LOW VS HIGH POSITION UMBILICAL ARTERY CATHETER OF CLINICAL OUTCOMES AMONG NEONATES: A SYSTEMATIC REVIEW AND META-ANALYSES

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LIST OF ABBREVIATIONS

UAC	Umbilical artery catheter
HUSM	Hospital Universiti Sains Malaysia
NICU	Neonatal intensive care unit
RCT	Randomized Controlled Trial
LBW	Low birth weight
IVH	Intraventricular haemorrhage
NEC	Necrotizing enterocolitis

MANUSCRIPT

TITLE PAGE

Low vs high position umbilical artery catheter of clinical outcomes among neonates: A systematic review and meta- analyses

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ABSTRACT

OBJECTIVE: To determine whether the position of the tip of an umbilical arterial catheter (UAC) influences the frequency of clinical vascular compromise, aortic thrombosis, intraventricular hemorrhage, necrotising enterocolitis, hypertension, hematuria and mortality rate in neonates requiring UACs.

DESIGN: Systematic review with meta-analyses of randomized controlled trials (RCTs) and quasi-RCT.

DATA SOURCES: Cochrane central register of controlled trials (CENTRAL), PubMed and ProQuest from inception to 1st July 2022. Reference lists of identified trials and systematic review were assessed.

TRIAL SELECTION: Published and unpublished randomised clinical trials that evaluated the comparison of clinical outcomes in neonates with placement of UACs at low or high position, published in English language; irrespective of blinding procedure, publication status, publication year, or sample size. Seven trials included in this systematic review and meta-analysis including one trial which only published as thesis publication.

DATA EXTRACTION: One author independently screened titles and abstracts of trials identified, and relevant trials were evaluated in full text for eligibility. One reviewer then independently extracted data on methods, interventions, outcomes, and risk of bias from included trials. These data were cross-checked by two different authors. Random effects models were used to estimate odd ratios and mean differences with 95% confidence intervals.

RESULTS: Seven trials totalling 1809 neonates were included. There were increased in the events of clinical vascular compromise (OR 2.77, 95% CI 1.85 to 4.15) and aortic thrombosis (OR 4.67, 95% CI 1.3 to 16.7) in low UACs position compared to high UACs position. No increased risk of incidence of the other clinical outcomes including mortality rate. However, the quality assessment of the trials is of low and moderate quality according to GRADE quality assessment.

CONCLUSION: Low UACs position resulted in slightly higher risk incidence of clinical vascular compromise and aortic thrombosis but not associated with increased incidence of other UAC-related clinical outcomes including mortality rate. Low UACs position is still generally safe and acceptable practice based on latest RCT. However, more safety data would be needed for full assessment before deciding on the appropriate placement of UACs.

BACKGROUND

Umbilical arterial catheterization among neonates is a common practice in the neonatal intensive care unit (NICU). Umbilical artery catheters (UAC) are used mostly in preterm neonates and critically ill neonates for various reasons including performing arterial blood gas analyses, continuous monitoring of blood pressure, facilitating repeated blood sampling, and exchanging transfusion.[1,2]

Despite their many valuable applications in the NICU, the use of UAC carries many risks. Several complications have been identified: clinical vascular compromise ranging from blanched toes to thromboembolic phenomena,[3] aortic thrombosis,[4,5] intraventricular hemorrhage,[6] necrotizing enterocolitis,[7,8,9] hypertension,[10,11] aneurysm/pseudoaneurysm,[12] blood-stream infection,[13] hematuria,[14] hypoglycemia,[15] and death. These adverse events significantly impact the morbidity and mortality rate among neonates and have been evaluated in previous trials[16-22].

A high position umbilical artery catheter is placed so that the tip is in the descending aorta above the level of the diaphragm and below the left subclavian artery,[23,24] which correlates with the 7th to 10th thoracic vertebra on chest X-ray. This position will bypass the main branches of abdominal aorta namely celiac trunk and renal artery.

The low position of the umbilical artery catheter is placed so that the tip is above the aortic bifurcation and distal to the branch of celiac trunk and renal arteries, which correlates with the 3rd and 4th lumbar vertebra on chest X-ray.

Theoretically, the low position of UACs in neonates will give rise lower risk of complications compared to a higher position of UACs however other factors need to be considered such as turbulence of blood flow around the catheter tip and the effects on flow dynamics of flushing the catheter after blood draw.

Previous Cochrane systematic review[25] support the usage of high position UAC due to lower incidence of clinical vascular compromise events. From the previous review, the usage of high position is supported by the evidence which showed statistically significant of higher incidence of clinical vascular compromise with the low position UAC. It has been a common practice for years that a high UAC position is preferred compared to a low UAC position. However, all these trials were conducted mostly in the 70's till 90's and there were limited studies to re-examine the reliability of maintaining the practice of placement of umbilical artery at a high position.

