8,43,44]. In this study, a broader range of complaints was observed, and two patients experienced more serious anaphylactic-like reactions. It is considered unlikely that taurolidine itself caused these reactions, as taurolidine degrades into the naturally occurring amino acid taurine, carbon dioxide and water [45]. Side effects have previously been attributed to other constituents than taurolidine, in particular its vehicle polyvinylpyrrolidone [7,46]. Since there was no evidence for a decreased effect of 0.9% saline in preventing CLABSIs during study follow-up, most patients switched to 0.9% saline. A switch was made either because the treating physician considered a

rechallenge with taurolidine as unsafe, but usually it was the patient's preference to discontinue taurolidine. Unfortunately, a switch to saline resulted in an increased CLABSI rate. These observations are in line with a recently published double blinded randomised trial, where HPN patients on 0.9% saline had an increased risk for CLABSIs, when compared with 2% taurolidine [47]. As an effective alternative for taurolidine currently lacks, we suggest to discuss with patients the benefits and risks of discontinuing taurolidine and, if possible, to perform a (blinded) rechallenge in a controlled environment, especially in patients who are considered at risk for recurrent CLABSIs.

A strength of this study is that it contains systematically collected real-world long-term data from a single-centre registry, and comprises by far the largest cohort of patients on taurolidine described to date. In addition, practices on catheter handling, HPN training procedures and the use olive oil-based parenteral nutrition formulations did not change during the observation period and therefore were less likely to bias the results. Finally, with the use of the Nijmegen IF Registry, we were able to analyze a broad range of potential relevant (modifiable) patient−, parenteral nutrition− and CVAD-related risk factors.

Obviously, the retrospective study design has its limitations. Although clinical data was systematically and thoroughly collected, complications still could have been missed. Furthermore, clinically undetectable small blood clots occluding CVADs may have resulted in a overestimation of CVAD occlusions, and vice versa, an underestimation of the CRVT incidence. Finally, despite correction for possibly relevant baseline confounders, there may still be a difference between patients with and without adverse events, and a certain degree of selection in patients reporting adverse events cannot be excluded.

Our centre is unique worldwide by using arteriovenous fistulae in a substantial proportion of HPN patients to minimize vascular access−related complications (in particular bloodstream infections) [23]. The current clinical setting with taurolidine as usual care urged us to plan a new study, where we will reassess the contribution of arteriovenous fistulae.

In conclusion, this study provides an overview of long-term clinical outcomes achieved in a large HPN population while using taurolidine as CVAD lock solution. Overall, CVAD-related complication rates remained low in the long-term and use of taurolidine was generally safe. The identification of risk factors for CLABSIs (lower age, nontunneled catheters, infusion frequency), CRVTs (site of vein insertion), and CVAD occlusions (type of CVAD) may help to create new strategies to further prevent CVAD-related complications and improve HPN care in the future.

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Authors contributions

In alphabetical order. YW conceived and designed the study and produced the protocol. BR, EC and YW acquired the data. BR, HG, WK, and YW analysed the data. YW produced the first complete draft and updated subsequent drafts. BR, EC, GW, HG, WK, and YW interpreted the data, critically revised the manuscript and approved all drafts and the authorship list. GW is guarantor for the study report.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf. GW reports grants from Fresenius Kabi and BBraun Medical outside the submitted work. GW is consultant for Shire.

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Appendix A. Supplementary data

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