ARTICLE

Adverse events associated with umbilical catheters: a systematic review and meta-analysis

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OBJECTIVE: To determine the incidence of adverse events (AEs) associated with umbilical catheters in the neonatal population.
STUDY DESIGN: Systematic review and meta-analysis of observational studies and randomized controlled trials published between 2010 and 2020.
RESULTS: In total 14,226 umbilical venous catheters (UVCs) and 4228 umbilical arterial catheters (UACs) were included. Overall, 13.4% of UVCs were associated with an AE (95% CI: 10.1–17.0) or 2.4 per 1000 catheter days (95% CI: 1.8–3.0). UACs had an AE rate of 9% (95% CI: 5.9–12.8) or 0.87 per 1000 catheter days (95% CI: 0.4–1.3). UVC malposition was the most common (41.7% [95% CI: 27.6–56.5]). Local injury from UAC taping was the most common AE in one study.
CONCLUSIONS: Umbilical catheters have a high incidence of AEs. Research into accurate methods of tip verification, tip surveillance, and securement is required.

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INTRODUCTION

Umbilical catheters are commonly inserted in acutely unwell or extremely preterm newborns to facilitate clinical care. High-osmolarity fluid, medication, and blood products are administered through the umbilical venous catheter (UVC) [1], and continuous monitoring of arterial blood pressure and regular blood sampling is enabled by an umbilical arterial catheter (UAC) [2].

Despite the clinical utility of umbilical catheters, adverse events (AEs) may occur both during catheter insertion and dwell time. Umbilical catheters are commonly malpositioned directly after insertion and require manipulation, necessitating additional x-rays and radiation exposure [3]. Additionally, damage to the umbilical vessels and surrounding organs can occur during problematic insertions, such as pseudoaneurysm, aortic and peritoneal perforation, and liver hematoma [4–6]. Major AEs during catheter dwell include bloodstream infection (BSI), tip malposition and migration, and thrombosis. BSI is of major concern due to the association with increased length of stay, neurological injury, and mortality [7, 8]. Umbilical catheter tip migration may cause damage to organs, compounded by infusing hyperosmolar fluids causing extravasation [9]. Thrombosis can occur due to endothelial damage as a result of umbilical catheters [10, 11], with serious complications such as renal failure, hypertension, and septicemia, where a 21% mortality rate has been previously reported [12].

Individual studies have examined the incidence of AEs associated with umbilical catheters during insertion and whilst indwelling at single institutions. An overall estimation of all AEs associated with umbilical catheters for the neonatal population has not been previously established. The objective of this review and meta-analysis was to systematically review existing evidence to determine the incidence of AEs associated with UVCs and UACs. This may inform future research into the risk factors for AEs and clinical practice recommendations to reduce the incidence.

METHODS

This study was conducted using standard methods for a systematic review and meta-analysis. The reporting of this study was informed by the recommendations for the Meta-analysis of Observational Studies in Epidemiology [13]. The study protocol was registered with the international prospective register of systematic reviews (ID: CRD42020209219).

Eligibility criteria

Published randomized controlled trials (RCTs) and observational studies (cohort, case-control, or cross-sectional) were eligible for inclusion if they described the incidence of AEs associated with umbilical catheters. Studies only reported as abstracts were eligible for inclusion if incidence data could be extracted, or missing data were later provided by the author when contacted. Qualitative research, case studies, and non-peer-reviewed publications were excluded.

