Clinical trial protocol

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A GAVeCeLT bundle for central venous catheterization in neonates and children: A prospective clinical study on 729 cases

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Abstract

Background: In the pediatric patient, central venous catheterization may be associated with relevant complications. Though, most of them may be prevented by a wise choice of materials, methods, and techniques. Evidence-based insertion bundles for central venous catheterization have been developed in the adult patient, but not in neonates and children.

Methods: The Italian Group for Long Term Venous Access Devices (GAVeCeLT) has developed an insertion bundle for central venous catheterization in neonates, infants, and children, which includes seven evidence-based strategies: (1) preprocedural ultrasound evaluation, (2) appropriate aseptic technique, (3) ultrasound guided venipuncture, (4) intraprocedural tip location by non-radiological methods, (5) proper choice of the exit site by tunneling, (6) sutureless securement, and (7) protection of the exit site using glue and transparent membranes. The effectiveness and safety of this bundle has been tested in a prospective study.

Results: All neonates, infants and children requiring a non-emergency central line (except for umbilical venous catheters and epicutaneo-cava catheters) were included in the study. Out of 729 central line insertions, there were no immediate complications (no pneumothorax, no arterial puncture, no malposition); the incidence of early and late complications (local ecchymosis, dislodgment, local pain, exit site infection) was 3.7%; in the first 2 weeks after insertion, no catheter-related bacterial infection or catheter-related thrombosis was recorded.

Conclusion: The results of this prospective study strongly validate the hypothesis that an insertion bundle is highly effective in optimizing the safety of the maneuver, reducing immediate, early, and late complications.

Keywords

Central venous catheterization, neonates, infants, children, ultrasound, intracavitary ECG, sutureless securement, tip location

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Introduction

Central venous access devices (CVAD) are largely used in pediatric and neonatal patients for infusion of drugs, parenteral nutrition, chemotherapy, blood sampling, dialysis, and hemodynamic monitoring. CVAD-related complications are not uncommon and may result in interruption of treatment with worsening of the clinical outcome, prolonged hospital stay, and increased costs of the health care system.[1] CVAD-related complications can be (a) immediate—due to difficult venipuncture (pneumothorax, hemothorax, hematoma, arterial, or nerve injury) or to inappropriate location

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of the catheter (primary malposition, arrhythmia, etc.), (b) early (occurring within 48 h), and (c) late (occurring after 48 h). Late complications may be related to the insertion maneuver (early infection, venous thrombosis, secondary malposition, dislodgment, etc.) or to the maintenance maneuvers (lumen occlusion, late infection, etc.).

In the last decade, the introduction of "bundles," regarded as a set of recommendations based on scientific evidence, has been found effective in reducing central line the incidence of catheter-related bloodstream infection (CRBSI) in adults.[2] More recently, specific "insertion bundles" have been implemented to reduce any type of complication due to central venous catheterization in adults.[3–5] Most of these bundles include pivotal recommendations such as: (a) use of ultrasound for the choice of the vein, for real time ultrasound-guided venipuncture, for tip navigation, tip location, and for early detection of complications[6]; (b) proper choice of the exit site[7,8]; (c) skin antisepsis using 2% chlorhexidine in alcohol[9]; (d) maximal barrier precautions[9]; (e) intraprocedural tip location by intracavitary ECG[10] or ultrasound[11]; (f) consistent use of sutureless devices[9]; (g) use of cyanoacrylate glue for sealing the exit site.[12,13] All these new methodologies and technologies have contributed to reduce the incidence of complications, increasing the cost-effectiveness of CVAD insertion in adults.[14]

The aim of this study was to evaluate the rate of complications directly or indirectly related to the maneuver of central venous catheterization in neonates, infants, and children, adopting an evidence-based insertion bundle developed by GAVeCeLT (the Italian Group for Long Term Venous Access Devices).

Methods

This is a single center prospective observational study conducted in the pediatric and neonatal intensive care unit of a large university hospital in the metropolitan area of Rome, Italy. The study protocol was approved by the local Ethics Committee. The guardians and parents were informed of the study objective and signed an informed consensus form. All patients (age ranging from birth to 17 years old) candidate to central venous catheterization in a 4-year period (from 2017 to 2020) were included in the study. Only elective CVAD insertions were considered. All CVADs were included, as long as they were inserted in the deep veins of the arms (PICC = peripherally inserted central catheters), of the lower limb (FICC = femorally inserted central catheters), or of the supra/infraclavicular area (CICC = centrally inserted central catheters) (according to the current classification of CVADs).[6] Both cuffed and non-cuffed VAD were included, as well as totally implanted VADs (port) and dialysis catheters.

