**Title: Alcohol Impregnated Port-Protectors to Reduce Central Line-Associated Bloodstream Infection in the Neonatal Intensive Care Unit: A Quality Improvement Study**

**Abstract**

**Title:** Alcohol Impregnated Port-Protectors to Reduce Central Line-Associated Bloodstream Infection in the Neonatal Intensive Care Unit: A Quality Improvement Study

**Objective:** To investigate the effect of AIPPs on neonatal CLABSI rates.

**Design:** A quality improvement study.

**Setting:** A tertiary neonatal unit in the United Kingdom.

**Patients:** Babies > 72 hours of age with a central line.

**Intervention:** AIPPs were applied to intravascular access ports not allocated for fluid infusion from March 2018 – February 2020. Daily audits were performed for 3 months post-implementation, with quarterly audits thereafter.

**Main Outcome Measures:** CLABSI rates were calculated pre and post implementation with a 3-month washout period (March-May 2018). Logistic regression was used to analyse the risk of CLABSIs between periods adjusting for important differences between cohorts.

**Results:** There was no difference in overall CLABSI rates per 1000 central lines days between the pre- and post-implementation periods (5.5 vs 6.6, p=0.5) However, rates of CLABSI involving confirmed pathogens rather than Coagulase Negative Staphylococcus (CoNS) were higher post implementation (0.5 vs 2.7, p=0.012). After adjusting for birthweight, gestational age at birth, gender, central line duration and length of stay, there was no significant differences in the overall risk of CLABSI between the two periods (OR 1.05, 95%CI 0.57-1.91, p=0.886) or the risk of CLABSI involving pathogens (OR 3.54 95% CI 0.77 – 16.06, p =0.102) or CoNS (OR 0.76 95% CI 0.39 – 1.46, p =0.406).

**Conclusions:** AIPPs did not result in reduced CLABSI rates. The use of AIPPs cannot currently be recommended.

**What is already known:**

* Decontamination of central venous catheter (CVC) needleless connectors by “Scrubbing the Hub” is susceptible to sub-optimal practice, a possible cause of CLABSIs.
* AIPPs, containing an isopropyl-alcohol-impregnated sponge, offer a potential solution although evidence of efficacy of these devices in the neonatal population is lacking.
* The National Institute of Clinical Excellence have recognised that the evidence for AIPPs is limited and support further research into their efficacy.

**What this study adds:**

* There was no reduction in CLABSI rates following the introduction of AIPPs in a UK tertiary neonatal intensive care unit, even when adjusting for important confounding variables. There was some evidence they may increase the risk of CLABSIs caused by pathogenic organisms rather than Coagulase Negative Staphylococci (CoNS)
* Given that AIPPs are more costly than standard ‘scrub the hub’ practices, and a current lack of evidence for their efficacy, it is currently hard to recommended them for routine clinical practice based on the present study.

**How this study might affect research, practice, or policy**

* Given the limited evidence for AIPPs, we strongly urge NICUs that are using AIPPs to publish their experiences to contribute to the scientific evidence to further inform practice and policy development.
* There is a need for larger scale, multi-centre research to determine the effectiveness of AIPPs in the neonatal population, including high-risk sub-groups.

**BACKGROUND**

Late onset neonatal sepsis (LOS), defined as systemic bacterial or fungal infection occurring in babies who are at least 72 hours of age, is associated with increased neonatal mortality, morbidity, and increased length of hospitalisation [1-3]. Invasive medical devices are an important risk factor for LOS [4], and bacterial infection in the presence of a CVC is referred to as a central line-associated bloodstream infection (CLABSI). Whilst CVCs are lifesaving in sick and preterm neonates, they are a source of entry for microorganisms, which can enter either at the point of insertion or via extraluminal entry as a result of colonisation of needleless connectors attached to the central line. Less common aetiologies include seeding from another site of infection. While data concerning the economic impact of CLABSIs in NICUs are lacking in the UK, in the US it has been estimated that each episode of LOS prolongs hospitalisation by approximately 2 weeks, at a cost of $25,000 per episode [5]. With reports of vancomycin resistant *Staphylococcus capitis* in NICUs, and an association between LOS and morbidities such as bronchopulmonary dysplasia and impaired neurodevelopment, preventing these infections should be considered a key priority [6-9].