Outcome measures

The main outcome measure was umbilical catheter-related AEs; defined as a non-intentional event directly attributable to the device itself, which may result in extended hospitalization or death [14, 15]. Secondary outcome

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measures include: (1) central line associated bloodstream infection (CLABSI) according to international guidelines [16], defined as a primary BSI in a patient that had a central line within the 48-h period before the development of the BSI that is not related to an infection at another site; (2) catheter-related septicemia, defined as clinical manifestations (clinical symptoms plus laboratory findings) and >1 positive blood culture for definite pathogens or >1 positive culture for other organisms, with a catheter in place [17]; (3) catheter-associated thrombosis; diagnosed by radiography or by clinical signs suggestive of thrombosis; (4) malposition of the catheter tip; with the correct position for UVCs defined as between T9 and T10 on radiography or at the inferior vena cava–right atrial junction and T6–T10 for UACs [18]; (5) migration of the catheter tip after initial correct position determined via radiography, ultrasonography or echocardiography; (6) extravasation of fluid from the vessel into the tissue [19]; (7) iatrogenic events associated with insertion such as direct damage to the umbilical vessels; (8) external leakage or hemorrhage from the insertion site from equipment detachment or unsuccessful ligature; (9) retained or broken catheter; (10) hepatic, cardiac or pulmonary complications, as defined by study investigators; and (11) local injury.

Search strategy

The search strategy and search terms were developed in consultation with an Academic Librarian. The Medical Subject Headings 'infant, newborn' and 'catheterization, central venous' were used in addition to keywords 'arter* catheter*' to obtain studies relating to arterial catheterization. The US National Library of Medicine National Institutes of Health, Embase, Emcare, and the Cochrane Central Register of Controlled Trials were systematically searched on the 16th of September 2020. Limits to studies published in the English language from 2010 to 2020 were applied to maximize and reflect contemporary practice. We also searched for other relevant citations from the reference lists of the included studies. Newly published articles were identified by creating an alert in Google Scholar during study screening.

Study selection

Studies retrieved from the databases were imported into EndNote™ (Clarivate Analytics) and then into Covidence [20] for screening purposes. Each phase of screening was initially conducted by author KG and confirmed by either RS or AU in accordance with the pre-determined inclusion criteria. A third reviewer was used to adjudicate where there was disagreement until consensus was established.

Data extraction

Study data were extracted by author KG. Data from a random sample of studies (40%) were checked by authors RS or AU to ensure accuracy of data extraction. Utilizing a standardized data extraction tool in Microsoft Excel, extracted data included the following key information: main author, title, year of publication, country, study design, aim, setting, participant characteristics and results. Study authors were contacted via email or through ResearchGate to source missing data. For RCTs, if both the intervention and control groups received care consistent with international standards [21], then intervention and control group data were combined, otherwise, only control group data were used in the meta-analysis.

Statistical analysis

Descriptive statistics were used to provide a summary of the study population and results. Statistical analysis was conducted using MedCalc Statistical Software (version 19.6.4) and Stata (version 16.2). Rates of AEs were calculated for each type and presented as a proportion (%) and incidence rate (IR) per 1000 catheter days and 95% confidence intervals (CI). Meta-analysis for the incidence and proportional data were calculated using Freeman–Turkey double arcsine transformations. Standard errors were calculated and for studies where there were no AEs reported, a half event was added so that the study could be included in the meta-analysis. The generic inverse variance method was used to calculate pooled IR outcomes. Pooled estimates were calculated with random-effects models due to significant heterogeneity amongst studies. Heterogeneity was assessed with the I^2 measure and categorized as either low (<25%), moderate (25–75%), or high (>75%). A sensitivity analysis using a meta-regression model was conducted to assess the influence of two different diagnostic methods in determining catheter malposition and migration.

Quality of included studies

The risk of bias of each observational study was determined in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [22]. The 22 items of the checklist help evaluate the rigor of study methods and reporting of outcome measures. A traffic light system used in Cochrane reviews [23] was modified and implemented to map the quality of the study and provide a visual risk of potential bias. Each item number in the STROBE checklist was allocated one point. Studies assigned a total score of 1–7 were allocated a red light, studies with a score of 8–14 a yellow light and 15–22 a green light. For RCTs, study quality was assessed using the CONSORT 2010 checklist [24] with each item number allocated one point. Studies assigned a total score of 1–8 were allocated a red light, studies with a score of 9–16 a yellow light and 17–25 a green light.

