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Original Article

Paediatrics Section

Quality Improvement Initiative for Neonates: Use of In-line Endotoxin Filters in Central Venous Catheters: A Prospective Interventional Study

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ABSTRACT

Introduction: Sick newborns often require central venous catheters for prolonged periods of time when admitted to the Neonatal Intensive Care Unit (NICU). These central lines, hence, raise the problems of sepsis, thrombus and other potential line-related complications. In-line endotoxin filters are found to be an effective intervention to remove potential sepsis causing bacteria, endotoxins and other particulates there by reducing the mortality and morbidity of these newborns.

Aim: To determine the effect of in-line endotoxin filters on mortality and occurrence of venous thrombosis, sepsis and Necrotising Enterocolitis (NEC) in sick newborns with central venous catheters.

Materials and Methods: This single-centre, prospective interventional study was conducted over a period of 12 months, where, all sick babies admitted to the NICU for more than 24 hours with a central venous catheter were eligible for the study. They were grouped into those which received the in-line filters (study group) and those with standard care without filters (control group). The primary outcome variables studied were sepsis, thrombus formation, NEC, ventilator days and death. Secondary outcomes were days of hospital stay, line days, and length of ICU stay.

Results: Out of 137 eligible neonates, 127 were finally included in the study; 66 were in the control group while 61 in the study group, seven were excluded and a total of 54 in the study group were included. A total of 20 cases developed NEC in the control group while only six in the study group (p-value=0.03). Thrombus formation was lesser in the study group 3 (5.6%) compared to the control group 14 (21.2%). Thrombus formation was also found to be less likely to occur when an in-line filter is attached as compared to not using one (OR 0.232; 95% CI 0.628-0.858; p-value=0.02). The odds of occurrence of NEC (OR=0.307; 95% CI=0.113-0.834) also were found to be significantly less in the study group.

Conclusion: A simple intervention like addition of in-line endotoxin filters to the central venous catheters in sick newborns in NICU decreases the risk of thrombosis, risk of NEC and overall complications, in critically-ill NICU patients.

Keywords: Intensive care, Infection control, Neonatology

INTRODUCTION

Central venous catheterisation is an essential tool in NICU for the easy administration of medications, fluids, blood and blood products and total parenteral nutrition in sick preterm and term newborns for prolonged periods of time [1]. Peripheral venous cannulation is the first vascular access obtained when a baby arrives to the NICU, however, it is shown to have a median lifespan of 23-40 hours [2]. This, along with the common problems associated with peripheral line like thrombophlebitis and blockage, necessitates the need for a central venous catheter commonly in babies whom peripheral access may be difficult. However, the use of central venous catheters does not come without its associated complications including bacterial septicaemia, venous thrombosis and mechanical obstruction due to particulate matter [3].

Central Line Associated Blood Stream Infections (CLABSI) is one of the most common nosocomial infections in the newborn which leads to prolonged stay and death in the NICU [4]. Contamination can occur from organisms present on the skin, catheter hub or infusate. Other risk factors also include number of days the catheter is in-situ, low birth weight babies, low gestational age babies, presence of a femoral catheter and use of parenteral nutrition [1,4,5]. The commonly seen pathogen are gram positive cocci; *Staphylococcus* and coagulase-negative Streptococci being the most prevalent but, gram negative bacilli have an extremely high prevalence in the NICU which include *Klebsiella* and *E. coli*. The endotoxins released from these bacteria multiply rapidly and adhere to the catheter by formation of a biofilm [4-6]. These endotoxins can have devastation effects on the newborn causing intestinal ischaemia and periventricular leukomalacia [7,8].

Venous thrombosis is another complication frequently associated with placement of a central venous catheter. In fact, with the placement of a central line in a newborn, the occurrence of venous thrombosis can vary widely and the chance of developing a thrombus can be as high as 67%. Occurrence of thrombosis however, depends on various risk factors starting from size and type of the catheter used, number of times catheter insertion was attempted, pre-existing illness in the newborn like coagulopathies, etc., [3,9].

Particulate contamination of infusates can occur while reconstitution or handling of medication or during manufactures itself [10]. These particles can mechanically obstruct the microvessels and local inflammatory activation and subsequent generation of microthrombi [6]. This further leads to ischaemic necrosis which is seen in NEC [11].