Reported CLABSI rates in neonatal settings vary, ranging across the US and Europe from zero to 21.8 CLABSIs per 1,000 central line days,though variations in surveillance definitions make direct comparisons between centres difficult [10]. Whilst the UK National Neonatal Audit Programme (NNAP) no longer reports CLABSI rates, a 2022 report [11] suggested CLABSI rates of 2.9 per 1000 central line days in babies >32 weeks gestation, and 7.9 per 1000 central line days in those <32 weeks gestation. Variations are not explained by differences in case mix, suggesting that there may be opportunities to reduce these infections through changes in local practices [12].

Strategies aimed at reducing CLABSIs commonly include multi-modal interventions such as care bundles, focusing upon CVC insertion practices and decontamination of needleless connectors [13]. The decontamination of needleless connectors using ‘scrub-the-hub’ techniques - cleaning with a chlorhexidine and alcohol-based solution for 15 to 30 seconds with 15 to 30 seconds drying time - has remained the focus of central line maintenance bundles. However, this practice is prone to human error and has shown to be not fully adhered to, which may result in the nosocomial introduction of bacteria into the catheter [14].

Alcohol-impregnated Port Protectors (AIPPs) are plastic caps with an isopropyl-alcohol-impregnated sponge inside, which screw onto needleless connectors. They offer a solution to the variable adherence to the scrub-the-hub procedure and have the potential to reduce the use of antibiotics in an environment which is known to promote the development of antimicrobial resistance [15].

Whilst a meta- analysis of data from nine studies, in a variety of healthcare settings, found a statistically significant difference in CLABSI rates favouring AIPPs, there was no difference when analysing the data from the only two included RCTs alone (RR 0.79 [0.29, 2.21] [16]. Only one study was performed in the paediatric and neonatal ICU setting [17], and whilst there was a reduction from 3.1 to 2.1 CLABSIs per 1000 central line days in the NICU, this was not statistically significant. The National Institute of Clinical Excellence [18] have recognised that the evidence for AIPPs is limited and support further research into their efficacy.

The aim of this study was to determine whether, in neonates > 72 hours of age with a CVC, AIPPs were more effective in reducing CLABSIs compared with the scrubbing the hub technique.

**METHODS**

This was a prospective before-and-after study performed in a 37-bed tertiary NICU in the U.K. The service has approximately 750 neonatal admissions, annually. In 2015 a multi-disciplinary team was formed to address local CLABSI rates. A care bundle was implemented between 2015- 2017 which included a two-person technique and a checklist for CVC insertion as well as education, audit, and feedback [19]. Further details on the local context are reported elsewhere [19].

Prior to the introduction of AIPPs in March 2018, standard practice was to decontaminate the ports of intravascular catheter hubs with 2% Chlorhexidine and 70% Isopropyl Alcohol impregnated swabs for 30 seconds with a 30 second drying time. Accessing CVCs was performed using a two-person surgical Aseptic-Non-Touch Technique (ANTT). Standard practice for CVC insertion involved a two-person technique with an insertion checklist. Chlorhexidine 2% with 70% isopropyl alcohol was used to clean the skin of neonates > 28 weeks, and chlorhexidine 0.05% aqueous solution for neonates <28 weeks, prior to central line insertion.

In March 2018, AIPPs (Curos Caps©) were introduced and attached to all peripheral and central venous catheter needleless connectors that did not have a continuous infusion attached. Needleless hubs were considered to have been decontaminated if the AIPPs had been attached for one minute and were routinely replaced if they had remained in situ for more than seven days. Following the introduction of the AIPP, there were no further changes to central line care during the study period. All nursing staff received training prior to implementation. Information was disseminated throughout the nurseries to act as reminders.

Period 1 (pre-implementation) was 12 months from March 2017-February 2018, with a three-month washout period between March 2018-May 2018 to allow for the AIPPs to be adopted into routine practice, prior to the intervention period, Period 2 was from June 2018 to February 2020.

