Delayed umbilical cord clamping effects on caesarean delivery neonates under general anaesthesia: A prospective cohort study

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Short title

Delayed cord clamping under general anaesthesia

Abstract

Objective: To investigate the effect of delayed umbilical cord clamping on neonatal outcomes following caesarean delivery under general anaesthesia.

Design: Prospective cohort study.

Setting: West China Second University Hospital

Sample: Neonates born by caesarean delivery under general anaesthesia after 35 gestational weeks.

Methods: Neonates were assigned to Groups A or B if they received early or delayed cord clamping, respectively.

Main Outcome Measures: Umbilical arterial blood gas analysis indicators, Apgar scores, resuscitation procedure incidence, peak bilirubin, and neonatal morbidity were compared between the two groups.

Results: Group A had 29 and Group B had 21 participants. There were no significant differences in any of the outcome measures between the two groups. We classified five periods during caesarean delivery: aesthetic induction (Period 1), skin incision (Period 2), myometrium incision (Period 3), delivery of the neonate (Period 4), and time of cord clamping (Period 5). One-minute Apgar scores were negatively correlated with cord-clamping time (r=-0.426, P=0.002). Peak bilirubin value was correlated with Periods 2, 3, and 5 (r=0.347, P=0.014; r=0.411, P=0.003; r=-0.289, P=0.042, respectively). The remaining secondary outcomes were not correlated with any of the five periods. The peak bilirubin value was(9.712+0.006 × Period 2+0.006 × Period 3-0.026 × Period 5) (R^2=0.313).

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Conclusions: In caesarean delivery under general anaesthesia, delayed cord clamping within a certain period may partially prolong the duration of neonatal exposure to general

anaesthesia drugs. However, delayed cord clamping is a safe and feasible technique for clinical application.

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Keywords: Early cord clamping; Delayed cord clamping; General anaesthesia; Caesarean delivery; Neonatal outcomes; umbilical artery pH

Tweetable abstract:

Delayed umbilical cord clamping during caesarean delivery is a safe technique for clinical application.

Introduction

For deliveries not requiring resuscitation, delayed umbilical cord clamping (DCC) for more than 30–60 s after delivery is recommended by organisations around the world[1–6] due to its favourable effects for term neonates, such as higher blood volume,[7] haematocrit,[8,9] haemoglobin,[8–10] ferritin,[8,9] iron stores,[8,9] and improved long-term neurodevelopment[11,12] as well as lower rates of intraventricular haemorrhage (IVH), chronic lung disease, and necrotising enterocolitis (NEC).[10,13] To date, there is little evidence that DCC is appropriate following deliveries under general anaesthesia, and as such it is uncommon. It is well known that the transplacental passage of anaesthetic agents occurs when the mother is under general anaesthesia, and this may lead to depression in the neonate, which presents as decreased neonatal activity and Apgar scores after delivery,[14] as well as respiratory depression, poor muscle tone, and trouble suckling.[15] General anaesthesia may also increase the incidence of maternal airway complications,[17,18] such as difficult ventilation or aspiration.[19] The American Society of Anesthesiologists and the Society for Obstetric Anesthesiology and Perinatology recommend that staff "consider selecting neuraxial techniques in preference to general anaesthesia for most caesarean deliveries".[16] However, although obstetric anaesthesia guidelines recommend neuraxial anaesthesia (i.e., spinal or epidural block) for caesarean delivery in most patients, there are still some indications for general anaesthesia, such as emergency caesarean deliveries (e.g., profound foetal bradycardia, ruptured uterus, severe haemorrhage, and severe placental abruption),[20] or scenarios in which neuraxial anaesthesia cannot be performed or has already failed.[15]

Currently, the side effects of general anaesthesia on neonates have decreased due to the use of ultra-short-acting anaesthetics, such as propofol and remifentanil.[14] However, considering the adverse effects of the drugs on the neonate under general anaesthesia, it is preferable to clamp the cord as soon as possible after delivery, which is contradictory to the common practice of delaying cord clamping, which is the standard of care for all vigorous newborns.[21]

Therefore, this prospective study was undertaken to investigate the effect of DCC on neonatal outcomes in caesarean delivery under general anaesthesia.

