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ORIGINAL ARTICLE

EFFECTIVENESS OF ASCORBIC ACID AND SALINE SOLUTION IN PEDIATRIC CENTRAL VENOUS ACCESS: RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Objective: to compare the effectiveness between the use of ascorbic acid and 0.9% saline solution in the prevention of pediatric central venous catheter obstruction. Method: randomized clinical trial conducted in a public hospital in Paraná, between the months of June 2018 to October 2019 with 152 participants, of which, 73 in the experimental group and 79, control group) who underwent central venous catheter insertion and randomized to receive the flush intervention with ascorbic acid or 0.9% saline solution. Results: Catheter obstruction occurred in 17 cases (11.2%), nine (11.4%) in the control group and eight (10.9%) in the experimental group. Thrombotic obstruction occurred in 15 cases, in a similar way, in both groups (p=0.88). Catheter removal occurred in 82 cases for elective reasons and in 63 cases for complications. Conclusion: the use of ascorbic acid is as efficient as 0.9% saline solution in preventing central venous catheter obstruction. The study expands the possibilities of interventions within the theme.

DESCRIPTORS: Catheters; Permeability; Ascorbic Acid; Saline Solution; Nursing.

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INTRODUCTION

The use of central venous catheters (CVC) is common in pediatrics, with the purpose of ensuring a safe and permanent access route for infusion of fluids, total parenteral nutrition (TPN), drugs and blood products for patients in outpatient or inpatient treatment, when there is need for intravenous therapy for more than a week[1]. Short-term CVCs are polyurethane devices with 4 to 8 French caliber, single or multiple lumens, for continuous use exclusively in hospitals. They are inserted into deep vessels by direct percutaneous puncture with a tip positioned in the superior vena cava[2,3,4].

According to the protocols of the related entities, the CVC should be kept patent by performing a flush - a procedure that consists in washing the catheter lumen before and after the administration of any substance, with an infusion of 0.5 ml of 0.9% saline solution (0.9% saline solution) and with a flushing technique, applying light pressure and using a 10 ml syringe[5].

Thanks to its safety, low complication rate, ease of implantation, and effectiveness, CVC has been considered an important tool in the treatment of critically ill children and in the outpatient management of pediatric oncologic diseases. Although its use has been encouraged as a safe option, some adverse events may be observed, such as catheter-associated infection (16.4 to 28.8%), venous thrombosis (13-91%), and mechanical complications like migration, obstruction, and fracture (35 to 48%)[1,6]. In the pediatric population, the complication rate is usually lower, ranging from 1.11 to 19.3/1,000 catheter days, and its patency, as well as the incidence of complications, also vary according to the child's clinical and immunocompetence conditions, as well as the routine of insertion and maintenance procedures[1].

Among the main complications, the occurrence of obstructions, which may be total or partial[7], thrombotic or no thrombotic, is more frequent in pediatric practice due to the smaller caliber (French) of venous catheters used[8]. Thrombotic events are characterized by clot formation or fibrin accumulation in the lumen, thrombi formed by the backflow of blood into the catheter or by platelet and residue accumulation after hemotransfusion[9]. Non-thrombotic events are associated with residual drug deposits or due to drug incompatibilities, or even mechanical causes such as kinking and contact with the vessel wall, which, for the most part, can be solved by repositioning the catheter[10,11].

The obstruction can still be partial whose signs include absence of reflux, resistance to fluid infusion, or slow infusion, while signs of complete obstruction include absence of flow and reflux and leakage at the insertion site, both with insistent alarms by the infusion pumps[12].

This is a problem that is a constant concern for the professionals involved in this activity, because the loss of the catheter due to failure in its maintenance implies relevant damage to the patient.

Recognizing the importance of the flush technique to be performed primarily in CVC maintenance, the solutions used are being studied to reduce obstruction, which is totally preventable. Although 0.9% saline solution is indicated for catheter permeability maintenance[5], other substances have been studied to prevent and reverse obstruction, such as citrate, urokinase, alteplase, and streptokinase[14,15,16].

The use of heparin was, for a long time, the focus of several studies conducted with high potential for adverse events when compared to saline solution. The results of comparisons between heparin and saline solution 0.9% vary, some pointing to benefits and others not[1]. In addition to the lack of consensus and variety of studies on the use of heparin for CVC maintenance, there is also variation in concentrations and intervals, and associated risks[1].