Patient characteristics were collected from the electronic admissions system Badgernet (CleverMed) [20] for all babies > 72 hours of age with a CVC during the study period. Babies admitted ex-utero from other centres were included. Data on AIPP compliance were collected daily during the 3-month washout period by the nurse co-ordinator on each shift. After this, retrospective spot audits were performed every 3 months, for all neonates with a CVC who were an inpatient on the NICU on the first day of each quarter using nursing daily checklists, which required nurses to check if AIPPs were in situ on all needless connectors not attached to a continuous infusion.

CLABSIs were defined using a modified CDC definition in keeping with previous studies (21). This requires a laboratory confirmed infection (positive culture) in the presence of a CVC or umbilical venous catheter which has been in place for > 2 calendar days on the date of the event. In cases where a CVC was in place for >2 days and removed, the day of the laboratory confirmed infection must be the day of removal or the following day. Duplicate blood cultures, defined as a blood culture growing the same organism within 72 hours of a previous blood culture, were excluded, and any discrepancies discussed with a consultant neonatologist. Microorganism data were collected, which was categorised as either a pathogen (for example, Escherichia coli, Staphylococcus aureus) or a CoNS. In our neonatal unit CoNS are the commonest organisms associated with CLABSIs.  These organisms are thought to enter the blood of the babies via the CVC as a result of contamination from the handling of the ports by staff or from the babies' skin [21]. CLABSIs associated with CoNS might, therefore, be expected, to be reduced by the use of AIPPs. Other organisms, including gram-negative bacilli, may enter the blood as a result of membrane barrier injury, particularly in the gut [22] and the frequency of CLABSIs associated with these organisms might be less influenced by AIPPs.

Total central line days were collected from Badgernet [20]. A central line was defined as a peripherally inserted central catheter, an umbilical venous catheter, jugular catheter, or surgically inserted central venous catheter, where the catheter tip is in a central vein. CLABSI rates were reported per 1000 central line days.

**ETHICS**

As AIPPs are CE marked and already the standard of care in many UK units, they were introduced as part of a local change in the standard of care and so ethical approval was not required. Local Trust approvals were obtained. Ethical approval was obtained via the University of Southampton for collection of audit data (ERGO 51412), forming part of a wider service evaluation project and was anonymised for analysis. Vygon, who manufacture Curos Caps©, had no involvement in any aspect of this study.

**STATISTICAL ANALYSES**

Descriptive statistics were used to present patient characteristics data. Data were tested for normality using Kolmogorov-Smirnov test., with median and inter-quartile ranges used to describe data with a non-normal distribution and mean and standard deviation used for normal data. Run charts of monthly CLABSI rates were used as part of routine clinical surveillance.

Microsoft Excel (2016) and SPSS (v26) were used to analyse data. Mann Whitney tests were used for continuous data, and Chi-squared tests for categorical data. Spearman’s correlation was used to describe the relationship between AIPP adherence and CLABSI rates. For the main outcome of the difference in CLABSI rates per 1000 days between the study periods, exact Poisson regression was used to compare ratio ratios. Logistic regression (Stata v16.1, StataCorp LLC, College Station, Texas) was used to analyse the risk of CLABSIs between periods with adjustment for birthweight, gestational age at birth, gender, central line duration and length of stay.

**RESULTS**

A total of 819 babies had a CVC in situ during the entire study period, of which 66 had a positive blood culture in the presence of a CVC (see Tables 1 and 2). There were no statistically significant difference in clinical characteristics of babies with a CVC during each period (see Table 1).

**Table 1 Clinical characteristics of the babies with CVCs in each period**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Period 1 (n=324)** | **Period 2 (n=495)** | **p Value for difference** |
| Sex (female: n (%)) | 142 (43.8) | 278 (43.8) | 1.00 |
| Gestational Age (weeks)\* | 32.9 (29.2 – 37.8) | 32.5 (28.9 – 38.3) | 0.88# |
| Birthweight (grams)\* | 1639 (1058 – 2913) | 1700 (1000 – 3070) | 0.88# |
| Diagnosis: n (%) |  |  |  |
|  Preterm (<37 weeks) | 224 (69) | 326 (66) | p=0.32 |
| Extremely preterm (<28 weeks) | 55 (17) | 100 (20.2) | p=0.25 |
| NEC | 13 (4) | 24 (4.9) | p=0.32 |
| Ventilation (days)\* | 2 (0 – 5) | 2 (0 – 6) | p=0.93# |
| Length of Stay (days)\* | 16 (5 – 46.5) | 14 (5 – 45) | p=0.99# |
| Days with central line | 7 (3-15.5) | 8 (3-18) | p=0.85# |
| No of central line days | 3790 | 6788 |  |