RESULTS

Figure 1 details the study selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25]. Over 1300 studies were imported from database searching. After duplicates were removed, 1061 studies were screened and 212 were evaluated at full-text review. An additional 10 studies were identified from hand-searching the reference list of the included studies. The authors of 25 studies were contacted to source missing data; nine did not reply and were thus excluded at full-text review. 15 authors provided additional data, most commonly for the total catheter days [10, 26–39]. A total of 63 studies were included in the review.

Characteristics of included studies

Of the 63 studies included in the review, 57 were observational (38 prospective cohort studies, 18 retrospective cohort studies, one case-

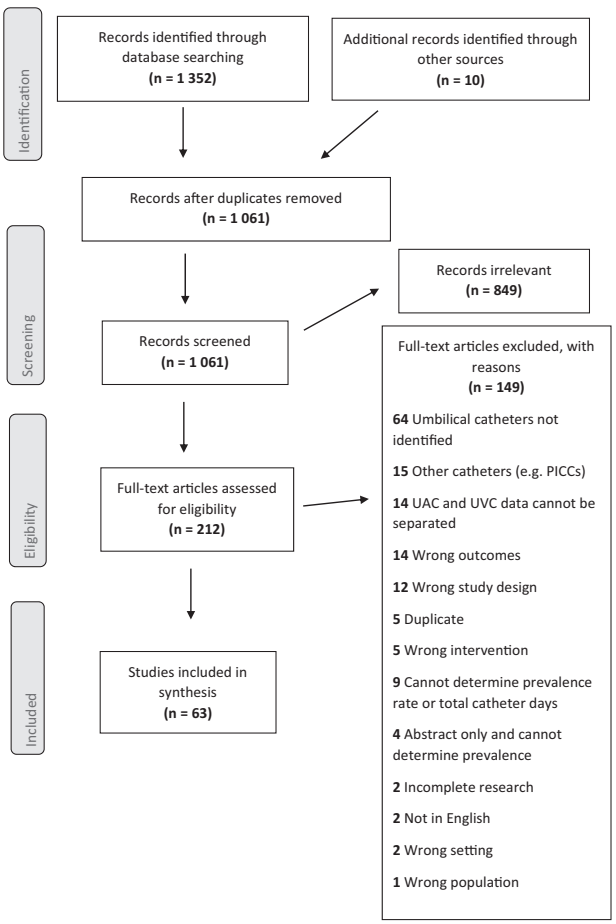

Fig. 1 Study Selection Process: PRISMA flowchart.

Observational Studies			Randomized Controlled Trials		
	15-22	(10, 19, 26, 27, 29, 30, 32, 33, 35, 36, 38-50, 53, 54, 56, 58-71, 73-76, 78, 80-85)		17-25	(28, 31, 51, 52, 72)
	8-14	(57)		9-16	-
	1-7	(34, 55, 86)		1-8	(77)

Fig. 2 Study Quality: The modified traffic light system of study quality for observational studies and RCTs.

control study) and there were six RCTs. The clinical sites were either Neonatal Intensive Care Units or Pediatric Intensive Care Units. Studies were undertaken in Australia [30, 40–42], Europe [19, 27, 31, 34–39, 43–60], United States [26, 32, 61–70], Asia [28, 71–80], South America [81, 82], Middle East [10, 33, 83], and Canada [29, 84, 85]. We could not determine the location of one study which was published as an abstract [86].