Following the search for a solution that may offer more adequate maintenance for catheter patency with low costs and related risks, the use of Ascorbic Acid (AA) has been considered[16]. The Interdisciplinary Committee on Catheters of the National Cancer Institute (INCA) has recommended the use of 2 mL of AA in maneuvers of catheter clearance that do not respond to the use of 0.9% saline solution[17]. The use of AA is also recommended for CVC clearance by another Brazilian health institute, which recommends its use after an attempt to restore the catheter permeability through the negative pressure technique with a three-way device in the dilution of 0.5 ml of AA and 4.5 ml of total solution[19].

When used *in vitro*, AA acts on blood thrombi, especially in the clot pre-formation stage, changing its structure from the periphery to the central region, promoting lysis, reducing, and inhibiting the increase in size of the pre-formed clot and the generation of new clots, thus facilitating the reestablishment of local flow in catheters[18]. The recommended concentration dose is 50mg/mL[17].

Empirically, AA is used in CVC clearance, and it is believed that, due to its pharmacological characteristics and low associated risk, it may be an alternative solution for maintaining their permeability, preventing obstruction by clots, and undoing possible blood adhesions in the lumen. This could prolong the life of the CVC as well as reduce the adherence of blood components that favor bacterial adhesion and growth. However, there are few studies involving the use of this solution.

Therefore, this study proposes to compare the effectiveness between the use of ascorbic acid and 0.9% saline solution in preventing pediatric central venous catheter obstruction.

METHOD

A randomized controlled, parallel, open-label, controlled clinical trial (RCT) was conducted at a Federal Public University Hospital with participants in the pediatric age group (between 29 days and under 14 years) who had short-stay CVC insertion, admitted to the Pediatric Intensive Care Unit (PICU) with inpatient follow-up in the Hematology, Pediatric Clinic, Pediatric Surgery, and Pediatric Emergency Units of the Institution in the period from June 2018 to October 2019. All infants, children and/or adolescents admitted to the Units during the RCT period were considered for participation in the study. The 178 participants were recruited by the researcher, soon after the insertion of the CVC with the approach of parents and/or guardians for signing the ICF and allocated with allocation rate of 1:1 to constitute the control group (CG) and the experimental group (EG) according to randomization generated by Random.org[20].

After allocation to the groups, the participant was identified, and their CVC was maintained according to the research protocol. The sample was generated by convenience, and during the study period, 465 infants, children and/or adolescents were admitted to the PICU, and the eligible population for this period was 179 infants, children and/or adolescents.

The non-eligibility criteria were kidney failure; coagulation disorders (hemophilia and thrombocytopenia); and parents or guardians under the age of 18.

While the exclusion criteria for participants in the research were: prescription of incompatible drugs in the AA group (etomidate, propofol, thiopental, amikacin, and vancomycin), two or more consecutive tests with thrombocytopenia (below 150,000/mm^6), evolution with acute renal failure requiring dialysis, transfer from hospital or to non-participating sectors, and signs suggestive of AA intoxication (nausea, vomiting, and diarrhea).

Renal failure or coagulation disorders were considered as exclusion criteria. In the CG, ten cases were lost, five due to intra-hospital transfer and five due to platelet count changes, with a final sample of 79 cases in the hospital environment and five due to platelet count changes, with a final sample of 79 cases. In the EG, there were 16 cases lost, four due to dialysis, eight due to use of incompatible medications, three due to loss of medical records and, consequently, of data, and one due to intra-hospital transfer.

The intervention, performed in both groups by the nursing team (after training, orientation, and clarifications made by the researcher about the research protocol, under the supervision of the researcher), consisted in the administration of 2mL of the solution in each CVC route, differing exclusively by its type according to the experimental group. In the intermittent drug and/or solution infusion routes, the catheter flush was performed every six hours, while in the continuous drug and/or solution infusion routes it was performed every 12 hours, respecting the hospital CVC maintenance protocol. The volume used corresponds to the minimum volume of twice the priming (internal volume) of the catheters[21].