All these anticipated problems can be alleviated with the use of an in-line endotoxin filter. The use of these filters for central lines has been recorded as early as the 1960s [1] to reduce the particle load and filter out the bacteria and endotoxins [12,13]. Thereafter, several adult and paediatric studies have been conducted on the use of these filters and have shown improvement in survival rates and reduction of complications [14-16]. The same, however, cannot be said regarding evidence and recommendation of endotoxin filters use in the NICU. The aim of the present study was to determine the effect of use of an in-line endotoxin filter in central venous catheters of sick neonates admitted to NICU on their morbidity and mortality.

MATERIALS AND METHODS

The single-centric, prospective, interventional study was conducted in NICU of Department of Paediatrics, A.J. Institute of Medical Sciences, Mangalore, Karnataka, India. The study was conducted

from October 2019 to October 2020. The study details were explained to all patients'parents/guardians in their own language and a written informed consent was ascertained for the same. Ethical committee clearance was obtained from the Institution's Ethics Committee (IEC) [AJEC/REV/198/2019 dated 22/10/19].

Inclusion criteria: All sick babies admitted to the NICU who were likely to stay in the NICU for longer than 24 hours and had a central line (umbilical/femoral/internal jugular/axillary) on arrival or had a central line inserted in their stay in the NICU were included in the study.

Exclusion criteria: Those babies who developed sepsis within 24 hours of life were excluded. Readmission to the ICU for a second central catheterisation, having already been included during their first stay were excluded from the study.

Sample size calculation: Presuming the intervention can reduce mortality by 25% in the study group, an estimated sample size of 54 babies in each group was calculated in order to achieve 80% power with alpha of 0.05 and beta of 0.2.

Study Procedure

Included patients were then assigned either to the study group to receive the intervention or to the control group to receive routine care depending on the affordability of the patient. Once patients were assigned the study group, an in-line endotoxin microfilter was attached to the central line, either immediately after admission or after insertion of the line during the NICU stay. Patients in the control group were given the routine line care as per NICU protocol.

The in-line endotoxin microfilter used was the neonatal in-line filter from the company VYGON™ with a 0.22 µm pore. The filter removes endotoxins associated with bacteria along with particulate matter. It has been recommended for use only with fluids and medications and not with blood or lipid containing products. The filtration membrane is made of polyether sulfone, known to have a low absorption profile, which allows it to be compatible with most drugs and colloid compounds and its positive charge helps to retain the endotoxins in its filter. It is latex and di (2-ethylhexyl) phthalate free, contains no biological or animal-based products and is non pyrogenic in nature.

Nurses who were trained in handling of the in-line filter would check the in-line filter at hourly intervals for blockage. The same filter can be used upto 96 hours and then warrants a change as per manufacturer. Filters were changed earlier, if they were suspected of contamination or blockage. The routine NICU line bundle of care protocol was followed for all patients.

Once the patients were included in the study, baseline characteristics including gender, gestational age, examination findings and provisional diagnosis were noted. Suspected sepsis was defined as clinical features suggestive of sepsis. Probable sepsis was defined as clinical symptoms and signs with two or more laboratory parameters supporting sepsis. Proven sepsis was defined as blood culture confirmed sepsis. NEC was defined as per Bell's criteria [17].

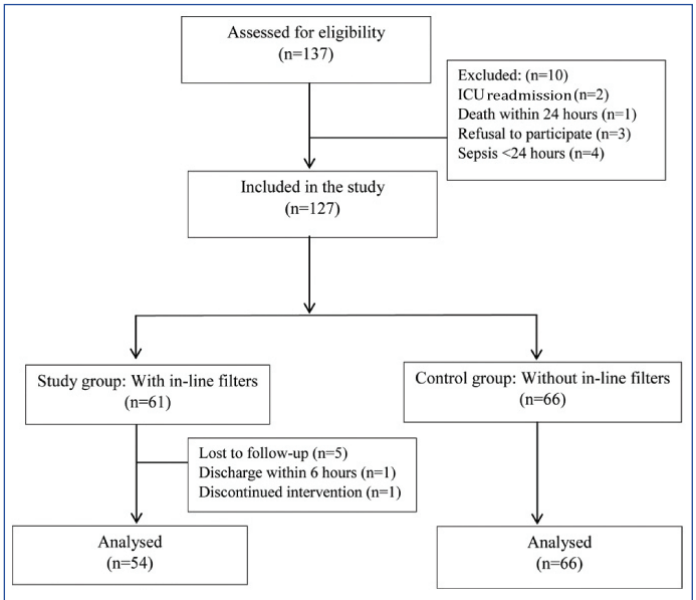
Primary outcome was occurrence of major events which included sepsis (suspected, probable and proven sepsis), thrombus formation, NEC (suspect, definite and advanced sepsis), need of mechanical ventilation and mortality. Sepsis prior to 24 hours of life was not taken into account. The secondary outcome variables studied were number of days the central line was in-situ, days of ICU stay and days of hospital stay.