In the modern era of neonatology, the practice has evolved with better ventilatory strategies, shorter ventilation duration, more widespread use of an antenatal steroid for premature neonates, and improvement in infection control in neonatology unit. Evidence from newer randomized

controlled trials is required to clarify the benefits and risks of catheter position. This review conducted to determine whether the position of the tip of a UACs influences the frequency of clinical vascular compromise, aortic thrombosis, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), hypertension, hematuria, or death in neonates.

METHODS

Eligibility criteria

Randomized control trials (RCTs) and quasi-RCTs comparing the outcomes for neonates with different levels of placement of umbilical artery catheter. We included blinded and open label studies.

Types of participants

Neonates at any gestational age and birth weight who require the placement of an umbilical artery catheter.

Types of interventions

Comparison of low position of umbilical artery catheter with high position of umbilical artery catheter.

Types of outcomes

Primary outcome

Frequency of clinical vascular compromise (ranging from blanching of toes to thromboembolic phenomena), aortic thrombosis, IVH, NEC, hypertension, hematuria, or death among neonates.

Search strategies

Electronic searches

We identified relevant RCTs through a systematic search strategy which included Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and ProQuest from inception to 1st July 2022. We used the search strategy in Appendix 1 to search for relevant publications in CENTRAL, PubMed, and ProQuest. We restricted the publications to English language only.

Searching other resources

We checked the reference list of identified RCTs and review articles in order to find unpublished trials or trials not identified by electronic researches. We also searched for RCTs in local databases. Other ongoing trials through the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) http://www.who.int/ictrp/en/ and www.clinicaltrials.gov were also searched.

Trial selection

We scanned the titles and abstracts from the databases and research platforms and obtained full-text articles that met the eligibility criteria. We assessed the eligibility of the trials independently and documented the reasons for exclusion. Any disagreements between the review authors were resolved by discussion.

Data extraction

The researcher was not masked to the author, institution, and publication source of trials at any time. Using preprepared data extraction forms the researcher independently extracted the characteristics of the trials (single or multicentre, country), baseline characteristics of the patients (gestational age, birth weight), inclusion and exclusion criteria, the description of intervention (high and low position of umbilical artery catheter), and outcomes (frequency of clinical vascular compromise, aortic thrombosis, IVH, NEC, hypertension, hematuria, and death) among neonates.

Risk of bias assessment

Risk of bias assessment is performed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) version of 22 August 2019.[26] We reviewed the major domains of bias (random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting)

Grading quality of evidence

We assessed the quality of evidence for primary outcomes according to GRADE methodology[27] for risk of bias, inconsistency, indirectness, imprecision, and publication bias; classified as very low, low, moderate, or high.

Statistical analyses

Data synthesis

Statistical analysis was performed using Review Manager 5.4 software[28] and used random-effects model to pool data. Thresholds for the interpretation of the I^2 statistic can be misleading, since the importance of inconsistency depends on several factors. We used the guide to interpretation of heterogeneity as outlined: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% would be considerable heterogeneity.[29]

Assessment of heterogeneity

We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions, and outcomes. Second, we assessed statistical heterogeneity by means of the I^2 statistic.[30]

Measures of treatment effect

We measured the treatment effect for dichotomous outcomes using odds ratio (OR) and absolute risk reduction, and for continuous outcomes we used mean differences (MDs); both with 95% confidence intervals (CIs).

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses on birth weight, gestational age and duration of umbilical artery catheter in situ wherever possible.

Unit of analysis issues

We checked included trials for unit of analysis errors. Unit of analysis errors can occur when trials randomized participants to intervention or control groups in clusters, but analyzed the results using the total number of individual participants. We adjusted results from trials showing unit of analysis errors based on the mean cluster size and intra-cluster correlation coefficient.[30]

Dealing with missing data

We contacted the original trial authors to request missing or inadequately reported data. We performed analyses on the available data in the event that missing data are not available.

Sensitivity analysis

We performed a sensitivity analysis to investigate the impact of risk of bias for sequence generation and allocation concealment of included studies.

Reporting biases

If there are sufficient studies, we used funnel plots to assess the possibility of reporting biases or small study biases, or both.

RESULTS

Trial selection

We identified 455 records in the systematic search strategy, of which nine were assessed in full text for eligibility to supplement the former six[16-21] published RCTs. We found only one eligible published record as thesis publication in the local database.[22] We excluded a total of eight records,[8,24,31-36] the reasons being a different study designs[31,32] (two records) and different intervention[8,24,33-36] (six records). There is no record related to the ongoing trial. Figure 1 summarizes the results of the search strategy.