Therefore, exclusion criteria were only the following: patients with age >17 years; refusal of the consensus; CVADs inserted in emergency conditions; umbilical venous catheters (UVC) and epicutaneo-cava catheters (ECC) in neonates.

Study design

This prospective study was designed to analyze the clinical impact of an evidence-based insertion bundle on the rate of any complication potentially related to central venous catheterization in a large population of neonates, infants, and children.

An insertion bundle was specifically developed by GAVeCeLT, adopting key recommendations for minimizing different types of insertion-related complications, with the purpose of increasing the safety of the maneuver. The bundle was nicknamed SIC-Ped (i.e. Safe Insertion of Central access in Pediatric patients) and it included seven evidence-based strategies:

(1) *Preprocedural evaluation* (adequate collection of clinical history and proper ultrasound examination of the venous patrimony): History of previous venous cannulation and/or of repeated difficult venipunctures, previous venous thrombosis, or an abnormal coagulation status, were all regarded as relevant for the proper choice of venous access. The most appropriate puncture site was chosen after a systematic ultrasound evaluation of the veins, using protocols already described and adopted in clinical practice: Rapid Central Vein Assessment (RaCeVA),[15] Rapid Peripheral Vein Assessment (RaPeVA),[16] Rapid Femoral Vein Assessment (RaFeVA).[17] The puncture site was chosen based on the caliber and depth of the vein, but also considering the potential risk of accidental injury to nerves, arteries, or pleura. An ideal catheter/vein ratio of at least 1:3 was considered acceptable.

(2) *Appropriate aseptic technique* (hand hygiene, maximum barrier protections, skin antisepsis with 2% chlorhexidine): Hand hygiene was preferably performed with hydroalcoholic gel. For skin antisepsis, 2% chlorhexidine in 70% isopropyl alcohol was used, also in premature neonates. Maximal barrier precautions included non-sterile cap, non-sterile mask, sterile gown sterile gloves, full-size sterile drape over the patient, and sterile protection of the ultrasound probe (long enough to cover the probe and the wire).

(3) *Ultrasound-guidance*: Real-time ultrasound guided venipuncture of the chosen vein was consistently adopted, with different techniques in terms of vein view (short axis, long axis, oblique axis) and needle approach (in-plane, out-of-plane), depending on the vein considered and on the clinical situation.[6] Ultrasound was also used to assess the proper

direction of the guidewire and of the catheter (ultrasound-based tip navigation), according to the ECHOTIP-Ped[18] and to the Neo-ECHOTIP protocols.[19] In case of CICC insertion, ultrasound was also used to assess the absence of pneumothorax, immediately after venipuncture, as currently recommended.[6]

(4) *Intra-procedural verification of the central position of the tip by non-invasive methods*: Intracavitary ECG technique was used to control the correct position of the catheter tip,[20,21] in most cases. Ultrasound was often used as an additional method to confirm tip location,[18,19] in association with intracavitary ECG. In some cases of FICC insertion, if the tip had been planned to be in the inferior vena cava, the correct position of the tip was verified by ultrasound-based tip location only. Post-procedural X-ray was taken into consideration as an option only in case of failure (not feasibility or not applicability) of intracavitary ECG and ultrasound.

(5) *Tunneling*: The most appropriate exit site was defined in each clinical case, adopting tunneling whenever needed, so to move the exit site away from areas at high risk of bacterial contamination or dislodgment. Tunneling options were decided according to the RAVESTO protocol (Rapid Assessment of Venous Exit Site and Tunneling Options).[22] Tunneling was also adopted for other purposes: in patients with expected long-term venous access (to reduce the risk of bacterial contamination by the extraluminal route) and in agitated children who might have involuntary attempted to remove the device.

(6) S*utureless securement of the catheter*: As currently recommended,[7] sutures were never used for catheter securement. Securement was achieved exclusively by skin adhesive sutureless devices (StatLock, BD; GripLok, Zevon) or by subcutaneous anchorage (SecurAcath, Interrad), or by semipermeable transparent membrane integrated with a stabilization device (SorbaView Shield, Centurion).