STATISTICAL ANALYSIS

All collected data were filled into a Microsoft excel sheet. Statistical analysis was conducted by International Business Machines (IBM®) Statistical Package for the Social Sciences (SPSS®) version 16.0. Mean±standard deviation was calculated for continuous while frequencies and their corresponding proportions were calculated for categorical data. Qualitative data was then analysed using Chi-square test, while quantitative data was analysed with Independent t-test.

RESULTS

Total 137 sick babies admitted to the NICU were assessed for eligibility to be included in the study. After excluding 10 patients, 127 were finally included in the study. There were 61 in the study group and in 66, no intervention was done. A total of only 120 neonates were finally analysed, as five were lost to follow-up, one each were discharged within six hours and discontinued the intervention in the study group. So, a total of 54 in the study group and 66 in the control group were analysed [Table/Fig-1].



[Table/Fig-1]: Overview of patient enrollment.

The groups were compared in terms of demographic data as depicted in [Table/Fig-2]. A total of 20 cases developed NEC (suspect, definite, and advanced) in the control group, while only six developed it in the study group, among which none were noted to have advanced NEC. This was considered to be significantly less than the control group (p=0.03) [Table/Fig-3].

Baseline characteristics		Control group (n=66) n (%)	Study group (n=54) n (%)	p-value
Gender	Male	37 (56.1)	31 (57.4)	0.082
	Female	29 (43.9)	23 (4.6)	
Gestational age (in weeks)	Term	34 (51.5)	30 (55.6)	0.336
	Preterm	32 (48.4)	24 (44.4)	
Age in days, mean±SD		12.7±12.27	14.2±13.6	
Central line type	Umbilical	66 (100)	48 (88.9)	0.07
	Femoral	0	6 (11.1)	
Weight (in grams), mean±SD		2459.56±883.22	2256.49±689.45	0.165
Disease category at admission	Cardiac	7 (10.6)	4 (7.4)	0.331
	Neurological	5 (7.6)	4 (7.4)	
	Haematological	13 (19.7)	15 (27.8)	
	Respiratory	31 (47)	29 (53.7)	
	Surgical	10 (15.1)	2 (3.7)	

[Table/Fig-2]: Baseline characteristics both group.

Thrombus formation when a filter was used was significantly lesser 3 (5.6%) as compared to when it was not used in the control group 14 (21.2%). The incidence of sepsis was found to be the same in both groups. Although there were less number of babies requiring ventilation in the group which used the filter, it was not statistically significant when compared to the group which did not. The use of in-line filter did not reduce the mortality.

The secondary outcomes showed no statistical difference when the mean length of ICU stay, number of line days and mean length of hospital stay were compared between the two groups [Table/Fig-4].

Outcome		Control group (n=66) n (%)	Study group (n=54) n (%)	p-value
Thrombus		14 (21.2)	3 (5.6)	0.014
Necrotising enterocolitis	No	46 (69.7)	48 (88.8)	0.03
	Suspect	15 (22.7)	3 (5.6)	
	Definite	3 (4.6)	3 (5.6)	
	Advanced	2 (3)	0	
Sepsis	No	4 (6.1)	4 (7.4)	0.45
	Suspect	13 (19.7)	10 (18.5)	
	Probable	44 (66.7)	31 (57.4)	
	Proven	5 (7.6)	9 (16.7)	
Ventilatory use		56 (84.8)	39 (72.2)	0.09
Mortality		30 (45.5)	18 (33.3)	0.19

[Table/Fig-3]: Primary outcomes.

