Does performing Placental Transfusion during Neonatal Resuscitation have a negative impact on Resuscitation attempts by First Responders compared to Standard Care? A Systematic Review.

Abstract

Objective Placental transfusion (the transfer of blood from placenta to neonatal circulation post birth using delayed cord clamping (DCC); the practice of waiting for the umbilical cord to stop pulsating prior to clamping and cutting the cord, or umbilical cord milking (UCM); clamping and cutting the cord immediately before milking the cord towards the neonate to expel left over volume) has been shown to decrease overall neonatal mortality. This systematic review aimed to determine whether placental transfusion negatively impacts resuscitation by delaying the initiation of resuscitation or has any impact on infant mortality and to identify any barriers to performing it.

Methods CINAHAL, MEDLINE, AMED and British Nursing Index (BNI) were searched using key terms to identify relevant English language publications between 2017-2019.

Results Five papers were selected for critical analysis; three randomized control trials (RCTs) and two cohort studies.

Conclusion Placental transfusion was not found to have a negative impact on neonatal resuscitation but equally had no significant effect on Apgar at 5 minutes, although Apgar is a crude measure of infant mortality and the question remains around the proven multifaceted benefit in the prehospital environment for which further research should be sought. There is evidence to suggest prehospital clinicians should be looking to change practice. Further research, considerations and consultations are required to ascertain the best way to implement the procedure with a balanced and proportionate approach considering neonatal thermoregulation and maternal management.

The main reported barrier to placental transfusion was equipment.

Background

Evidence shows that placental transfusion (the transfer of blood from placenta to neonatal circulation post birth), can improve blood volume by up to 30% and decrease overall neonatal mortality (Backes *et al* 2014). Currently only vigorous (healthy) babies benefit from this treatment strategy (Mercer Erickson-Owens 2014; Song *et al* 2017). Worldwide, 5% of babies born every day will require some form of resuscitation to promote adequate ventilation (Blank *et al* 2018). Despite the potential benefit that placental transfusion can bring, the need to resuscitate can often interfere with the prehospital clinician's ability to perform transfusion.

When a newborn is delivered in a compromised state, the current relevant prehospital guidelines from the Resuscitation Council UK (2015) and JRCALC (2017) advocate cutting the umbilical cord immediately. This is in order to remove the newborn to an appropriate setting to initiate resuscitation. The resuscitation algorithm accepted internationally for newborns is quite different from that of adult or child life support. The focus is on optimizing airway management and inflating the lungs as for most babies this will be all that is needed (Resuscitation Council UK 2015). It has been widely accepted that placental transfusion by DCC or UCM should be undertaken for all vigorous newborns and this is reflected in current guidelines.

DCC is the practice of waiting for the umbilical cord to stop pulsating prior to clamping and cutting the cord, whereas UCM is clamping and cutting the cord immediately before milking the cord towards the neonate to expel left over volume. Standard care for the ambulance service in the UK is DCC, or to cut the cord immediately if the baby is compromised (JRCALC 2017). The reason behind this is predominantly practical such as the presence of a short cord or where concerns about leaving the cord intact may delay or negatively impact resuscitation efforts due to space confines and human factors. In an

empirical study paramedic resuscitation skills of neonates and knowledge were shown to improve significantly following education (Mileder *et al* 2019) demonstrating the skill fade within this field related to a lack of exposure leading to decreased decision making ability due to stress (McLelland, Morgans and McKenna 2012). There is a significant lack of evidence into prehospital use of transfusion strategies and current guidelines are based on consensus opinion.

In a systematic review of placental transfusion strategies Backes *et al* (2014) and Rabe *et al* (2012) found that placental transfusion in hospital versus none, significantly decreased mortality, lowered the incidence of blood transfusions and lowered the incidence of intraventricular hemorrhage. Incidences of necrotizing enterocolitis, sepsis and hospital stay have also been found to be significantly lower in neonates receiving longer DCC (Chiruvolu *et al* 2018). Placental transfusion is thought to decrease mortality by increasing the circulating blood volume which may contribute to stabilizing the cardiovascular system and increasing end organ perfusion. By increasing organ perfusion Mercer *et al* (2014) discuss how this reduces the severity of the inflammatory response and prevents damage from ischemia. There is little known about transitioning neonatal blood volumes as the procedure is considered too invasive and has therefore not been ethically approved for human studies. Studies in newborn lambs show that DCC improved blood volume when transitioning from placental to neonatal circulation (Mercer Erickson-Owens 2014; Blank *et al* 2018).