(7) *Protection of the exit site with glue and semipermeable transparent membranes*: Cyanoacrylate glue was consistently used to seal the exit site, with the purpose of stabilizing the catheter, reducing the oozing/bleeding, and decreasing the risk of bacterial contamination by the extraluminal route. Either butyl or octyl-butyl cyanoacrylate was indifferently used. The exit site was consistently covered with transparent dressing with high permeability (high MVTR = high Moisture Vapor Transfer Rate) (Tegaderm Advance, 3M; IV3000, Smith & Nephew; SorbaView, Centurion); a value of MVTR > 1500[23] was considered acceptable.

All procedures were performed in the neonatal intensive care unit (NICU) or in a dedicated procedure room of the pediatric intensive care unit (PICU). Sedation, analgesia, and/or anesthesia were used in all patients, with different protocols ranging from general anesthesia to local anesthesia, with or without sedation, depending on the age of the patient and his/her clinical status. Different levels of intraprocedural monitoring of vital signs were used, depending on the clinical conditions, but always including ECG monitoring, since intracavitary ECG was adopted as first option for tip location. Using a standard ECG monitor, ECG trace was recorded with an output speed equal to 50 mm/s and a sensitivity of 10 mm/mV, switching from a surface lead-II to an intracavitary lead-II when intracavitary ECG was required; the CVAD was connected with the ECG monitor by a dedicated sterile cable (Vygocard, Vygon).

Ultrasound imaging was performed with different ultrasound devices, equipped with linear probes (13–6 MHz), micro-convex probe (5–8 MHz), and small sectorial probe (4–8 MHz), so to fulfill all requirements for venous assessment, venipuncture, tip navigation, tip location, and detection of insertion-related complications. The ultrasound device most frequently used was a portable laptop device (Turbo or Edge II, Sonosite-Fuji); in some cases, a wireless ultrasound probe with three transducers (linear-convex-sectorial) was used (Cerbero, ATL Milano).

Different central VADs of many different brands were used. In most cases, both in neonates and in children, 3–4Fr single or 4–5Fr double lumen polyurethane catheters were used. Catheters currently marketed as PICCs were used "off label" also as CICCs or FICCs, as previously described.[16,24,25] This has allowed us to use micro-introduction kits with 21G echogenic needle, soft straight tip 0.018″ guidewire for most procedures. For special catheters of large caliber (dialysis catheter), a two-step insertion was adopted, first cannulating the vein with the micro-introducer kit and then inserting the 0.035″ guidewire into the micro-introducer.

After insertion, the maintenance of all CVADs was carried out according to our hospital policies (routine dressing change every week, needle free connectors with neutral displacement, disinfecting caps, flush and lock with saline only, daily surveillance of the exit site, etc.)

All CVAD insertions were performed by a small group of four clinicians specifically trained in neonatal and pediatric vascular access (one surgeon, one nurse, two neonatologists). The analysis of the data was performed by another clinician (an intensivist expert in vascular access).

Endpoints

The primary endpoint was to evaluate the incidence of any immediate complication occurring during the procedure: failure of venipuncture, success after more than two

attempts, pneumothorax, accidental arterial injury, local hematoma, hemothorax, hemo-mediastinum, nerve injury, damage to the lymphatic duct, air embolism, hemopericardium, intraprocedural arrhythmias, failure to place the catheter tip in the planned location (primary malposition).

The secondary endpoint was to evaluate the incidence of any early (within 48 h from insertion) or late complication (after 48 h and within 14 days) potentially related to the insertion maneuver. Potential early complications included local hematoma, hematoma of the tunnel, bleeding from the exit site, early catheter malfunction, relevant local pain. Late complications potentially related to insertion included infective complications (exit site infection, infection of the tunnel, or CRBSI) and non-infective complications (catheter-related venous thrombosis; catheter breakage; tip migration; dislodgment), if occurring within the first 2 weeks.

Local skin infection was defined by the presence of erythema and/or tenderness over the exit site or the tunnel regardless of the presence of fever or purulent discharge. The diagnosis of CRBSI was based on the differential time to positivity (DTP).[26] Catheter-related thrombosis (CRT) was diagnosed by ultrasound examination, performed only on the basis of a clinical suspicion. Catheter malfunction was defined as persistent inability to infuse normal saline solution despite the manual pressure performed by a 10 ml syringe. Dislodgment was defined as catheter movement of more than 2 cm from the original position at the exit site.