The maintenance protocol contemplates the same volume and interval adopted by the researcher (flush with 2mL of solution in each pathway every six hours in the intermittent infusion pathways and every twelve hours in the continuous infusion pathways). The intervention in the EG consisted in the administration of 2mL of AA solution at 25mg/mL in the CVC according to the type of infusion, continuous or intermittent. The preparation of the solution was performed with aspiration of 0.5mL of the 100mg/mL AA ampoule (Farmace®) and filling of the syringe up to the 2mL mark with 0.9% SS, obtaining the final concentration of 25mg/mL. After the use of the required dose, the ampoule was discarded, and no stability was considered.

The control group intervention consisted in the administration of 2 mL of 0.9% saline solution into the CVC according to the type of infusion, continuous or intermittent. The solution for flush was aspirated from 0.9% SS flacons of the brand and lot available in the institution during the study period, containing 10mL, and the remainder was discarded.

The preparation of the two solutions for the EG and CG was performed immediately before use, by the professional responsible for their administration through prescription and checking, and the solution was administered in 10mL syringes employing the flush technique.

The AA ampoules and 0.9% saline solution flacons were available and unrestricted for the team responsible for CVC maintenance during the entire data collection period and in all services involved in the study. The choice of AA dose concentration was based on the values of its tolerable intake in children[19] with a limit of more than 400 mg/day in children aged one to three years. Thus, we considered the maximum use value, in other words, four flushes/day/CVC route that, according to the catheter, can total eight flushes/day, each of 25mg/mL with 2mL, corresponding to 50 mg per flush.

Blinding was not performed for the participants, team, and researcher due to the ease of recognition of the fluids by their coloration at the time of infusion in the transparent material CVCs. Furthermore, the researcher started to collect data daily, and there was identification in each bed with the solution to be infused.

Participants were followed until the primary endpoint (total obstruction) or termination of participation in the study (removal of the CVC). For the purposes of data analysis, drug obstructions were considered those that occurred during or immediately after the infusion of intermittent medications. The remaining obstructions were classified as thrombotic obstructions.

Other variables studied included: CVC dwell time, signs of AA intoxication, CVC type, CVC gauge, blood product administration, total parenteral nutrition administration, number of flushes, continuous infusion volume, use and days of associated peripheral venous access, and days of CVC resistance. The mono-lumen (ML) CVCs used were PICC

French 2.0, PICC 3.0, PICC 4.0, and PICC 5.0. The double lumen (DL) CVCs used were PICC French 2.0 (each lumen with 1.0 French), 4.0 and 7.0.

In the statistical analysis, the Kolmogorov-Smirnov and Shapiro-Wilks tests for normality and Pearson's Chi-square, Fisher's Test, and Mann-Whitney test were applied to compare the primary outcome and secondary outcomes between the groups, and univariate logistic regression (R Program for Data Science).

The research was approved by the Research Ethics Committee of the institution where it was conducted under number 65887416.3.0000.0096 and is registered in the Brazilian Registry of Clinical Trials under number RBR-4tg72t.

RESULTS

According to the characteristics of the participants, we observed homogeneity of the sample between the groups (Table 1).

Table 1 - Characteristics of the participants included in the sample. Curitiba, PR, Brazil, 2021

Variable	CG n = 79 (%)	EG n = 73 (%)	p
Gender			
Male	56 (70.9)	47 (64.4)	0.31
Female	23 (29.1)	26 (35.6)	
Age group			
< 1 year old	47 (59.5)	38 (52)	0.27
≥ 1 and< 5	14 (17.7)	21 (28.8)	
≥ 5	18 (22.8)	14 (19.2)	
Main Diagnosis			
Surgical	18 (22.8)	10 (13.7)	0.22
Clinical	61 (77.2)	63 (86.3)	
CVC type			
Mono-lumen	16 (20.3)	16 (21.9)	0.96
Double lumen	63 (79.7)	57 (78.1)	
Insertion site (vein)			
Axillary	1 (1.3)	2 (2.7)	-
Cephalic Region	3 (3.8)	1 (1.4)	
Femoral	6 (7.6)	3 (4.1)	
Jugular	64 (81)	59 (80.8)	
MMSS	3 (3.8)	3 (4.1)	
Subclavian	2 (2.5)	5 (6.9)	

Note: Pearson's Chi-square test

Legend: CVC - Central Venous Catheter - MMSS - upper limbs; CG - Control Group; EG - Experimental Group.
Source: The authors (2021).