Prehospital resuscitation of newborns does not happen often, but can be an overwhelming situation for clinicians to be in. In view of the benefits that have been proven, the potential negative impact of DCC and UCM on resuscitation attempts should be evaluated.

Research question

Table 1 PICO was used to develop the research question as shown below:	
Population	Newborn babies requiring resuscitation
Intervention	Placental transfusion by either DCC or UCM
Comparison	Immediate clamping of the umbilical cord.
Outcome	Time to initiating resuscitation/Time to first inflation breath/Impact on APGAR score at 5 minutes.

As there are already many reviews that found them to be equally effective the author has grouped DCC and UCM together in order to consider both strategies for placental transfusion rather than compare (Backes *et al* 2014). For comparison immediate cord clamping was used, as this is currently what is recommended. In order to accurately measure an outcome, Park *et al* (2018) found that APGAR score at 5 minutes was the best predictor of mortality amongst neonates. This is an internationally accepted method to assess a newborn considering Appearance, Pulse, Grimace, Activity and Respiration, which yields a score out of 10. A score of 10 is associated with a healthy newborn, and 0 being no signs of life. To establish whether there was a delay to resuscitation efforts with placental transfusion, the time to resuscitation commencing or time to first inflation breath was also included as an outcome, so it could be compared against the control group.

Aims

To determine whether placental transfusion is practical for prehospital clinicians to undertake in the community, and whether it negatively impacts resuscitation by delaying the initiation of treatment or has any impact on infant mortality.

Objectives

- To determine whether adding placental transfusion to resus efforts has an effect on time to initiating resuscitation or time to first inflation breath
- To determine whether adding placental transfusion to resus efforts has an effect on Apgar score at 5 mins
- To identify barriers to undertaking placental transfusion

Methodology

CINAHAL, MEDLINE, AMED and British Nursing Index (BNI) were searched on 10th March 2019. These databases were chosen to try to capture all relevant studies across a range of medical specialties that may be involved in the resuscitation of newborns. Background reading and pilot searches were used to identify search terms demonstrated in Table 2. Titles were screened for relevance and then abstracts read for suitability. Not all studies included looked at time to resuscitation as a primary outcome and APGAR at 5 minutes, but it was recorded as a secondary outcome therefore they were picked up during examination of the abstract.

Table 2. Search terms and Boolean operators		
Resuscitation	And	Umbilical Cord OR
		Umbilical Cord Clamping OR
		Umbilical Cord Milking

Exclusion/Inclusion Criteria

Table 3. Inclusion and Exclusion Criteria	
Inclusion	**Exclusion**
Studies that compare placental transfusion vs immediate cord clamping.	Full text not available
Studies that included neonates requiring resuscitation	Not written in English
RCT and Cohort studies*	Direct comparisons of DCC and UCM
Published between 2017-2019	Animal studies

*Cohort studies are Levels 2&3 according to the Centre For Evidence-Based Medicine (CEBM) (Howick *et al* (no date))

The databases were filtered for peer-reviewed articles from 2017-2019. Using a limited timescale ensured that the most recent research was captured. Articles involving animals were excluded due to the fact that this review focuses on humans and it can be difficult to extrapolate animal data to apply it to human outcomes. Expert opinion and low grade research, as described by Aveyard (2014), were excluded as this review looks specifically at time outcomes which requires a level of statistical analysis from reliable data. Due to the large amount of research comparing DCC and UCM, articles were excluded if they didn't directly measure either time to first breath or time to commencing resuscitation attempt. Due to the financial limitations of the researcher, papers not written in English were excluded.

Results

The outcome of the search is shown in the PRISMA diagram in figure 1 (Moher et al, 2009). Five papers were found to be inclusive of all set criteria and were selected for critical analysis. Three were RTCs and two were cohort studies. It was therefore appropriate to analyse separately according to level of evidence, to obtain the most efficient comparison. A critical appraisal tool (Joanna Briggs Institute 2018) was applied to each category of evidence to allow for systematic appraisal.

Search strategy

Figure 1: Prisma flow chart of results.