A specific database was developed, so to collect relevant details about the patient (demographics, clinical history, reason for inserting the CVAD), the insertion maneuver (type of venous access, type of catheter, etc.) and the periprocedural complications. Follow up of each catheter lasted 14 days, considering that complications occurring after 2 weeks (in particular, infection) are less likely to be related to the maneuver of insertion.

Statistical analysis

The statistical analysis of the anamnestic characteristics of the sample and of the incidence of intra and post-procedural complications was performed on Excel files. The incidence of complications was compared with the figures reported in the literature. Data were normalized considering the different characteristics of the individual devices used and the other characteristics shown on the data collection sheet.

As this was a prospective uncontrolled study, the calculation of the number of cases to recruit was based on the expected incidence of the most frequent complications, assuming a 50% reduction with minimum significance $p < 0.05$. As evident from literature, the risk of expected intra-procedural complications is attested to values between 5% and 20%; late mechanical complications between 10% and 40%; infections between 10% and 22%; thrombotic complications between 5% and 8%. On this basis, it was estimated to reach at least 600 patients.

Results

Over a period of 4 years, 729 consecutive CVAD insertions were included in the study. The neonatal population (0–30 days old) included 68 patients, the infants (1–12 months old) were 173, and the children (1–17 years old) were 488.

Table 1 shows the CVADs inserted in neonates: mean age was 10 days and mean weight was 2700 g (range 950–4700). At the time of CVAD insertion, 54 newborns were hospitalized in the NICU, 6 in the surgical ward, 5 in the neonatology ward, and 1 in neurosurgery. All insertions were performed either in the NICU or in the procedure room of the PICU. As shown in Table 1, the great majority of CVADs were CICCs inserted in the right brachiocephalic vein: catheter tip was placed at the junction between superior vena cava and right atrium, by intracavitary ECG. The only FICC was inserted in the right common femoral vein, and the tip located in the right atrium. All CICCs were tunneled to the infra-clavicular area, so to move the exit site to a clean and stable position. The FICC was tunneled to mid-thigh. Intracavitary ECG was used in all patients; in 32.3%, tip location was additionally verified by ultrasound. X-ray confirmation was never required. Several brands of catheters were used, mostly 3Fr, single lumen, non-cuffed polyurethane catheters. One catheter was inserted by replacement over guidewire: also in this case, ultrasound was used for tip navigation and intracavitary ECG for tip location. Subcutaneous anchorage was used in all patients. In this group of patients, no immediate or early or late complication was recorded. In particular, all central veins were punctured successfully at first attempt; femoral venipuncture was achieved by two attempts.

Table 2 shows the CVADs inserted in infants: mean age was 4.5 months. At the time of CVAD insertion, 93 patients were hospitalized in the PICU, 28 in the pediatric neurosurgical ward, 14 in pediatric surgery, 14 in pediatric oncology, 6 in the pediatric ward. All insertions were performed in a procedure room of the PICU. As shown in Table 2, most catheters were CICCs, inserted accessing the brachiocephalic vein. All FICCs were inserted accessing the common femoral vein. In all CICCs and FICCs, the tip was placed in the right atrium by intracavitary ECG. Ultrasound-based tip location was added to ECG-based tip location in 30% of cases. Tunneling was adopted in 90.8% of cases, both for CICCs and FICCs. No PICC was inserted in this group of patients. Most catheters were 3Fr or 4Fr single lumen polyurethane catheters, though a few silicon catheters (cuffed and non-cuffed) were also used. Securement by subcutaneous anchorage was used in 81% of patients.

In this group, the only recorded complications were: one accidental dislodgment (0.6%) (in an infant with a

Table 1. Central venous access devices in neonates.

	CICC	FICC	Total
	n = 67	*n* = 1	*n* = 68
Vein			
Right brachiocephalic	61		61
Left brachiocephalic	5		5
Right internal jugular	1		1
Right femoral		1	1
Technique			
Tunneling	67		68 (100%)
Ultrasound-based tip location	22		22 (32.3%)
Exchange by guidewire	1		1 (1.5%)
Catheter caliber (Fr = French)			
3Fr	57		57
3Fr*§	3		3
4Fr	7		7
5Fr	1		1
Lumen			
Single lumen	59	1	60
Double lumen	8		8
Patients			
Mean age (days)	10.1 ± 8.9	2	10 ± 8.8
Mean weight (Kg)	2.76 ± 0.7	3.4	2.77 ± 0.7
Gender (M/F)	26/41	0/1	26/42

All catheters in polyurethane except * = silicon; all catheters non-cuffed except § = cuffed.

skin-adhesive sutureless securement); two local ecchymoses (1.15%), without evidence of local hematoma. No CRBSI and no CRT was recorded in the first 2 weeks after insertion.