Considering all participants, CVC obstruction was observed in 17 cases (11.2%), nine in the CG (11.4%) and eight in the EG (10.9%) (p = 0.94). Thrombotic obstruction occurred in seven cases in the CG (8.9%) and eight cases in the EG (10.9%) (p = 0.88); and drug obstruction occurred in two cases in each group (2.5% *versus* 2.7%, p = 0.66) (Table 2). Drug obstructions occurred during infusion of furosemide (one case), phenytoin (two cases), and linezolid (one case).

Infusion resistance was reported in nine cases in the CG (16.1%) and six cases in the EG (12.8%) (p = 0.76), however, the number of days of resistance was lower in the EG [11 (1.1%) versus 32 (2.8%), p = 0.01]. In 86.6% of the thrombotic obstructions (13 cases) no previous and/or last 24 hours resistance was reported. In two cases (13.3%) resistance was reported on the day of obstruction. CVC removal due to complications was observed in 33 cases in the CG (50.6%) and 30 (41.1%) in the EG (p = 0.96). Elective removal occurred in 40 cases in the CG (50.6%) and in 42 (57.5%) in the EG (p = 0.56). One patient died in the EG (1.4%) and six in the CG (7.6%) (p = 0.19) (Table 2).

Table 2 - Outcomes of the participants included in the sample. Curitiba, PR, Brazil, 2021

Final outcome of the CVC	CG (n = 79)	EG (n = 73)	p
Obstruction	9 (11.4)	8 (10.9)	0.94
Thrombotic Obstruction	7 (8.9)	6 (10.9)	0.88
Medication	2 (2.5)	2 (2.7)	0.66
Number of catheters with reported resistance	9 (16.1)	6 (12.8)	0.76
Days of reported resistance	32 (2.8)	11 (1.1)	0.01*
Elective Removal - Discharge	40 (50.6)	42 (57.5)	0.56
Non-Elective Removal - Complications	33 (41.8)	30 (41.1)	0.96
Death	6 (7.6)	1 (1.4)	0.19

Notes: Pearson's chi-square test
Legend: CVC - Central Venous Catheter MMSS - upper limbs CG - Control Group GE - Experimental Group.
Source: The authors (2021).

The distribution of obstruction cases according to the type of catheter is shown in Table 3. Obstructions occurred in two PICC 2.0 (CG) and 11 DL 4.0 (five in the CG and six in the EG).

Table 3 - Distribution of obstructions by type of central venous catheters. Curitiba, PR, Brazil, 2021

Type of CVC	CG (n = 9)		EG (n = 8)		General Total
	Type of Obstruction		Type of Obstruction		
	Medication	Thrombotic	Medication	Thrombotic	
DL 4,0	0	5	1	6	12
DL 7,0	1	0	0	0	1
PICC 2,0	0	2	1	0	3
PICC 3,0	1	0	0	0	1
General Total	2	7	2	6	17

Note: CVC - Central Venous Catheter DL - Double lumen; CVC - Central Venous Catheter; CG - Control Group; EG - Experimental Group.
Source: The authors (2021).

In the catheters in which thrombotic obstruction occurred, the length of stay ranged from 30 to 51 days in the CG, with a median of 10, and from two to 67, with a median of six days in the EG ($p = 0.51$). The median continuous infusion volume in the distal port of the obstructed DL 4,0 catheters was significantly lower ($p < 0.001$) in the CG (6.4 mL/h) when compared to the EG (23 mL/h), a fact not observed in the proximal port ($p = 0.67$). The median number of intermittent infusions in both routes was significantly lower in the CG compared to the EG ($p < 0.001$).

The data referring to continuous infusion and intermittent infusion in LD CVCs are presented in Table 4. Only greater volume was observed in the proximal pathway with continuous infusion in the CG ($p < 0.001$). No difference was observed in flushes between the two groups.