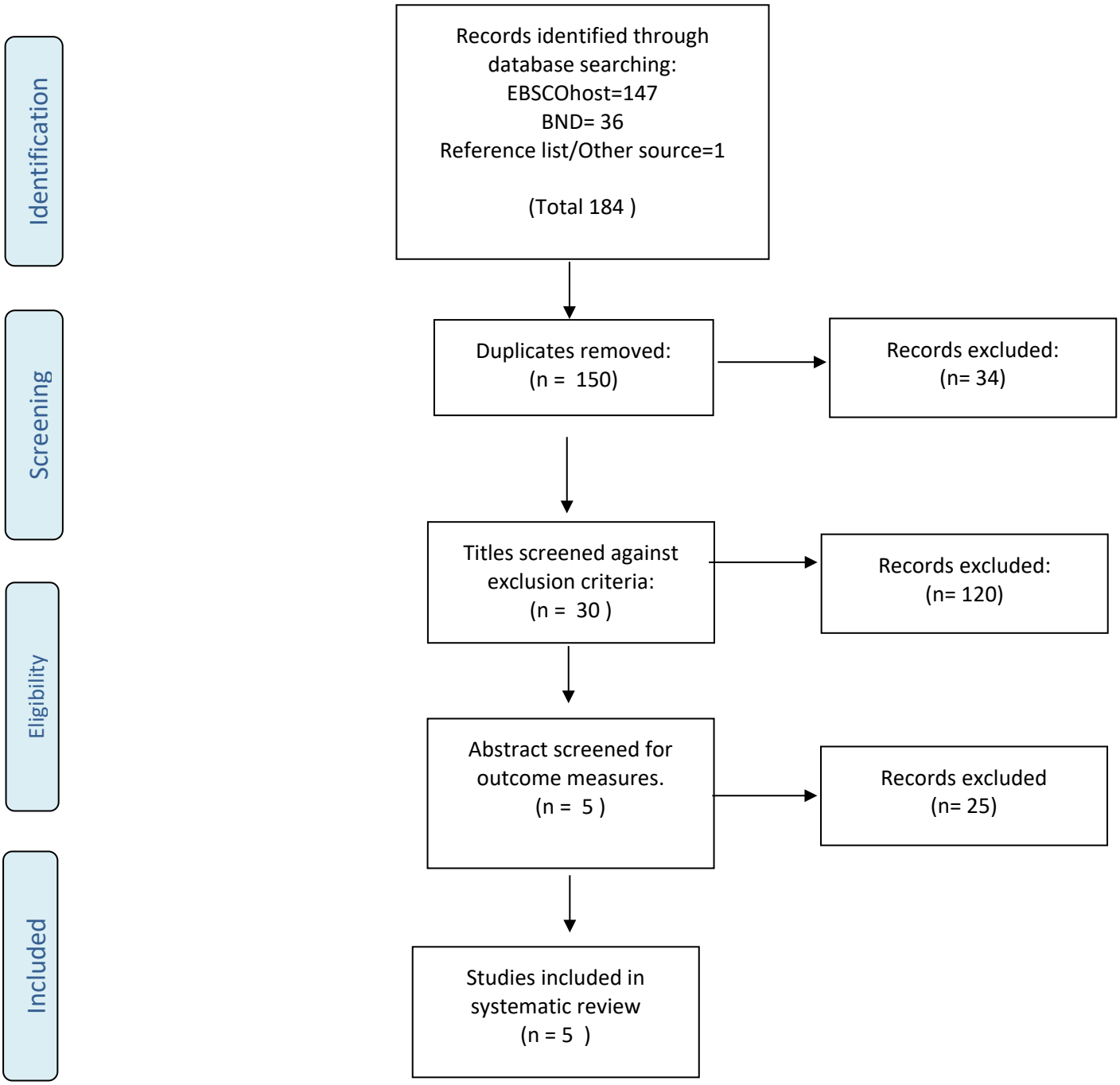

Table 4. RCTs			
Study:	**Anup *et al* (2017)**	**Girish *et al* (2018)**	**Mohan *et al* (2018)**
Aim	Identify the benefit of resuscitation with intact umbilical cord.	Feasibility and safety of UCM in neonates depressed at birth.	Evaluate effect of UCM on short term morbidity in preterm neonates requiring resuscitation.
Study Length	July 2016-Sept 2016.	Jan 2015-Oct 2016.	Feb 2015-March 2016
Population	San Diego, California. Not stated.	2 sites in India. 18,000 deliveries a year.	Bangalore, India. 542 premature births during study period.
Intervention	Randomized to receive either <1 minute DCC or >5 minutes.	Quasi-randomized to receive UCM x3 or immediate cord clamping.	Randomized to receive either UCM x3 or no milking.
Outcome	**Safe to perform 5 minute DCC without compromising resuscitation.**	**UCM is feasible for late preterm and term neonates and did not cause any significant delay to resuscitation.**	**Can be used as a placental transfusion strategy with no adverse effect on resuscitation attempts.**
Results:			
Number of patients	60	101	60
Mean gestation	39 weeks in both groups	38.3 weeks	33 weeks
Delivery room deaths	0	0	Not stated
Mean APGAR @ 5 minutes (/10)	Control: 8 DCC: 9	8 in both groups	8 in both groups.
Mean Time to Resuscitation/ First inflation breath	**Control (1 min): 36s DCC (5 mins): 25s**	**Resuscitation started within 30 second in both groups.**	**Control: 60s UCM: 60s**