Table 3 shows the CVADs inserted in children: mean age was 7 years. At the time of CVAD insertion, 72 children were hospitalized in the pediatric oncology ward, 64 in the PICU, 44 in the pediatric neurosurgery ward, 12 in the pediatric ward, and 4 in pediatric surgery. All insertions were performed in a procedure room of the PICU. As shown in Table 3, 488 catheters were inserted: 279 PICCs (57%), 196 CICCs (40%), and 13 FICCs (3%). Most CICCs were inserted in the brachiocephalic vein. The tunneling technique was used in 58.6%, in all CICCs but also in many FICCs and PICCs. Ultrasound-based tip location was added to ECG-based tip location only in 15.2% of cases. All CICCs had their tip placed at the junction between superior vena cava and right atrium or in the upper part of the atrium. In six cases (including the dialysis catheters), the tip of the FICC was placed in the inferior vena cava, using ultrasound-based tip location only, and not intracavitary ECG. Most CVADs were 3–4–5Fr single lumen polyurethane catheters. A few CVADs were in silicon (cuffed and non-cuffed); a few ports and a few dialysis catheters were also inserted. Subcutaneous anchorage was used in most cases (72%).

In this group, no major complication (pneumothorax, arterial puncture, CRBSI, CRT, etc.) was recorded. Minor post-procedural complications included: local pain (2.9%); local ecchymosis (1.4%); one infection of the exit site occurring 10 days after insertion (0.2%) (as the local infection occurred in a tunneled CICC, it was treated conservatively, and the device was not removed). Two cases of bacteremia occurred in the first 2 weeks, but in both cases the DTP excluded the diagnosis of CRBSI. In the 2-week follow-up, two dislodgments were reported, both in CVADs secured by skin-adhesive sutureless device and not by subcutaneous anchorage.

In summary, considering the whole population of patients enrolled in our study, there was no episode of accidental arterial puncture or pleura-pulmonary injury during the insertion maneuver; proper tip location was successfully verified during the procedure by intracavitary ECG and/or ultrasound in 100% of cases, without any need for post-procedural X-ray. Only minor post-procedural complications were reported (see Table 4); during the 2-week follow-up, there were no episodes of CRBSI or of CRT.

Discussion

As far as we know, this is the first prospective study evaluating an evidence-based insertion bundle specifically designed for central venous catheterization in neonates and children. Most interestingly, in this large cohort of patients—multifaceted in terms of age, weight, underlying disease, clinical condition, type of CVAD, etc.—no major

Table 2. Central venous access devices in infants.

	CICC	FICC	Total
	n = 155	*n* = 18	*n* = 173
Vein			
Right brachiocephalic	124		124
Left brachiocephalic	21		21
Right internal jugular	4		4
Left internal jugular	2		2
Right external jugular	1		1
Left external jugular	1		1
Right axillary	1		1
Left axillary	1		1
Right femoral		13	13
Left femoral		5	5
Technique			
Tunneling	149	8	157 (90.8%)
Ultrasound-based tip location	46	6	52 (30%)
Exchange by guidewire	3	2	5 (2.9%)
Catheter caliber (Fr = French)			
2.7Fr*§	2	1	3
3Fr	93	14	107
3Fr*	4		4
4Fr	50	2	52
5Fr	4	1	5
5.5Fr*§	2		2
Lumen			
Single lumen	120	17	137
Double lumen	35	1	36
Patients			
Mean age (months)	4.55 ± 3	4.05 ± 2.5	4.49 ± 2.9
Gender (M/F)	95/60	12/6	107/66

All catheters in polyurethane except * = silicon; all catheters non-cuffed except § = cuffed.

complication potentially related to the insertion maneuver was reported. The results of this prospective study strongly validate the hypothesis that an insertion bundle is effective in optimizing the safety of the maneuver, reducing immediate, early, and late complications.