Table 4 - Continuous infusion and intermittent infusion in double lumen catheters. Curitiba, PR, Brazil, 2021

Type of CVC	Variables	CG (n = 79)	EG (n = 73)	p
Double Lumen	CI volume via distal (ml/h)	9.0 (0.2-110)	10.0 (0.2-115.9)	0.49
	CI volume proximal port (mL/h)	13.0 (0.1-143)	5.5 (0.3-188)	< 0.001
	Number II distal access	5.0 (1-27)	5.0 (1-30)	0.80
	Number II proximal access	5.0 (1-19)	5.0 (1-20)	0.79
Mono Lumen	CI volume via (mL/h)	3.5 (0.3-50.7)	3.5 (0.2-76.0)	0.82
	Number II access	6.0 (1-9)	4.0 (1-16)	0.10

Note: Mann Whitney test. Values presented in median (minimum-maximum)
Legend: CVC - Central Venous Catheter CI - Continuous infusion II - Intermittent infusion CG - Control Group EG - Experimental Group.
Source: The authors (2021).

The performance of flushes in DL CVCs in the CG had a mean of 1.2 ± 0.8 and 1.3 ± 0.7mL for continuous infusion pathways, and 2.3 ± 1.6 and 2.3 ± 1.5mL for distal and proximal intermittent infusion pathways, respectively. In the EG, this mean was 1.4 ± 2.1 and 1.4 ± 0.6mL for continuous infusion pathways and 2.1 ± 1.5 and 2.2 ± 1.4mL for distal and proximal intermittent infusion pathways, respectively (Table 5).

Table 5 - Number of flushes performed per day according to type of catheter and infusion. Curitiba, PR, Brazil, 2021

Type of catheter	Infusion	Pathway	Flushes number	CG (n=79)	EG (n=73)	p
Double Lumen	Continuous (mL/h)	Distal	Mean ± SD	1.40 ±0.77	1.49 ±0.70	0.05
		Proximal	Mean ± SD	1.45 ±0.77	1.52 ±0.68	0.11
Mono Lumen	Continuous (mL/h)		Mean ± SD	1.39 ±0.84	1.42±0.80	0.74
Double Lumen	Intermittent	Distal	Mean ± SD	2.52 ±1.48	2.61 ±1.43	0.41
		Proximal	Mean ± SD	2.47 ±1.52	2.46/1.51	0.97
Mono Lumen	Intermittent		Mean ± SD	2.14 ±1.34	2.55 ±1.24	0.09

Note: Student's t test
Legend: CG - Control Group EG - Experimental Group.
Source: The authors (2021).

The report of resistance by days of catheter stay prior to obstruction occurred on 14 (87.5%) days of CVC stay in the CG and two days (12.5%) in the EG ($p < 0.01$). The median time of CVC stay in both groups was one day, ranging from one to 80 days in the CG and two to 78 days in the EG.

The use of another concomitant venous access corresponded to 37.0% of the CVC duration of stay in the CG and 32.8% in the EG. Peripheral venous access was the most frequent (35.3%), corresponding to 15.8% of the CVC duration of stay in the CG and 19.5% in the EG ($p < 0.01$), while the use of another CVC was higher in the CG (20.8% versus 13.1%, $p < 0.01$).

To identify whether the variables continuous infusion, intermittent infusion and days of resistance reported interfered with the rates of thrombotic obstruction, univariate logistic regression analysis was applied to assess the impact of days of resistance on the occurrence of this complication, and for each day that resistance was reported, the chance of occurrence of thrombotic obstruction in CVCs increased by 45.1%.

No participant showed signs of intoxication, and the dose used was considered safe for patients in the age range of the research, even for those who remained with the CVC for a prolonged time.

DISCUSSION

Although CVC occlusion is a common problem in the daily practice of pediatric patient care, management varies widely in different institutions due to the lack of consistent evidence in the literature regarding best practices for its prevention. In a recent systematic review conducted in Australia and published in the Cochrane database in 2020, only four studies (255 participants) were selected for the review, all evaluating the benefit of intermittent flushing with 0.9% saline *versus* heparin for the prevention of occlusion in long-term catheters in infants and children. Still, these are studies with low to moderate evidence, unblinded, heterogeneous, inconsistent, and with wide confidence intervals[1].