Study quality

Quality assessment is provided in Fig. 2. Of the 57 observational studies included in this review, 53 were allocated a green light (15–21) when assessed for quality. The most common omissions in reporting were lack of study size justification, reported efforts to address potential sources of bias, and discussion of external validity. Three were abstracts and one was an oral presentation and therefore received scores of 1–9. Of the six RCTs included, five were allocated a green light [28, 31, 51, 52, 71]. In the study by Krishnegowda et al. [76], information was missing regarding the specific RCT design, method of randomization, statistical analysis, recruitment data, interpretation of results, and protocol registration. In 29 studies we were unable to determine the number of catheter days, or these data were not collected by the study researchers when contacted [10, 19, 28, 30, 34, 38, 39, 43, 45, 46, 48, 49, 51–54, 56, 57, 59, 63, 65, 69, 70, 73–75, 81, 83, 86]. Therefore, they were excluded from the meta-analysis reporting the IR of AEs per 1000 catheter days.

Overall pooled results

There were 14,226 UVCs and 4228 UACs (48,253 and 12,773 catheter days, respectively) included in the meta-analysis. As per Table 1, 13.4% of UVCs were associated with an AE (95% CI: 10.11–17.02), with an IR of 2.4 per 1000 catheter days (95% CI: 1.77–2.99). In total, 9% of UACs resulted in an AE (95% CI 5.86–12.76) with an IR of 0.9 per 1000 catheter days (95% CI: 0.39–1.34). The heterogeneity of studies reporting incidence proportions for UVCs and UACs was high ($I^2 = 97.26$–98.63) and moderate to high for IR per 1000 catheter days ($I^2 = 70.12$–94.66).

Umbilical venous catheters

Table 2 reports the proportion and IR for specific AEs associated with UVCs. UVC malposition was the most common AE (41.7% [95% CI: 27.63–56.46]; 24 studies; 2 522 UVCs), followed by migration, occurring in 36.7% of UVCs (95% CI: 15.01–61.84; 5 studies; 2170 UVCs) and 38.09 per 1000 catheter days (95% CI 0–85.74; 2 studies; 15,743 UVC days). We only identified 1 study reporting incidence of local injury such as epidermal stripping (18.6%; 366 UVCs). UVC-related septicemia was more prevalent than CLABSI (6.9% [95% CI: 3.54–11.21]; 6 studies; 1926 UVCs) with an IR of 15.3 per 1 000 catheter days reported in one study. 13 studies reported the incidence of UVC-associated thrombosis with a pooled incidence proportion of 6.5% (95% CI: 2.28–12.61). 17 studies investigated CLABSI incidence (3.9% [95% CI: 2.34–5.80]; 8744 UVCs) with an IR of 3.51 per 1 000 catheter days (95% CI: 1.80–5.22; 11 studies; 44,308 UVC days). UVC

Table 1. Pooled proportion and IR of all AEs for UVCs and UACs.

	Proportion of AEs					Incidence rates of AE per 1000 catheter days				
Device	Studies	UVCs	Outcomes	Proportion (%)	95% CI	Studies	Outcomes	Catheter days	IR (per 1000 catheter days)	95% CI
UVC	54	14,226	2082	13.4[d]	10.11–17.02	14	561	48,253	2.38[d]	1.77–2.99
UAC	22	4228	352	9.0[d]	5.86–12.76	4	54	12,773	0.866[c]	0.39–1.34

Heterogeneity: negligible[a], low[b], moderate[c], or high[d].

Table 2. Pooled incidence proportion and IR for specific AEs associated with UVCs.