Immediate complications during CVADs insertion (pneumothorax, arterial puncture, local hematoma or hemorrhage, and cardiac arrhythmias) are not uncommon in the pediatric population. Overall, CVAD insertion-related complications have been reported with an incidence of 7%–18%[27,28]; about 25% of pediatric CVADs develops complications before the treatment being complete.[1] Some late complications (partially or totally dislodgment, venous thrombosis, bloodstream infections, catheter breakage or occlusion, exit site inflammation or infection) may be related to the insertion technique.

CVADs related complications may have serious consequences, such as premature removal of the catheter, interruption of the therapy, and/or the onset of secondary clinical problems, with prolonged hospital stay and an increased risk of mortality, which can be as high as 35%.[27,28] In neonates with low birth weight (<1.500 g) a blood stream infection increases in average the hospital costs by $5875 per infant,[29] with risk of neurodevelopment impairment[30] and cerebral palsy.[31]

Evidence is accumulating that most complications are preventable by appropriate training of the operators and with the use of evidence-based insertion and maintenance bundles. This has been validated in the adult population[2] but studies in the pediatric population are limited.[32–34]

In this prospective observational study, we tested a well-designed insertion bundle with the purpose of reducing the incidence of CVAD-related complications in neonates and children. For the CVAD insertions in the adult patient, the Italian group GAVeCeLT has developed "*insertion bundles*" for PICC insertion (peripherally inserted central catheters),[4] for CICC insertion,[3] for FICC insertion,[5] and for long-term VAD insertion.[35] The "*bundle*" used in this study (SIC-Ped) consists of seven strategies, all of them evidence-based:

Table 3. Central venous access devices in children.

	CICC	FICC	PICC	Total
	n = 196	*n* = 13	*n* = 279	*n* = 488
Vein				
Right brachiocephalic	174			174
Left brachiocephalic	17			17
Right internal jugular	1			1
Left internal jugular				
Right axillary	3		69	72
Left axillary	1		17	18
Right basilic			139	139
Left basilic			28	28
Right brachial			21	21
Left brachial			5	5
Right femoral		12		12
Left femoral		1		1
Technique				
Tunneling	196	5	85	286 (58.6%)
Ultrasound-based tip location	45	4	25	74 (15.2%)
Exchange by guidewire	4	1	30	35 (7.2%)
Catheter caliber (Fr = French)				
2.7Fr*§			2	2
3Fr*	2			2
3Fr	56	3	113	172
4Fr	76	2	115	193
5Fr	34	4	47	85
5Fr§	6			6
5.5Fr*§	8			8
6Fr	2			2
6.6Fr*#	4			4
7Fr*§	9			9
11.5Fr@		4		4
Lumen				
Single lumen	122	4	174	300
Double lumen	70	9	105	184
Triple lumen	4			4
Patients				
Mean age (year)	4.24±3.8	7.85±5.3	8.9±5	7±51
Gender (M/F)	129/67	7/6	169/110	305/183

All catheters in polyurethane except * = silicon; all catheters non-cuffed except § = cuffed; # = totally implanted venous access device (port); @ = dialysis catheter.

Table 4. Post-procedural complications.

	Neonates (*n* = 68)	Infants (*n* = 173)	Children (*n* = 488)
Dislodgment	—	1 (0.6%)	2 (0.4%)
Local ecchymosis	—	2 (1.16%)	7 (1.4%)
Infection of the exit site	—	—	1 (0.2%)
Local pain at the exit site	—	—	14 (2.9%)

(1) The systematic ultrasound examination of the veins of the cervico-thoracic zone (RaCeVA)[15,36] or the arm (RaPeVA)[16] or the leg (RaFeVA)[17] before the venipuncture allows the operator to choose the most appropriate vein in terms of caliber, depth and potential risk of arterial or pleural damage. Particularly attention is given to the diameter of the vein, which is measured and chosen according to the Nifong rule,[37] which recommends cannulating veins whose internal diameter is at least three times greater than the external diameter of the catheter, for the prevention of venous thrombosis. The principle behind the first recommendation of the bundle is that there is no ideal vein for every pediatric patient and the vein must be identified through an accurate ultrasound examination.[6,38–40]

(2) Insertion site protection from microbial contamination through proper hand hygiene, maximum barrier protection and skin antisepsis with 2% chlorhexidine is of paramount importance.[7,9] According to most guidelines,[39–41] also in neonatal and pediatric patients the use of maximum barrier protections is mandatory; in our study, we have consistently adopted in all neonates and all children the recommendation of cleansing and disinfecting the skin with a single application of 2% chlorhexidine in 70% isopropyl alcohol for at least 30 s, followed by a pause of 30 s before starting the procedure.[42–44]