Data are median (IQR) unless otherwise stated. p Values are from X2 tests unless marked with #, indicating Mann-Whitney test.

Table 2 describes the blood culture results. There were 21 positive blood cultures in period 1, and 45 positive blood cultures in period 2, with the majority being gram positive organisms in both pre and post periods (95% and 89% respectively). Coagulase Negative Staphylococci (CoNS) accounted for the majority of positive blood cultures in both the pre and post periods (90% and 60% respectively).

The number of CVC days was 3812 in the pre-period and 6788 in the post period. Median AIPP adherence was 93%, ranging from 77% to 100% (see supplementary Figure 1). There was no correlation found between AIPP adherence and CLABSI rates at 12 months (*p*= 0.84) or 21 months (*p=*0.94) post implementation. A run chart showing CLABSI rates during the study period is available in supplementary Figure 1. The estimated annual cost of AIPPs was £10,000.

**Table 2 Description of Blood Culture Results**

|  |  |  |
| --- | --- | --- |
|  | **Period 1**  | **Period 2** |
| **Total positive blood cultures**  | 21 | 45 |
| Pathogen positive blood cultures | 2 | 18 |
| CoNS positive blood cultures | 19 | 27 |
| **Gram Positive**  |
| Total CoNS  | 19 (90%) | 27 (60%) |
| Staphylococcus aureus | 0  | 12 (27%) |
| Enterococcus faecium | 1 (5%) | 1 (2%) |
| **Total Gram Positive** | **20 (95%)** | **40 (89%)** |
| **Gram negative**  |  |  |
| Escherichia coli | 1 (5%) | 2 (4%) |
| Enterobacter spp | 0 | 2 (4%) |
| Klebsiella | 0  | 10 |
| Pseudomonas | 0 | 1 (2%) |
| **Total Gram Negative** | **1 (5%)** | **5 (11%)** |

Legend : CoNS= coagulase negative staphylococcus

For all babies admitted to the neonatal unit during the study period, in the post-period there was no significant change in the overall CLABSI rate following the introduction of AIPPs compared to the pre-period (6.6 vs 5.5 per 1000 central line days, p=0.505, table 3). Similarly, there was no significant difference in the percentage of infants with CLABSIs, or those caused specifically by CoNS. There was a significant increase in both the number of infants with CLABSIs caused by pathogens, and the rate of pathogen associated CLABSIs (table 3)

**Table 3: CVC and CLABSI rates in each study period**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pre** | **Post** | **p Value**  |
| Total pathogen rate per 1000 central line days | 0.5 | 2.7 |  0.012 |
| Total CoNS rate per 1000 central line days | 5.0 | 4.0 |  0.441 |
| Total CLABSI rate per 1000 central line days | 5.5 | 6.6 |  0.505 |

Legend: CoNS= Coagulase Negative Staphylococci, CI = Confidence interval. p values are from Exact Poisson method based on rate ratio

Table 4 presents the characteristics of babies with a CLABSI in the pre and post period. There were no differences in median gestational age, birthweight or the number of males between the two periods.

**Table 4: Population Characteristics of Babies with CLABSIs**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pre** | **Post** | **p Value** |
| No of CLABSIs | 21 | 45 |  |
| Gestational age\* | 27.6 (25.9-30.7) | 27.0 (25.7-28.9) | 0.121# |
| Birthweight \* | 926 (760-1260) | 800 (700-1000) | 0.350# |
| Male (%) | 14 (67) | 28 (62) | 1.00 |

\* Median (inter-quartile range), p Values are from X2 tests unless marked with #, indicating Mann-Whitney test.