	Proportion of AEs					Incidence rates of AE per 1000 catheter days				
Adverse event	**Studies**	**UVCs**	**Outcomes**	**Pooled (%)**	**95% CI**	**Studies**	**UVC days**	**Outcomes**	**Pooled IR**	**95% CI**
CLABSI	17	8744	259	3.91[d]	2.34–5.80	11	44,308	182	3.51[d]	1.80–5.21
Septicemia	6	1926	119	6.88[d]	3.54–11.21	1	979	15	15.32	n/a
Thrombosis	13	3445	95	6.48[d]	2.28–12.61	5	19,543	70	5.27[d]	0–10.67
Occlusion	5	2326	18	2.34[d]	0.11–7.38	3	17,556	16	1.17[d]	0–3.16
Malposition	24	2522	1 162	41.68[d]	27.63–56.46	n/a				
X-ray	22	2405	1 129	42.83[d]	27.78–58.60	n/a				
US	10	701	400	46.27[d]	29.92–66.23	n/a				
Migration	5	2170	300	36.76[d]	15.01–61.84	2	15,743	261	38.09[d]	0–85.74
X-ray	2	2058	251	26.50[d]	2.11–64.81	1	15,286	232	15.17	n/a
US	3	112	49	44.19[d]	21.76–67.96	1	454	29	63.88	n/a
Extravasation	4	2402	10	1.04[d]	0.02–3.64	2	16,268	2	0.13[a]	0–0.30
Leakage	4	572	30	5.53[c]	2.67–9.36	1	979	3	3.06	n/a
Local injury	1	366	68	18.58	n/a	0				
Hepatic	2	1457	5	1.51[d]	0.45–9.55	1	8315	1	0.12	n/a
Cardiac	2	1397	3	0.26[a]	0.06–0.60	1	8315	3	0.36	n/a
Breakage	1	2017	8	0.40	n/a	1	15,289	8	0.52	n/a

Heterogeneity: negligible[a], low[b], moderate[c], or high[d].

extravasation, breakage, cardiac and hepatic complications, and catheter occlusion all had the lowest incidence proportion (0.3–1.5%; 0.12–0.52 per 1000 catheter days; 14 studies; 9599 UVCs). Due to a lack of data, an IR for local injury associated with a UVC could not be estimated.

Umbilical arterial catheters

Table 3 reports the incidence proportion and IR for specific AEs associated with UACs. The most common AE was local injury such as epidermal stripping (33.3%; 27 UACs), however only 1 study reported this. Malposition was the second most common (20.8% [95% CI: 8.86–36.17] 9 studies; 722 UACs), followed by thrombosis (8.2% [95% CI: 1.91–18.20; 7 studies; 2631 UACs]). UAC-related septicemia was more prevalent than CLABSI (3.9% [95% CI: 2.34–5.93]; 449 UACs) versus 0.4% (95% CI: 0–1.43; 3 studies; 2 422 UACs) and IR of 0.49 per 1 000 catheter days (95% CI: 0–1.52; 12,727 UAC days). UAC breakage, migration, and catheter occlusion all had a low incidence proportion and IRs (0.49–0.98%; 0.89–1.78 per 1000 catheter days; 2 studies; 4125 UVCs). Due to a lack of data, an IR for other types of sepsis, leakage and local injury could not be estimated.

Sensitivity analysis

The proportion of malpositioned or migrated UVCs was higher for studies using ultrasonography or echocardiography compared to radiography for tip placement verification (Table 2) (malposition: 46.3% [95% CI: 29.92–66.23] versus 42.8% [95% CI: 27.78–58.60]; migration: 44.2% [95% CI: 21.76–67.96] versus 26.5% [95% CI 2.11–64.81]). However, based on a meta-regression, this difference was not statistically significant (UVC malposition: $P = 0.895$; 95% CI: 0–23.24; UVC migration: $P = 0.50$; CI: 0–83.93). UAC malposition determined by ultrasonography or echocardiography was lower than if diagnosed by radiography (4.32% [95% CI: 1.06–9.64] versus 20.7% [95% CI: 8.86–36.17]) although not statistically significant ($P = 0.20$, 95% CI: 0–13.58). We were not able to perform a regression analysis for UAC migration due to a lack of studies.

DISCUSSION

Umbilical catheters are frequently used for vascular access in critically unwell or preterm infants. This meta-analysis aimed to determine the incidence of AEs associated with UVCs and UACs in the neonatal population; determining that 13% of UVCs and 9% of UACs will likely result in an AE.