Methods

Patient involvement

The Ethics Committee of West China Second University Hospital, Sichuan University, approved this study **(K2017035).** Written informed consent was provided by the parent of each participant. The primary aim of this study was to evaluate the effect of DCC compared to early cord clamping (ECC) in neonates delivered through caesarean delivery under general anaesthesia. Neonates born after 35 gestational weeks were enrolled between June 2018 and October 2018, and the time of umbilical cord clamping after delivery was recorded according to clinical practice. ECC was defined as clamping within 30 s after delivery, and DCC as clamping 30 s or more after delivery, with the neonate held as low as possible below the placenta and without palpation of the cord. The participants were assigned to Group A if ECC

was performed and to Group B if DCC was performed. No cord milking was performed in either group. Inclusion criteria were delivery by caesarean section under general anaesthesia due to an emergent situation or a contraindication to neuraxial anaesthesia. Exclusion criteria included births before 35 gestational weeks, foetal distress, and severe maternal complications such as severe hypotension and placental abruption.

Funding

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Study design

This was a prospective cohort study conducted at the West China Second University Hospital, Chengdu, Sichuan, China. This study was registered in the Chinese Clinical Trial Registry Center on May 6, 2018 (No. ChiCTR1800016011).

Anaesthesia strategy

The general anaesthesia procedure was conducted according to the 2017 National Obstetrics Anesthesia protocol, as follows: the parturient was preoxygenated and administered an induction agent (1.5–2.5 mg/kg propofol) and a muscle relaxant (1.5–2.5 mg/kg succinylcholine) followed by intubation. After the airway was secured, anaesthesia was maintained with low concentrations of an inhaled agent (sevoflurane) until delivery of the neonate. Concentrations were kept low because of the effect of these agents on uterine tone.[15]

Opioid remifentanil (1 μg/kg) was used at induction to avoid intraoperative awareness.[22,23] To further analyse the effect of different periods of the total time from induction to cord clamping on neonatal outcomes, we divided this time into five different periods: anaesthesia induction (Period 1), skin incision (Period 2), myometrium incision (Period 3), delivery of the neonate (Period 4), and time of cord clamping after delivery (Period 5).

Outcomes

The primary outcome measure was the umbilical artery (UA) pH. Secondary outcomes included other indicators of arterial blood gas analysis, such as haemoglobin level, partial pressures of oxygen (PO_2) and carbon dioxide (PCO_2), base excess (BE), 1- and 5-min Apgar scores, and the incidence of resuscitation procedures, such as mask ventilation, chest compression, endotracheal intubation, and rescue drugs, as well as peak bilirubin level in the first week, requirement for phototherapy, pathological neonatal jaundice, admission to the neonatology department, or other major morbidities such as IVH, NEC, or death.

Statistical analysis

Descriptive statistics were used to describe the study population characteristics. Maternal and infant characteristics were compared among the two cord-clamping management strategy groups using the chi-squared test for categorical variables and the F-test or Kruskal–Wallis test, as appropriate, for continuous variables. We examined group differences in outcomes in a univariate analysis using the chi-squared test for categorical outcomes and Student's t-test or the Wilcoxon rank-sum test, as appropriate, for continuous variables. To further determine

the associations between the outcomes and the different periods of total induction to cord clamping time, we applied correlation analysis and linear regression models. Data management and statistical analyses were performed using SPSS 25 (IBM, Armonk, NY). Two-sided P-values of less than 0.05 indicated statistical significance.

Results

Trial infants

In total, 50 neonates born through caesarean delivery under general anaesthesia who satisfied the inclusion criteria were enrolled in our study (Figure 1). Of them, 29 were assigned to the ECC group and 21 to the DCC group. The mean cord-clamping time was 12.66 s in the ECC group and 48.48 s in the DCC group (P<0.001, Table 1). The mean maternal age and maternal weight between the two groups were not significantly different, as shown in Table 1. The mean gestational week of delivery was 36.84 weeks in the ECC group, and 37.29 weeks in the DCC group (P=0.867). The propofol and remifentanil dosages administered to the mother before delivery between the two groups showed no significant differences, as shown in Table 1 (137.48±12.83 mg/kg vs. 137.81±15.92 mg/kg, P=0.957 and 68.74±6.41 μg/kg vs. 68.91±7.96 μg/kg, P=0.935, respectively).