Analysis-

RCTs

RCTs are level 2 evidence and often aim to investigate whether something is effective or feasible (Aveyard, 2014). Both Girish *et al* (2018) and Anup *et al* (2017) conducted a feasibility trial on placental transfusion techniques with resuscitation, whereas Mohan *et al* (2018) evaluated the effectiveness of cord milking, measuring time to resuscitate as a secondary outcome. Anup *et al* (2017) and Mohan *et al* (2018) utilized true randomisation in the form of random number generators and opaque envelopes, however Girish *et al* (2018) randomised neonates by month of birth. This quasi-randomised technique can be criticised for not concealing treatment groups as they are not randomised at the point of intervention, therefore bias could be enacted. Similarly, due to the nature of the intervention the clinicians involved in all the trials could not be blinded, however both Anup *et al* (2017) and Mohan *et al* (2018) blinded their researchers during follow up which may limit any potential bias of the data collection. As Girish *et al* (2018) neither blinded the clinician or the researcher, the results risk being influenced by behavioral bias dependent on the individuals own opinion regarding the trial.

The similar exclusion criteria of the three trials possibly affected the validity of their results, but allowed for better baseline characteristic comparison. In all three studies, a selective group of health professionals were enrolled to provide the intervention but Mohan *et al* (2018) was the only paper to record exactly how they were trained and to have allocated a principle investigator to ensure adherence to the policy. Two studies were

conducted in India with Girish *et al* (2018) collecting data across two sites. The patient demographics and confounding factors may influence the generalisability of the results. Girish *et al* (2018) hypothesised that placental transfusion could be used as an alternative treatment for Hypoxic-ischemic encephalopathy (HIE). In developed healthcare systems neonates suffering from HIE are treated with therapeutic hypothermia, however this may not always be accessible in developing countries and is not always successful (Girish et al 2018). The results of this study may therefore be more applicable to healthcare deprived countries.

Follow up was completed in all three trials other than two patients in Mohan *et al* (2018) where parents discharged the neonate against medical advice. Girish *et al* (2018) found no significant difference between the groups to receive UCM compared to immediate cord clamping in regard to time to resuscitation. Despite having the largest sample size, it was the only trial with no power percentage to observe a relevant statistical difference recorded.

Anup *et al* (2017) were comparing specific timing of an intervention, therefore data collection was taken at a single point, primarily by calling out the numerical values and recording these in the delivery room. Data collection in this manner is subject to human error and could be less reliable as continuous measurement may yield a different result (Anup *et al* 2017). To mitigate this risk, data was also downloaded from the medical equipment. Anup *et al* (2017) observed no significant difference in timing to resuscitation in both groups but did find a trend towards improved APGAR scores and less resuscitation required in the intervention arm.

Comparably Mohan *et al* (2018) also did not find any statistically different value for time to resuscitation or resuscitation interventions between the control and intervention groups. Mohan *et al* (2018) used the same team for resuscitation and follow up, introducing a strong potential source of bias into this study, which may have affected the results positively or negatively dependent on how the collective team viewed the study and any bias they had for or against it.

Table 5. Cohort Studies		
Study:	**Blank *et al* 2018**	**Lefebvre *et al* 2017**
Aim	Feasibility of baby directed DCC technique	Evaluate feasibility and safety of intact cord resuscitation (ICR) on infants born with Congenital Diaphragmatic hernia. (CDH)
Study Length	Not stated	January 2012-April 2016.
Population	Royal Woman's hospital, Melbourne, Australia. 7500 deliveries a year.	Lille University hospital, Calais, France. Not stated.
Cohort observations	Vigorous cohort received 2 minutes DCC. Non-Vigorous >60 seconds after colorimetric co2 detector turned yellow.	Cohort 1 received Immediate Cord Clamping prior to intubation. Cohort 2 received Initial resuscitation including intubation with intact cord.
Outcome	**Feasible to provide resuscitation during DCC. Clamping only when the infant is ready.**	**It is feasible to intubate and mechanically ventilate patients with an umbilical cord intact.**
Results		
Number of patients	44	40
Mean gestation	39	ICC group 39. ICR group 38.
Delivery room deaths	Not stated.	Not stated.
Mean APGAR @ 5 minutes. (/10)	9 in both groups	ICC group 6. ICR group 9.
Mean Time to Resuscitation/ First inflation breath	**60 seconds**	**All patients underwent intubation as per guidelines for CDH. ICC group 2.5 mins. ICR group: 1.7 mins.**