(3) The third, innovative component of our bundle is the "global" use of the ultrasound for several goals: ultrasound-guided venipuncture, tip navigation, assessment of the absence of pneumothorax. Ultrasound-guided venipuncture has quickly become the gold standard for central venous cannulation in children and infants.[6] Several studies have demonstrated that ultrasound guidance reduces the number of venipunctures and the risk of immediate complications. In particular, the number of puncture attempts is one of the factors mainly associated with complications.[45–47] The US-guided supraclavicular BCV catheterization was associated with the lowest rate of central line-associated bloodstream infection and deep vein thrombosis in a cohort of 257 CVCs in a pediatric intensive care unit (PICU).[32] Ultrasound-guided venipuncture is feasible also in neonates, as shown in previous studies.[36,48,49] Ultrasound also allows to immediately exclude early pleuro-pulmonary complications (such as pneumothorax) and allows to verify the correct direction of the guidewire and/or of the catheter (tip navigation).[6]

(4) Intracavitary ECG as a non-invasive intra-procedural method of tip location has been often used in pediatric and neonatal patients.[20,21,50] The accuracy of IC ECG technique was reported to be 92.9%[50] and 95.8%[20] which is very close to the results from the adult multicenter study.[51] In our study, IC ECG was used in almost all patients, often associated with ultrasound-based tip location. In pediatric patients, ultrasound is considered the second and most reliable method for verification of the tip location.[6,18,19,38] A micro-convex probe (4–8 MHz) or small sectorial probe (3–7 MHz) was used for the tip location, in most cases with a subcostal bi-caval projection. The maneuver was particularly feasible in neonates and in infants, as reported in our data.

(5) The tunneling technique was used in 511 patients, including all newborns (100%), most of the infants (90.75%), and more than half (58.6%) of the children. The rationale for tunneling is to ensure the most appropriate position of the emergency site.[22] For example, many complications of central venous access in the cervico-thoracic site (CICC) are connected to difficulty in managing the emergency site and/or instability of the catheter; typically, a catheter with an emergency site in the cervical site will have a greater risk of dislocation (difficulty of stabilization and securement), greater risk of infection (difficulty in disinfecting and keeping a clean dressing), greater risk of venous thrombosis (excessive catheter mobility). In neonates and infants, the small caliber size of arm veins often requires a supraclavicular approach (CICC). In this study, a BCV approach was performed in 67 out of 68 of neonates, 155 out of 173 infants, and in only 196 children out of 488. The supraclavicular approach and the femoral approach are associated with high risk of infection,[52,53] but tunneling toward a more appropriate exit site can minimize such complication. In the past, tunneled CVADs were almost exclusively tunneled-cuffed CICCs. Recent studies have discussed the advantages of tunneling also non-tunneled CVADs, either CICCs, PICCs, or FICCs, both in adults and in pediatric patients (including neonates).[16,22,24,25,36,54] Tunneling per se in fact protects from bacterial contamination and enables an ideal emergency site, regardless the presence or the absence of the cuff.[55,56] Non-cuffed tunneled CVADs can be easily removed without surgical incision and without sedation/anesthesia[54] and this is a relevant issue in children.

(6) In our study, we had very few dislodgments in the first 2 weeks of follow-up. Adequate stabilization of the catheter by sutureless device plus glue plus semipermeable transparent membrane has surely played a role. Sutureless securement is recommended by current guidelines[7] and may have favorable effects also on the risk of infection. In our experience, the most effective securement—particularly in children—was subcutaneous anchorage. This method minimizes the risk

of dislodgment and may theoretically reduce the risk of infection and venous thrombosis.[57] In a pediatric study on 311 tunneled catheters, both cuffed and non-cuffed,[58] subcutaneous anchorage was associated with minimal incidence of local complications (2.6% dislodgment, 1.9% pain or inflammation) and very low incidence of CRBSI (less than 1 episode/1000 catheter days). In a study on 72 catheters (62 CICC and 10 FICC) in newborns, all secured by subcutaneous anchorage, no dislodgment was reported.[59]