Univariate logistic regression (table 5) showed that in infants with a CVC in situ, higher birthweight and gestational age at birth were associated with an increased overall risk of CLABSI, whilst higher duration of central line and length of stay were both associated with an increased risk of CLABSI. Study period had no significant effect. A multivariate logistic regression model considering study period, birthweight, gestational age at birth, gender, central line duration and length of stay (table 5), showed no difference in the risk of CLABSI between the two periods (OR 1.05, 95% CI 0.57-1.91, p=0.886). However, higher gestational age at birth continued to be associated with a reduced risk of CLABSI (OR 0.83, 95%CI 0.73-0.94, p=0.003), and the effect of longer central line duration on the increased risk of CLABSI also remained (OR 1.06, 95% CI 1.04-1.09, p <0.01). When looking at only pathogens, whilst there was significantly higher risk of a CLABSI by a pathogen in the intervention period (OR 4.54 95% CI 1.05 – 19.52, p =0.042), after adjustment for birthweight, gestational age at birth, gender, central line duration and length of stay, this was no longer significant (OR 3.54 95% CI 0.77 – 16.06, p =0.102). Repeating this analysis for only CLABSIs with CoNS, the was no significant difference between study periods before (OR 0.70 95% CI 0.39 – 1.26, p =0.242) and after adjustment (OR 0.76 95% CI 0.39 – 1.46, p =0.406).

**Table 5.** Logistic regression model for risk of any CLABSIs in each period, with adjustment for birthweight, gestational age at birth, gender, central line duration and length of stay

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Any CLABSI** | **Odds Ratio (95% Confidence interval)- univariate analysis** | **p Value** | **Adjusted Odds Ratio (95% Confidence interval)- multivariate analysis** | **p Value** |
| Period | 1.44 (0.84-2.47) | 0.182 | 1.05 (0.57 - 1.91) | 0.886 |
| Birthweight | 0.999 (0.998-0.999) | **<0.001** | 1.00 (1.00 – 1.00) | 0.821 |
| Gestational Age at Birth | 0.77 (0.72-0.83) | **<0.001** | 0.83 (0.73 - 0.94) | **0.003** |
| Gender | 0.66 (0.39-1.12) | 0.127 | 0.68 (0.37 - 1.23) | 0.202 |
| Central line duration (days) | 1.07 (1.06-1.09) | **<0.001** | 1.06 (1.04 - 1.09) | **<0.001** |
| Length of stay | 1.03 (1.02-1.03) | **<0.001** | 1 (0.99 - 1.01) | 0.466 |
|  |  |  |  |  |

**DISCUSSION**

To the best of our knowledge this is the first study reporting on the efficacy of AIPPs in a UK tertiary NICU. This study found that following the introduction of AIPPs, there was no change in the rate of CLABSIs overall and no impact on CLABSIs. AIPPs were associated with a significant increase in pathogens causing CLABSIs. Using logistic regression, after adjustment for birthweight, gestational age at birth, gender, central line duration and length of stay there was no reduction in the risk of CLABSIs in the period following the introduction of AIPPs. These findings contrast with the results of a meta-analysis of nine studies across a range of healthcare settings, suggesting AIPPs may reduce CLABSIs by 40% (95% CI 0.41-0.89) [16]. However, only two of the studies were randomised studies, and only one study was performed in paediatric and neonatal ICUs [17]. However, relatively small numbers of CLABSIs and variations in infection rates may increase the risk of type 2 errors in paediatric non-randomised studies [24]. A risk of publication bias was also considered likely within the evidence base.

The study by Helder *et al* [17], a before-and-after study investigating the efficacy of AIPPs in both NICU and PICU in the Netherlands, found that whilst CLABSI rates reduced from 3.2 to 2.4 CLABSIs per 1000 CVC days, this was not statistically significant despite reporting adherence of 95.2%. Median adherence in our study was 93%. In a systematic review of AIPPs across a range of healthcare settings, adherence rates were between 60-95%, though this was not reported in 10 of the 14 included studies [16].