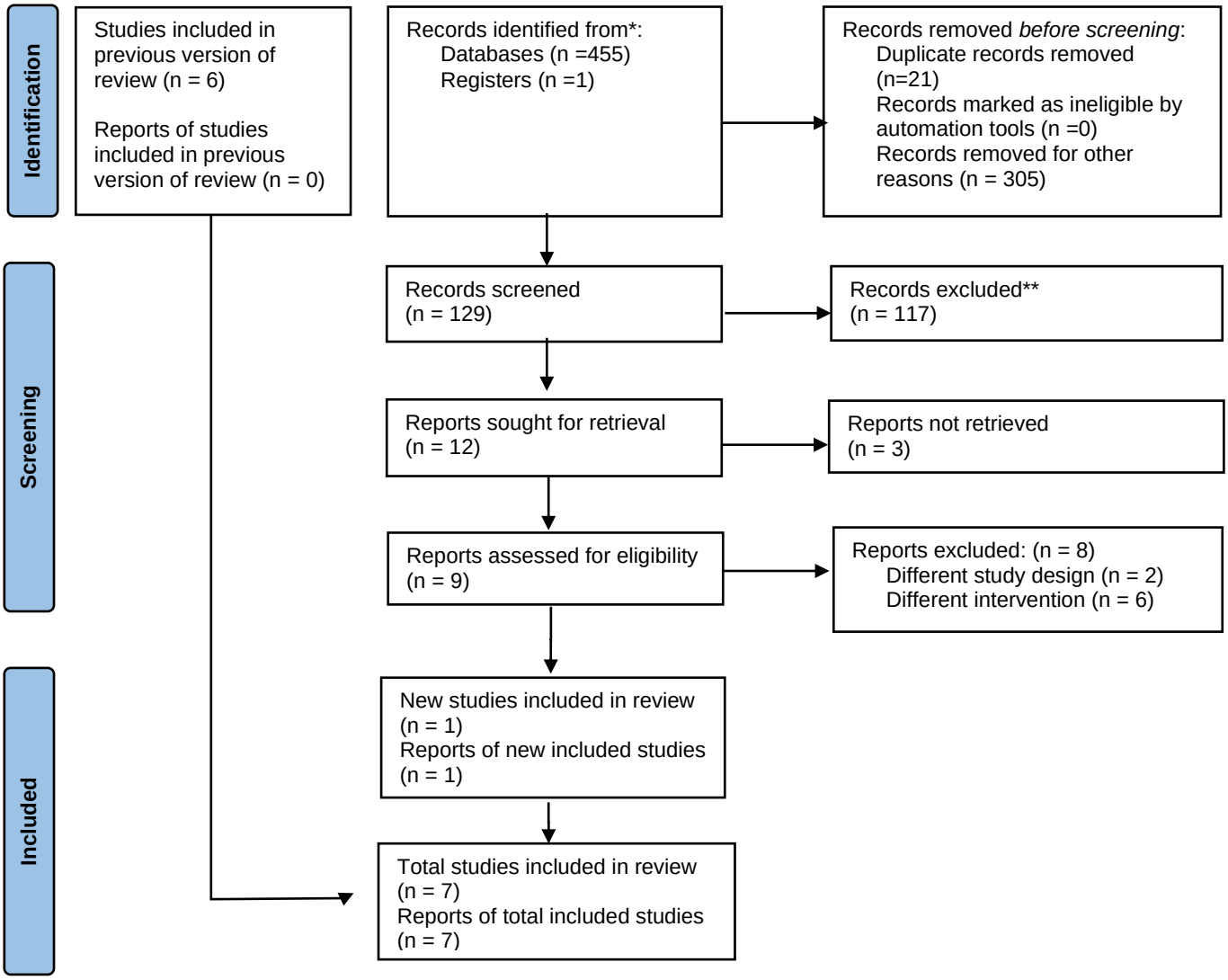

Figure 1. PRISMA flow chart

Characteristics of trials

We included six single[17,18,19,21,22] and one multicentre[20] randomized controlled trials. There is one quasi-RCT involving single centre[16]. Population sizes ranged from 36[16] to 970[20] patients. Six trials were on both term and preterm neonates [16-19,21,22] and one on preterm neonates only[20]. Table 1 summarises the characteristics of the included trials. The infants requiring the UACs placement need intensive care at the respective centers, with the predominant reasons for umbilical catheterization due to respiratory illnesses and preterm infants.[18,20,21,22] All the placement of UACs was confirmed by radiography.