This is consistent with the benchmarked meta-analysis of pediatric central venous access device failure conducted in 2015 [87], which reported a UVC failure of 11%. Our previous work [88] identified a broad range of risk factors for umbilical catheter-associated AEs such as increased dwell time, prematurity, low birth weight, catheter material, malposition, and maternal characteristics. As there has been no improvement in umbilical catheter outcomes over the last 5 years, there is a need for research to determine strategies to reduce the risk of AEs for this vulnerable population.

Umbilical catheter research has primarily focused on UVC-associated infection with one-third of studies incorporated in this review investigating its incidence. Ullman et al. [87] reported a pooled UVC-associated BSI rate of 4% with an IR of 5.86 per 1000 catheter days, similar to the IR calculated in this meta-analysis. BSI can be catastrophic and is the cause of 13% of all neonatal deaths and 42% of deaths within the first week of life [89]. Cohort studies have reported an association between catheter dwell-times of 4–10 days and UVC-associated BSI, recommending their early removal [17, 32, 37, 42, 45, 69, 81, 90]. This is consistent with the Centers for Disease Control and Prevention (CDC), which endorse early removal of a UVC as soon as possible when no longer needed and replacement with a peripherally inserted central catheter (PICC) [91]. However, for infants who require long-term vascular access, the replacement of a UVC with a PICC can result in BSI (8.6%; IR 3.06 per 1000 catheter days) [87]. To date, only one RCT investigated the effect of planned early UVC removal with replacement of a PICC in preterm infants [92]. This study did not find any difference in the incidence of catheter-related BSI and hospital mortality or morbidity compared to prolonged UVC dwell-time. Similarly, other studies have not demonstrated a reduction in CLABSI rates despite a decrease in central line days [69, 93]. Further RCTs are required to evaluate the risk of early UVC removal and replacement of a PICC compared with longer UVC dwell-time.

An alternative to solely reducing umbilical catheter dwell-time is the implementation of central line infection prevention bundles to reduce catheter-associated BSI. Bundles include best practice in

Table 3. Pooled incidence proportion and IR for specific AEs associated with UACs.

	Proportion of AEs					Incidence rates of AE per 1000 catheter days				
Adverse event	**Studies**	**UACs**	**Outcomes**	**Pooled (%)**	**95% CI**	**Studies**	**UAC days**	**Outcomes**	**Pooled IR**	**95% CI**
CLABSI	3	2422	5	0.40[c]	0–1.43	3	12 727	5	0.49[b]	0–1.52
Septicemia	2	449	17	3.94[a]	2.34–5.93	0				
Thrombosis	7	2631	62	8.16[d]	1.91–18.20	1	11 214	8	0.71	n/a
Occlusion	2	2090	11	0.86[c]	0.03–2.79	2	11 260	11	0.89[a]	0.35–1.44
Malposition (X-ray)	9	722	216	20.82[d]	8.86–36.17	n/a				
US	2	83	3	4.32[a]	1.06–9.64	n/a				
Migration	1	2035	10	0.49	n/a	1	11 214	10	0.89	n/a
Leakage	1	19	2	10.53	n/a	0				
Local injury	1	27	9	33.33	n/a	0				
Breakage	1	2035	20	0.98	n/a	1	11 214	20	1.78	n/a

Heterogeneity: negligible[a], low[b], moderate[c], or high[d].

skin preparation, maximal sterile precautions, standardizing practices for insertion, catheter hub decontamination, split-septum and single-use prefilled flushing devices, regular auditing of compliance and staff education [41, 53]. Cohort studies have demonstrated the effectiveness of these prevention bundles in reducing catheter-associated BSI, particularly for extremely premature and low birth weight neonates [41, 53], and should be integrated into standard practice regardless of catheter indwelling time.