The pattern of microorganisms found in this study was different to those reported by Helder *et al* [17], who found gram-negative organisms accounted for 75% of blood cultures. In our study, gram-positive organisms accounted for 91% of all positive blood cultures, with CoNS accounting for 69% of all positive blood cultures. This is similar to data from 30 NICUs in the UK which reported CoNS in 57% of LOS cases [25]. Reducing the burden of these infections has the potential to improve both the quality and safety of neonatal care.

There are several limitations to this study. This was not a randomised controlled trial, and as such there are inherent risks of bias. As a single-centre study, local CVC practices may be different compared to other centres, and differences in the sample characteristics between the pre- and post- intervention periods is a significant limitation. It may be that the more immature babies had CVCs that remained in situ for longer compared to the babies in the pre-intervention period, which may have included more mature babies with shorter durations of CVC use. It is of note that the introduction of AIPP, did not appear to impact the number of days with a central line in situ between pre- and post-cohorts. Helder *et al* reported a median CVC dwell time of 8 days, similar to our study (7-8 days). Whilst the risk of developing a CLABSI likely increases with increasing dwell times, the critical time point remains unclear [25-27]. Studies have suggested an increased risk with dwell times of >14 or >21 days [25-27], although one study found no increased risk concluding that clinicians should not routinely replace CVCs [26].

No adverse effects directly related to AIPP devices were reported in this study. Sauron *et al* [28] reported concerns that isopropyl alcohol may unintentionally be injected into the bloodstream if the alcohol had not evaporated. Alcohol levels were not tested in this study, though Helder *et al* [17] theorised that the maximum potential concentration that could be injected was 0.44 mmols after each removal of the cap. Whilst no adverse effects were reported by Helder *et al*, we have found no published studies which have prospectively measured isopropyl alcohol blood levels with these devices in the neonatal population.

However, this study also found an increase in the number and proportion of pathogenic bacteria, including Staphylococcus aureus and gram-negative bacteria. Whilst this may be an incidental finding, if AIPP devices were responsible for an increase in pathogens by settling out the CoNS, then this would be a strong argument against their use. Another possible explanation is that the AIPPs resulted in unintended changes in healthcare professional infection control behaviours.

Finally, this study used a modified CDC definition of CLABSI reflecting local practice and similar to that used by Helder *et al* [17]. To meet the definition of a CLABSI, the CDC require the same skin commensal to be identified on two or more specimens collected on separate occasions and, for a patient <1 year of age, there must also be one of three clinical signs (fever >38 degrees Celsius, hypothermia <36 degrees Celsius, apnoea or bradycardia). In this study, some babies would have had clinical signs other than those specified by the CDC, and confirmatory blood cultures for CoNS were not always obtained due to the perceived urgency for antibiotic treatment. Heijting *et al’s* consensus definition suggests that, in the case of skin commensals, to include c-reactive protein markers [29]. We did not include biomarkers in this study. The differences in definitions may partly explain the higher rates found in this study, which are higher than the EFCNI benchmarking standard of <5.1 per 1000 central line days [30]. However, the modified definition remained the same throughout the study and should not compromise reliability. A definition that is easy to apply and validated in the neonatal population is required for benchmarking and future research.

Based upon current evidence and the findings from our study, AIPPs cannot be recommended. Randomised controlled trials within a single unit may be impracticable and randomisation of entire neonatal units would require a large number of participants. Therefore, in line with the recommendations by Voor in ’t holt [31], we strongly urge NICUs that are using AIPPs to publish their experiences to contribute to the scientific evidence. Further research should focus upon finding effective ways to reduce CLABSIs in the NICU, including finding strategies to improve adherence to evidence-based practices.

**CONCLUSION**

The introduction of AIPPs into a UK tertiary-level NICU was not associated with a reduction in CLABSI rates. The routine use of these devices cannot currently be recommended.

**ACKNOWLEDGMENTS**

The authors would like to thank the nurses who contributed to the collection of AIPP adherence data and April Perry her contribution to audit data collection.

**CONTRIBUTORSHIP STATEMENT**

MH conceived the study. All authors were involved in the conduct of the study including data collection and analysis. VP drafted the manuscript. All authors were involved in reviewing, editing, and approving the final manuscript. MJ is the guarantor.

**COMPETING INTERESTS**

There are no competing interests to declare.

**FUNDING**

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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