Primary and secondary outcomes

There was no significant difference in the UA pH between the ECC and DCC groups (7.280±0.03 vs. 7.282±0.03, respectively; P=0.866, Table 2). The mean haemoglobin level of

the DCC group was 14.96 g/dL, which was higher than that of the ECC group (14.43 g/dL), but this difference was not significant (P=0.264). There was no significant difference between the two groups for the other arterial blood gas analysis indicators, including PO_2, PCO_2, and BE (P=0.376, P=0.335, and P=0.499, respectively), as shown in Table 2. The median Apgar scores at one min and five min were also not significantly different in the two groups (9.83±0.54 vs. 9.62±0.19, P=0.254 and 9.97±0.19 vs. 9.90±0.30, P=0.382, respectively; Table 2). The mean peak bilirubin levels of infants after ECC and DCC in the first week after delivery were 10.77±1.84 mg/dL vs. 10.20±3.12 mg/dL, respectively, also showing no significant difference (P=0.429). The incidences of mask ventilation, chest compression, pathological neonatal jaundice morbidity, phototherapy, and admission to the neonatology department were not significantly different between groups (P>0.05). There were no neonates with complications such as IVH, NEC, or death in our study, and no neonates needed endotracheal intubation or rescue drugs.

To further analyse which period in the time from induction to cord clamping had the most significant impact on neonatal outcomes, the time from induction to cord clamping was divided into five periods, as described earlier. Periods 1 to 5 accounted for 23%, 32%, 28%, 11%, and 6%, respectively, of the whole time from anaesthesia induction to cord clamping, as shown in Table S1. First, the relationship between the five periods with the arterial blood gas analysis indicators, including the UA pH, PO_2, PCO_2, BE, and haemoglobin levels, were investigated. None of these indicators correlated with any of the five periods of general anaesthesia (P=0.765, P=0.745, P=0.275, P=0.390, and P=0.450, respectively), as shown in

Table S2. Interestingly, when the other secondary outcomes were explored within the five periods, we found that the 1-min Apgar score was negatively correlated with cord-clamping time (r=-0.426, P=0.002, Table S3). In addition, the peak bilirubin value correlated with Periods 2, 3, and 5 (r=0.347, P=0.014; r=0.411, P=0.003; r=-0.289, P=0.042, respectively; Table S3). Furthermore, the incidence of chest compression was positively related with cord-clamping time (r=0.774, P<0.001, Table S3). The rest of the secondary outcomes, including the 5-min Apgar score, need for mask ventilation, phototherapy, pathological neonatal jaundice morbidity, and admission to the neonatology department, had no relationship with the five different periods (P=0.371, P=0.657, P=0.532, P=0.720, and P=0.532, respectively, Table S3). Results from linear regression analysis of the exact relationship between the peak bilirubin value and the three periods it was associated with are shown in Table S4. The equation was as follows: peak bilirubin value = (9.712+0.006 × Period 2+0.006 × Period 3-0.026 × Period 5) (R^2=0.313).

Discussion

Main findings

There were no significant differences in umbilical arterial blood gas analysis indicators, Apgar scores, resuscitation procedure incidence, peak bilirubin, or neonatal morbidity between infants with DCC and those with ECC. The 1-min Apgar score was negatively associated with cord-clamping time, the incidence of chest compression was positively

associated with cord-clamping time, and peak bilirubin values were correlated with Periods 2, 3, and 5.