There were wide variations in the neonates' birth weight in all trials. One trial specifically focused on low-birth-weight neonates and mentioned the range of required birth weight (500-1499 g) as inclusion criteria.[20] Two trials performed sub-analyses of birth weight to stratify the risk further according to different range of birth weight.[20,22] In the UACTSG trial,[20] complications were observed among neonates with a birth weight range 1000 g to 1499 g while in the Mohamed trial,[22] complications were observed the most in the range of 1501 to 2500 g.

Another aspect of all trials was describing the relationship between gestational age and the position of UACs.

Most of the trials described the duration of the catheter in situ in hours,[16-18] except for one trial[22]. The catheter's duration in situ averaged from less than 24 hours[16] to 9 days.[22]

Table 1. Characteristics of included studies (n=7)

References	Country	No of patients/ no of trial sites	Study design	Inclusion period	Population	Clinical setting
Harris 1978[16]	USA	36/1	Quasi RCT	NA	Term Preterm	Respiratory illnesses
Mokrohisky 1978[17]	USA	73/1	RCT	September 1976 - May 1977	Term Preterm	Respiratory illnesses, birth asphyxia, CHD
Wesstrom 1979[18]	Sweden	62/1	RCT	NA	Term Preterm	LBW, prematurity, birth asphyxia, respiratory illnesses
Stork 1984[19]	USA	182/1	RCT	1981	Term Preterm	NA
UACTSG 1992[20]	USA	970/12	RCT	October 1989 - April 1991	Preterm	Respiratory illnesses
Kempley 1993[21]	United Kingdom	308/1	RCT	NA	Term Preterm	LBW, birth asphyxia, respiratory illnesses
Mohamed 2013[22]	Malaysia	178/1	RCT	March 2012 - August 2013	Term Preterm	Respiratory illnesses, birth asphyxia, sepsis

RCT=randomized controlled trial, NA=not available
CHD=congenital heart disease, LBW=low birth weight
* Respiratory illnesses include respiratory distress syndrome (RDS), transient tachypnoea of newborn (TTN), congenital pneumonia, meconium aspiration syndrome (MAS)

Risk of bias assessment

Two trials showed low risk of bias for bias arising for randomization process.[20,22] In UACTSG trial[20] and Mohamed trial,[22] the envelopes were sequentially numbered and allocation was co-ordinated centrally. Four trials showed an uncertain risk of bias.[17,18,19,21] In Mokrohisky trial[17], the masking of allocation was uncertain, but participants were assigned from a random-number table. The randomization procedures were not detailed in the Wesstrom trial[18] and the Stork trial.[19] In the Kempley trial[21], the randomization method was not clearly described. One trial was categorized as high risk whereby allocation was by alternate assignment and not masked at all.[16]

Only one trial was categorized as low risk of bias[22] when assessing bias due to deviations from intended interventions. There was no protocol violation as all participants recruited adhered to the allocated group until the end of the trial. The remaining trials[16-21] were categorized as high risk of bias as these trials could not provide evidence to estimate the effect of assignment to the intervention. All trials[17-22] except for one[16] were single-blinded as participants were blinded from intervention; however, the health workers who placed the UACs were not blinded.

All seven trials showed a low risk of bias[16-22] in terms of bias due to missing outcome data. In these trials, all data for the participants recruited were available and there was no missing data.

For bias due to bias in the measurement of outcome, one trial[20] was categorized as low risk. In the UACTSG trial,[20] the outcome measurement is appropriate and principal investigators remained blinded with these analyses. Two trials[21,22] were categorized as unclear risk of bias. This was because even though the measuring of the outcome was appropriate; however, the outcome assessor was not blinded. The other four trials were categorized as high risk of bias[16-19]. The method of measuring outcome was inappropriate as there was variation in defining the outcome and the outcome assessor was aware of the intervention received by participants.

Only one trial[22] was categorized as low risk in evaluating the risk of bias in selecting the reported result. Mohamed trial[22] described the analysis plan before to the outcome data was available for analysis and subsequent data analysis was in accordance with the plan. Six other trials were categorized as high risk.[16-21] In the Mokrohisky trial,[17] the analysis plan was described but the author did not analyze the event of aortic thrombosis in detail even though the event was mentioned in the trial. In the UACTSG trial,[20] the analysis plan was predefined, however the outcome for death affected the overall analysis and additional recruitment was made to complement the affected data. In the Kempley trial,[21] they included necrosis and gangrene as a collective outcome for the clinical vascular outcome even though other trials did not describe necrosis and gangrene as part of the clinical vascular outcome. Another three trials[16,18,19] did not describe the analysis plan.