Cohort studies

Cohort studies are observational studies often used to try to understand causation links and are valuable when an RCT might not be ethical or possible (Aveyard, 2014). Benefits can include financial impact, ethical committee approval and establishing links where it would have not been possible to undertake an RCT. Blank *et al* (2018) and Lefebvre *et al* (2017) undertook feasibility cohort studies, both with specific aims. Although the sample size is relatively similar in both, it is difficult to compare study designs as Lefebvre *et al* (2017) recorded a study length of four years whereas the Blank *et al* (2018) study length is not recorded possibly because Lefebvre *et al* (2017) recruited patients from a very specific disease profile. Nevertheless, the outcome measures were similar with time to resuscitation recorded and APGAR score at 5 minutes documented.

Blank *et al* (2018) recorded data using a colorimetric device to indicate when pulmonary gas exchange had begun. This allowed them to standardise the intervention for participants. Video camera placement on the machines enhanced data collection by recording exact timings. Lefebvre *et al* (2017) relied on human counting to record when intubation took place. As all the participants in the Lefebvre *et al* (2017) study suffered from Congenital Diaphragmatic Hernia (CDH) they all received intubation as standard, therefore the two groups can still be compared on time to resuscitation, however, the data collection was subject to human error as it was predominantly times recorded by the researchers. As they were not blinded and were aware of whether each particular neonate was to receive intact cord

resus or not, there is a bias risk. Other sources of bias in both cohort studies were selection bias and financial support although Blank *et al* (2018) state the funders had no role in the study design, outcomes or publishing.

Baseline characteristics for both mother and baby were similar in all groups and none were lost to follow up. Due to the amount of variables in treatment post intervention, both cohort studies used similar statistical tests such as the Bonferroni significance test to account for variables. Although Blank *et al* (2018) recorded time to first cry as an outcome they did not statistically analyses that data. They found no significant difference between APGAR scores at 5 minutes between vigorous and non-vigorous neonates demonstrating that UCM did not negatively impact resuscitation results. Lefebvre *et al* (2017) found that despite the fact time to intubation was shorter in the intact cord resuscitation group, it was not significantly different. APGAR score at 5 minutes however, was significantly higher in the intact group. This has little generalizability to the wider population due to the cohort all suffering from a specific disease, however the incidence of this disease is high (8% of all major neonatal congenital abnormalities) and therefore the results are considered by the researchers as significant (Lefebvre *et al* 2017).

Discussion

In relation to the research question of this review, placental transfusion doesn't appear to have a negative impact on neonatal resuscitation timing or efforts but equally has no significant effect on Apgar at 5 minutes. Apgar was used as a crude measure of infant mortality and the question still remains around the proven multifaceted benefit to these infants (Backes *et al* 2014, Mercer Erickson-Owens 2014, Song *et al* 2017, Chiruvolu *et al* 2018) in the prehospital environment, for which further research should be sought prior to enacting a change in practice for prehospital clinicians. There has been a shift away from "scoop and run" within the ambulance service; introducing placental transfusion may make a positive impact on clinicians to do the basics well before transporting to hospital. Basile *et al* (2018) have demonstrated in a meta-analysis that UCM has as much benefit as DCC and therefore prehospital clinicians, first responders and midwives could still remove the neonate to a suitable platform for resuscitation whilst allowing the infant to benefit from the placental transfusion by UCM which takes only 20 seconds (Basile *et al* 2019). DCC can have negative connotations when used as part of a resuscitation strategy as it suggests "delay". By encouraging the use of "Intact" cord resuscitation instead; this may help promote a more positive culture around its use in this scenario.