Parameter	Study group	Control group	p-value
Line days	7.26±4.327	6.12±4.270	0.151
ICU stay	8.76±5.549	7.11±5.225	0.096
Hospital stay	12.52±7.642	10.09±7.971	0.094

[Table/Fig-4]: Line days, ICU days and hospital stay in the two groups.
Values presented in Mean±SD

The Odds Ratio (OR) for thrombus formation in filter group was 0.232 with 95% confidence interval (0.628-0.858) which indicates that thrombus formation is less likely to occur when an in-line filter is attached as compared to not using one (p=0.02). The odds of occurrence of NEC (OR: 0.307 95% CI: 0.113-0.834) also were found to be significantly less in the study group. However, the odds of incidence of sepsis, use of ventilator and mortality was lesser when compared to that in the control group with OR of 0.806 (95% CI=0.192-3.387), 0.58 (95% CI=0.228-1.476) and 0.655 (95% CI=0.308-1.387), respectively, but were not found to be statistically significant (p=0.76, 0.25, 0.26) [Table/Fig-5].

Parameter	Odds ratio value	95% Confidence interval		p-value
		Lower	Upper	
Thrombus	0.232	0.628	0.858	0.028
Sepsis	0.806	0.192	3.387	0.768
NEC	0.307	0.113	0.834	0.02
Ventilator	0.58	0.228	1.476	0.253
Death	0.655	0.308	1.387	0.268

[Table/Fig-5]: Odds ratio of thrombus formation, ventilator use and mortality with use of endotoxin filter.

DISCUSSION

In the present study, the use of endotoxin filters for central venous catheters in sick newborn babies in NICU considerably reduced morbidity without having significant effect on the mortality. A significant reduction in the risk of thrombus formation and occurrence of NEC was demonstrated for filter group. Occurrence of sepsis was the same in both the groups, however, the ventilator use and death although lower in the study group, was not statistically significant. Similarly, the use of endotoxin filterssaw a decrease in the length of NICU stay and total length of stay in the hospital, although statistically found not to be significant.

A Cochrane analysis [1] reviewed 704 neonates who were using in-line filters in their central line. Published data from four studies showed no reduction in mortality (RR 0.87, 95% CI) with use of the filters. There was also no effect on occurrence of sepsis, NEC or any of the other predicted complications in the neonates who used the filters. It was concluded by the authors that, there is not sufficient amount of evidence to recommend routine usage of filters in newborns. Unlike these results, the present study showed significant reduction in the thrombus formation and NEC in filter group. Occurrence of sepsis however, was found to be alike in the most studies which was the same, as the present study had determined [1,18].

In a study done by Van Lingen RA et al., [19] published in 2004, the authors were successful in proving that the use of in-line filters significantly not only reduced the incidence of complications like sepsis and bacteraemia but also phlebitis and thrombus formation. Interestingly, they also showed cost effectiveness where the group using the filters had to spend considerably lesser amount of money for disposables than the group that didn't have the filters.

Virlouvet AL et al., conducted a randomised control trial on the use of filters in 147 sick very preterm newborns. The results were similar to the present study, where the neonatal mortality rates were not significantly low in filter group compared to the study group. However, when incidence of pulmonary haemorrhage was studied, it did show a significantly less incidence in the filter group and also a lower incidence of long-term complications like severe retinopathy of prematurity in those with filters [20]. Unlike in the study done by Brivet FG et al., specific extrapulmonary organ functions such as renal or haematological functions were not evaluated. However, the impact of organ functions would have had a considerable effect on the length of NICU or hospital stay; which was found to be similar in both the groups in the present study [21].

The present study, is one of the only studies done to know the effectiveness of in-line endotoxin filter in reducing the complication and mortality of neonates in an Indian population.

Limitation(s)

The present study wasn't blinded as sham filters in the control group were not used. Due to this open-label design, authors cannot refuse the possibility of additional risk of sepsis and contamination in the group of babies who had the endotoxin filter. The present study was a single-centric study, done on both term and preterm babies. Outcomes were analysed together for both and not considered separately for term and preterm babies. Other confounding factors like low birth weight and asphyxia were not considered. The study group and the control group varied in the sample size which causes bias. Finally, the use of in-line microfilters was associated with additional cost of purchase however, the overall cost-effectiveness was not studied.

CONCLUSION(S)

The present study shows that a simple intervention like addition of in-line endotoxin filters to the central venous catheters in sick newborns in NICU goes a long way, in preventing major complications such as thrombus formation and NEC. It decreases the risk of thrombosis, risk of NEC and overall complications in critically-ill NICU patients. However, further studies are needed to prove the efficacy of endotoxin filters in neonates, in order to formulate recommendations for routine use of these in the NICU.

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