Studies on the effectiveness of AA in CVC clearance are still rare. Only Rabe et al. (2002) evaluated the rates of CVC obstruction in adults, comparing the use of 0.9% saline, heparin 5000 IU/mL and AA 200 mg/mL. Of the 99 CVCs evaluated, the lowest incidence

of obstruction was observed in the group receiving heparin, while in the groups receiving 0.9% SS and AA there was no statistically significant difference.

In this study, the obstruction rate observed in the EG, conducted with the use of AA (10.9%) was like that of the CG, maintained with 0.9% SS (11.4%), indicating equal effectiveness of the two procedures in preventing this adverse event. Considering only the thrombotic obstructions, the same result was observed (10.9% *versus* 8.9%) and, in general, the obstruction rate of 11.2%, considering the total sample, is consistent with that described in the literature, which ranges from 6.9 to 25%[24,25].

However, it was observed that CVCs maintained with AA had lower rates of resistance on infusion (1.1%) compared to those maintained with 0.9% SS (2.8%), and 86.6% of thrombotic obstructions had no reports of previous resistance and/or in the last 24 hours. In two of the CVCs (15.4%) there was resistance reported on the day of obstruction, which may suggest previous partial obstruction.

Although it is known that flushing is the best practice to avoid catheter obstruction,[13] the performance of flushes in this sample did not correspond to what was proposed, both in routes with continuous infusion and in those with intermittent infusion, and, although it did not interfere with the result, it shows the difficulty in compliance with care protocols by the teams, even after training and elucidation of the established routines.

The infusion of blood products is also known to be a risk factor for CVC obstruction, observed in 18 cases in the sample, of which one culminated in thrombotic obstruction. The recommendation for the infusion of blood products is the use of catheters with more than 3 *FR* and procedures such as evaluation of permeability before blood infusion, use of infusion pump and performance of flush after the end of infusion[12,26,27].

The most used CVC was the DL (78.9%), given the characteristics of the sample participants (intensive care patients), who usually require multiple therapies. The number of catheter lumens can be considered a risk factor for non-elective removal due to the increased risk of obstruction, because the presence of the second lumen implies the reduction of the routes' calibers, as it is difficult to increase their total caliber for insertion in the venous network of children[28].

Another controlled variable was the use of another associated catheter, considering 35.1% of the 2,111 catheter days followed, and the frequency of CVC with another associated central venous access was 25.7%, lower than the association with another peripheral venous access (69.7%). However, when comparing this frequency in the length of stay by days, it was noted that the use of another central venous access corresponded to 17.0% of the days, and the peripheral one, to 17.1%. And finally, the difficulty of blinding, related to the coloration of the solutions used and the transparency of the catheters.

Obstruction is a preventable and manageable event, in which the nursing team plays a key role, because the technical expertise (proper infusion and lavage practices and meticulous assessment) determines the outcome. Thus, continuous staff training, adoption of updated policies, and periodic evaluations are measures that modify care practice and CVAcomplication rates[1,5,10-13,18,23,24]. These interventions show modification in the results of obstruction rates within three months after the beginning of educational activities[29].

The diversity of protocols and professional conducts, the relevance of the topic within the concepts of quality of hospital care, the high costs related to the use of venous accesses for institutions, among other aspects, highlight the importance of the need to form an intravenous therapy team, with the purpose of reducing complications related to the intravascular device, and its main attribution is to guide professionals and monitor the results of standardizations (material and conduct) adopted[1,6,10,18,23,24].

Moreover, despite the number of existing studies on CVC maintenance, the study expands the possibilities of interventions to reduce the problem in care practice, since

it was applied in a population that has been scarcely studied (pediatrics). It assesses the various interfaces that culminate in the loss of a CVC due to obstruction, sometimes not explored in other studies and that translate the dimension of the problem, within which the solution is a bias in an extensive set of factors.

CONCLUSION

The use of AA seems to be as efficient as the use of 0.9% saline solution in preventing CVC obstruction (rejecting the hypothesis of the study). However, the evidence of lower frequency of partial obstruction in the group receiving AA, justified by the lower frequency of resistance to fluid infusion, points to the fact that further research should be conducted to elucidate the problem and standardize the best conduct for a procedure that constitutes the daily practice of caring for critically ill patients.

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