In our non-randomised prospective trial, we investigated the consequences of DCC in caesarean delivery under general anaesthesia, and no significant difference was found in the primary outcome (UA pH) between infants with ECC and those with DCC. There was also no significant difference in secondary outcomes, including haemoglobin level, PO_2, PCO_2, BE, Apgar scores at one min and five min, peak bilirubin level of infants in the first week, requirement of mask ventilation, chest compression, phototherapy, pathological neonatal jaundice morbidity, and need for neonatology hospitalisation. Even when the whole period from induction to cord clamping was divided into five different periods, the arterial blood gas analysis results and the 5-min Apgar score showed no relationship with any period. These results seem to contradict those reported by Erkkola et al.,[24] in which they delayed cord clamping to 1.5–3 min after delivery. The results of their study showed that the pH and PO_2 levels in the UA were significantly lower in the group with the longest delay when compared to the group with immediate clamping under general anaesthesia,[24] and they concluded that it was not possible to lengthen the delay time to over three min. However, they also mentioned that despite the deepening respiratory and metabolic acidosis during the delay time, the infants were in good condition and responded immediately to ventilation and stimulation on the resuscitation table. The median DCC time in our study was 48.48 s, which was far less than that of the study by Erkkola et al.[24] Our results showed that the 1-min Apgar score was negatively related to cord-clamping time, which meant that the longer the cord-clamping time

was delayed, the lower the 1-min Apgar score was. However, it did not affect the 5-min Apgar score. In addition, although chest compression was positively correlated with cord-clamping time in our study, when we analysed it in detail, we found that only one case with a DCC time of 172 s contributed to this correlation, and this was not an accurate representation of the actual situation. Another study conducted by Hu et al.[25] randomly divided 40 full-term infants into short-term and long-term groups according to the time from induction to cord clamping. The results showed that there was no obvious respiratory depression in either group, suggesting that prolonging the induction time to umbilical cord clamping within a certain range had no significant adverse effect on neonates. This result was consistent with the results of our study. In this study, the average time from induction to umbilical cord clamping was 6.9 min in the short-term group and 18 min in the long-term group. In our study, the average time from induction to umbilical cord clamping was approximately 7.2 min, close to 6.9 min and far less than 18 min. However, further studies are needed to investigate the best DCC time under general anaesthesia. We speculate that the possible mechanism for this conclusion is as follows. First, the muscle relaxant succinylcholine can barely cross the placenta. Second, propofol can cross the placenta and enter the neonate through the umbilical vein, and approximately 50% of propofol is metabolised by the neonate liver; the rest enters into the systemic circulation and the drug concentration in the brain is obviously lower than that in the umbilical vein. Third, the half-life of remifentanil in children of all ages is significantly lower than that of adults, and remifentanil is quickly metabolised and decomposes without accumulation, so it has little impact on neonates. Finally, the minimum

alveolar concentration (MAC) of inhalational anaesthetics in neonates is higher than that in mothers. For example, the MAC of sevoflurane in neonates is approximately 3.3%, which is higher than that in the maternal body (1.7%).

There was an exception in that the peak bilirubin value was positively related to the time of skin incision and the time of myometrium incision but negatively related to the time of cord clamping after delivery. Further research is needed into what caused this positive relationship. However, provided the two periods had no relationship with the need for phototherapy or complication morbidity, the two periods would not increase the need for clinical interventions. Our results indicated that the peak bilirubin value was negatively related to the time of cord clamping, which was in accordance with the results of another study by Zhang et al.[26] They investigated the Apgar score and peak bilirubin value of the different cord-clamping times of 129 neonates, finding that the longer the cord-clamping time was, the lower the peak bilirubin value of the neonate. This result was opposite to the existing concerns that DCC could increase the haemoglobin level, which might result in elevated peak bilirubin levels. We explored the possible mechanism in our study as follows: DCC improved the blood volume of the neonate, which increased the blood circulation of the liver, thus improving liver function and the ability of the liver to absorb, combine, and excrete bilirubin. In addition, the increased blood supply to the neonate gut can help the development of the mucosa and probiotics, accelerate the gut movement, and facilitate meconium exclusion (Figure 2). We speculated that the abovementioned possible mechanism led to the lower peak bilirubin value.

In addition, our study showed that the umbilical cord-clamping time only accounted for 6% of the whole period from induction to cord clamping, which indicated that the umbilical cord-clamping time has little effect on the whole induction to cord clamping time. This result further suggested that, in caesarean delivery under general anaesthesia, prolonging the umbilical cord-clamping time to a proper extent has no obvious adverse effect on the outcome of vigorous neonates.