(7) In our study, the absence of any case of bleeding by the exit site may be explained by the consistent use of cyanoacrylate glue. Recent data have already suggested that octyl- and/or butyl-cyanoacrylate are very effective in reducing bleeding from the exit site. In addition, the glue helps stabilizing the catheter effectively, albeit for a limited period of time.[40,59,60] Some reports also suggest that the glue may constitute a barrier against bacterial contamination, reducing the risk of infection.[12] There is currently no evidence that cyanoacrylate can have undesirable effects on the skin, not even in neonates[59] or that it may alter the chemical-physical characteristics of polyurethanes.[61] The stabilization of the catheter becomes even safer associating glue and sutureless securement with the use of transparent semipermeable membranes, which obviously have also a favorable impact above all on reducing the risk of bacterial contamination. The use of transparent membranes is strongly recommended by several guidelines.[43] In this regard, though skin damage may be an issue in neonates and infants, we did not report any case of CASI (Catheter Associated Skin Injury) in the first 2 weeks after CVAD insertion. Our current strategy of CASI prevention includes use of transparent membranes with high MVTR (Moisture Vapor Transfer Rate), use of minimal quantities of cyanoacrylate glue, appropriate policy of dressing change, and adequate policy of skin antisepsis. The adoption of subcutaneous anchorage – by avoiding securement with skin-adhesive sutureless devices—might also have reduced the risk of CASI.

Conclusions

The different components of our SIC-Ped bundle may have contributed synergistically to the minimization of insertion-related complications in our prospective study.

The absence of puncture-related complications is secondary to the wise choice of the vein by preprocedural ultrasound (point 1) and—most importantly—to the consistent use of ultrasound guidance (point 3).

The absence of primary malpositions is secondary to the consistent use of non-invasive intraprocedural method of tip location, such as intracavitary ECG and ultrasound-based tip location (point 4); interestingly, both methods have wider feasibility and applicability in pediatric patients than in adults. Postprocedural control by X-ray was never required.

The absence of CRBSI in the first 2 weeks of follow up is secondary to the appropriate use of the currently recommended strategies for infection prevention during the maneuver (point 2), to the adoption of the tunneling technique to optimize the exit site (point 5), to sutureless securement (point 6), and to the proper protection of the exit site (point 7).

The very low incidence of dislodgment is explained by the simultaneous adoption of two different strategies: tunneling (so to move the exit site to a stable area) (point 5) and sutureless securement (subcutaneous anchorage being particularly effective in this regard) (point 6).

The absence of any case of bleeding from the exit site and the very low rate of local complications may be related to the consistent use of glue on the exit site.

The absence of CRT in the first 2 weeks after the insertion is also the results of several "wise" choices: pre-procedural choice of the most appropriate vein by ultrasound examination, with special attention to the catheter/vein ratio (point 1), minimization of the trauma to the vein wall by ultrasound guided venipuncture (point 3), proper position of the catheter tip, verified by intra-procedural methods (point 4), and optimal stabilization of the catheter using a multimodal strategy including proper choice of the exit site (point 5), sutureless securement (point 6), cyanoacrylate glue and semipermeable transparent dressing (point 7). Even in children, where PICCs were extensively used, there was no CRT, confirming previous studies showing that PICCs are not significantly associated with increased risk of CRT, as long as a proper insertion bundle is adopted.

The absence of any case of tip migration with secondary malposition is probably related to the very accurate tip location by intraprocedural methods and by the prevalent use of use of polyurethane catheters. The very low use of silicon catheters may explain the absence of any case of catheter breakage in the first 2 weeks.

Interestingly, the SIC-Ped bundle was associated not only with and extremely low rate of complications, but also with low procedural costs, considering that no radiological control was required (fluoroscopy or post-procedural X-ray) and that all insertions were performed in NICU or PICU, avoiding expensive environments such as the operating room or the radiology suite. Further studies are warranted to further demonstrate not only the clinical safety of the SIC-Ped bundle, but also its cost-effectiveness.

Limitations of the study

The main limitation of the study is that all insertions were carried out by a small number of specifically, highly trained clinicians; the same results may not be reproduced by clinicians not properly trained in the use of ultrasound and/or in the use of intracavitary ECG.

Also, though we assumed that only complications occurring during the first 2 weeks might be related to the insertion maneuver, this contention may not be completely true.

Last, in our study only elective CVAD insertion were considered. The SIC-Ped bundle might be less feasible in emergency conditions, considering the time required for some of its steps (preprocedural examination; proper adoption of antiseptic technique; tunneling).

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