Catheter malposition can have important sequalae including hepatic damage, extravasation, and pericardial or pleural effusion. Our study found that tip malposition was the most common AE with nearly half of the UVCs malpositioned on first x-ray or ultrasound and has major implications for clinical practice. Established landmark criteria or a regression equation based on birth weight is currently used to estimate the required insertion length [94, 95]. Individual studies have compared the accuracy of current and new methods of determining insertion length with varying results [51, 52, 58, 60, 62, 71, 76–78, 80]. The most accurate methods for determining insertion length need to be established to inform safe insertion practice. Ultrasound-guided umbilical catheter insertion has been demonstrated to improve accuracy compared to standard landmark criteria or regression equations. The use of ultrasound has been shown to reduce line placement time, reduce manipulations required for optimal tip positioning, facilitate successful insertion, and detect malposition more accurately than by radiography [3, 33, 64, 96].

While most NICUs will obtain a radiograph immediately after central line placement, very few obtain a routine radiograph 24 h after line insertion or have a standard protocol [97]. This is of concern as UVCs migrate over time from their original correct position, more common during the first 48 h of dwell as the umbilical stump dries [30]. The influence of factors associated with catheter movement such as taping and securement [30] and abdominal girth changes [29, 98, 99] require further investigation to manage internal and external movement, minimizing the risk of damage to surrounding organs and extravasation of hyperosmolar fluids. There are reports of fatality in published autopsy case studies [100] where infants have died from sudden unexpected cardiac arrest due to pericardial effusion and cardiac tamponade. Extravasation of total parental nutrition was suspected due to UVC tips located within the right atrium at autopsy. In addition to insertion, the use of serial bedside ultrasound to survey tip position may prevent sequalae from catheter migration and alleviate the need for radiography; further reducing radiation exposure [101]. Serial surveillance policies need to be implemented to ensure the correct location of the catheter tip is maintained, particularly during the infusion of high osmolarity fluids.

Umbilical catheter-associated thrombosis is also of major concern due to the high incidence (6% for UVCs and 8% for UACs), and mortality rate of 21% [12]. Longer duration of umbilical catheter dwell (>5 days) has been associated with catheter-associated thrombosis in large cohort studies [10, 26, 32, 44]. Of the 20 studies reporting thrombosis incidence included in this review, 15 were prospective in design and used serial ultrasound to detect thrombi reducing progression to local and systemic symptoms, and should be considered for standardizing umbilical catheter care [10, 47]. The use of serial ultrasound may be particularly beneficial for detecting thrombi associated with umbilical catheters with a longer duration of dwell [10, 26, 27, 32, 38, 44].

Local injury was the most prevalent AE associated with UACs, the third most common for UVCs, and included iatrogenic skin damage from epidermal stripping after removal of adhesive material. As the preterm infant has a weak dermal–epidermal junction, the strong adhesive bond between the adhesive and epidermis can strip the epidermis on removal causing trauma and pain [102]. Improvement in umbilical catheter fixation

techniques and the adhesive material used may reduce this preventable AE.

Limitations

Broad inclusion criteria were used to capture epidemiological studies and therefore significant heterogeneity exists amongst study design. Not all authors were able to provide the total number of catheter days and were excluded from the IR meta-analysis. Some studies that reported incidence of malposition by both x-ray and ultrasound were included more than once in the sensitivity analysis and therefore lack study independence. This review is further limited in that it did not include publications in other languages.

CONCLUSION

This meta-analysis found that umbilical catheters have a high incidence of AEs which can significantly impact patient outcomes. Investigation into the risk factors for AEs and interventions to reduce incidence is a priority research area in neonatal care. Catheter malposition and migration are the most common AEs, and the need for routine catheter tip surveillance should be considered in clinical practice.

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All authors have approved the final article, have made substantial contributions to the review, are accountable for the work presented and acknowledge that they are entitled to authorship of this article. KG was responsible for investigation, writing-original draft preparation, RS for investigation, writing-reviewing, supervision, AU for investigation, writing-reviewing, supervision, SM for writing-reviewing, industry expertise, TK for writing-reviewing, industry expertise and AE for conceptualization, writing-reviewing, supervision.

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ADDITIONAL INFORMATION

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