Strengths and limitations

Our study had some limitations. First, considering the particularity of ethics, the trial was not designed as a randomised controlled trial. Furthermore, only short-term indices of neonates were observed, and no long-term follow-up was conducted, but this will be addressed in future studies. The results of this study showed that the average Hb level in the umbilical cord blood of the DCC group was higher than that of the ECC group, but the difference was not statistically significant. Considering the insufficient sample size, the next study will expand the sample size. Further studies are needed to determine the exact benefit of DCC time on neonate outcomes under general anaesthesia.

Interpretation

Delaying the cord-clamping time within a certain timeframe in caesarean section under general anaesthesia would not adversely affect neonatal outcomes.

Conclusion

During caesarean delivery under general anaesthesia, DCC may partly prolong the time of neonatal exposure to general anaesthesia drugs. However, according to our results, it seems to be a safe and feasible technique in clinical application, but it does need more supporting evidence from larger study populations to confirm the results.

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Disclosure of interests

The authors declare that they have no conflict of interests.

Contribution to authorship

Study design: FHL and LZ. Conduct of the study: QH and HRZ. Data analysis: QH, PB, and XX. Assistance in data analysis: TH and BZ. Data collection: HRZ. Preparation of the manuscript: QH. Writing of the manuscript: QH. All authors accept responsibility for the paper as published.

Details of ethics approval

The Ethics Committee of West China Second University Hospital, Sichuan University, approved this study **(K2017035,2018-04-24).**

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Tables and Figure caption

Table 1. Clinical data from the study groups

Characteristics	Early cord clamping (N=29)	Delayed cord clamping (N=21)	P value
Maternal age (years)	32.52±4.27	33.76±4.34	0.317
Maternal weight (kg)	68.74±6.41	68.91±7.96	0.936
Gestational week	36.84±1.33	37.29±1.08	0.210

Cord-clamping time (s)	12.66±5.08	48.48±30.94	<0.001
Dosage of propofol (mg)[a]	137.48±12.83	137.81±15.92	0.957
Dosage of remifentanil (ug)[a]	68.74±6.41	68.91±7.96	0.935

Note:[a] is the total dose of propofol or remifentanil given to the mother before delivery. Data are reported as the mean ± standard deviation.

Table 2. Outcomes with respect to the umbilical artery blood gas analysis and other secondary outcomes

Variables	Early cord clamping (N=29)	Delayed cord clamping (N=21)	P value
pH	7.280±0.03	7.282±0.03	0.866
PO_2 (mmHg)	19.59±6.01	18.19±4.55	0.376
PCO_2 (mmHg)	50.91±6.41	52.81±7.29	0.335
BE (mmol/L)	-3.24±2.21	-2.71±3.26	0.499
Hb (g/dL)	14.43±1.52	14.96±1.81	0.264
1-min Apgar score	9.83±0.54	9.62±0.19	0.254
5-min Apgar score	9.97±0.19	9.90±0.30	0.382
Peak bilirubin (mg/dL)	10.77±1.84	10.20±3.12	0.429
Incidence of mask ventilation (%)	13/29 (44.83)	7/21 (33.33)	0.560
Incidence of chest compression (%)	0/29 (0)	1/21 (4.76)	0.420
Incidence of admission to the neonatal department (%)	1/29 (3.45)	1/21 (4.76)	>0.999
Incidence of pathological jaundice (%)	1/29 (3.45)	0/21 (0)	>0.999

Incidence of phototherapy (%)	1/29 (3.45)	1/21 (4.76)	>0.999

Abbreviations: PO_2: partial pressure of oxygen, PCO_2: partial pressure of carbon dioxide, BE: base excess, Hb: haemoglobin level**.** Data are reported as mean ± standard deviation.

Figure legends

Figure 1. Flow diagram detailing the selection of patients included in the prospective analysis. Twenty-three patients were excluded upon failing to meet the inclusion criteria or failure to fully participate in the study.

Figure 2. The speculated mechanism of the lower peak bilirubin value due to delayed cord clamping.