The main reported barrier to placental transfusion considered in all five studies was equipment, this is likely to be similar for prehospital use of placental transfusion along with establishing enough space to commence resuscitation. Equipment used in all five studies was reported differently, so

no comparison could be conducted as some used tailor-made resuscitation trolleys and some only used a radiant heater mattress. The differing equipment causes a variable in both the space available to the clinicians and radiant heat available to the new-born. This is a significant limitation to this review as the specific equipment used is likely to have affected outcomes which could not be applied to the prehospital settings. Thomas *et al* (2014) conducted a trial using a new piece of equipment for in-hospital use, which allowed for bedside resuscitation. This mobile trolley was a miniature resuscitare which allowed for an equivalent radiant heat source to be bought to the mother's side allowing for intact cord resuscitation. Heat and working conditions; particularly height, are important factors when considering using it in the prehospital environment. Introduction of similar equipment with forward planning, and collaboration between community midwifes and ambulance services to address issues such as thermoregulation may increase the ability to perform neonatal resuscitation and decrease the risk of resuscitation on a kitchen or bathroom floor. Radiant heat mattresses could be considered and are already in use for some advanced Paramedics across the UK.

Bedside resuscitation in this way allows parents to witness resuscitation efforts, which has been proven to have a largely positive impact on the families coping and functioning post the event (Maxton 2008). Bedside resuscitation with intact cord would therefore facilitate parents to watch first responders perform the resuscitation, potentially limiting the amount of distress they feel when their newborn is immediately taken away to be resuscitated.

All papers analysed in this review defined resuscitation similarly, using a non-crying or non-breathing neonate at birth as the criteria. All papers recorded APGAR at 5 minutes and found either no statistical difference between intervention and control or an increase in APGAR with placental transfusion. As a result of their study Anup *et al* (2017) and Blank *et al* (2018) believe that placental transfusion yielded a greater blood volume which increased pulmonary circulation and cardiac output, leading to greater oxygen delivery and reduced resuscitation efforts. This corresponds with the practice of fluid resuscitation of severely depressed neonates in which intravascular volume is increased. Fluid replacement in the form of UCM was therefore suggested by Girish *et al* (2018) to prevent brain injuries associated with reduced cerebral blood flow at birth when intact resuscitation was impractical.

Resuscitation Council UK (2015) guidelines are due to be updated in the following year whereby a change of prehospital practice may be undertaken following a review of all the available evidence. Prehospital guidelines can be difficult to base on strong evidence and often follow best hospital practice. DCC and UCM have not been trialed in the prehospital environment and many other challenging environmental factors may influence the suitability of this practice in the community. Although a RCT would allow for the highest grade of evidence, a cohort study may be better placed to evaluate prehospital placental transfusion, due to the unpredictability of out of hospital neonatal resuscitation. Advanced Practitioners who are more likely to attend prehospital high-risk births, and therefore be exposed to higher rates of neonatal resuscitation, could undertake this study and the initial introduction of the procedure. A balanced and proportionate view of the importance of the

procedure should be taken, weighed against considerations such as neonatal thermoregulation and maternal management.

Ethical approval was gained in all studies included in this review, however future studies may find it challenging to gain institutional agreement. Anup *et al* (2017) acknowledge it is unclear if neonates already in asystole would benefit, or whether it would contribute to increased fetal blood loss. This would be beneficial to study but would be an invasive procedure to undertake.

Human factors influence the practice of ambulance clinicians and this is particular patient group trigger a highly emotional reaction (McLelland, Morgans and McKenna 2012). This may cause first responders to pre-emptively cut the umbilical cord in panic. UCM could be an alternative to intact cord resuscitation, especially in environments where space is lacking. To promote placental transfusion amongst first responders, education would be needed and appropriate equipment (such as heat mattresses) considered. McLelland, Morgans and McKenna (2012) recommend the development of specific protocols in this field which could be tailored into a flowchart to reduce stress and aid clinician decision making to facilitate use of the procedure when introduced.

Limitations

The many limitations of this review include a single researcher which potentially leads to selection bias of the chosen papers. Researcher and clinician bias is also evident in some of the studies and must be taken into consideration. Data available would allow for a meta-analysis, but time, educational and financial restraints prevented this. The studies were all conducted within the hospital environment with hospital equipment and are difficult to apply to the prehospital setting. The majority of the studies also took place outside of the UK and this limits their generalizability to UK practice. Babies born in developing countries that require resuscitation may have a different aetiology due to health of the mother and confounding factors such as socio-economic wellbeing.

Conclusion

This review has identified 5 papers that promote the use of placental transfusion with no adverse effects on resuscitation attempts or outcomes. This demonstrates that there is evidence to suggest prehospital clinicians should be looking to change practice. Further research, considerations and consultations are required to ascertain the best way to implement the procedure in the prehospital environment.

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