Effect of Delayed Cord Clamping on Systemic Blood Flow: A Randomized Controlled Trial

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Objective To determine whether delayed cord clamping improves systemic blood flow compared with immediate cord clamping in very preterm infants in the first 24 hours.

Study design Women delivering at <30 weeks' gestation at 5 tertiary centers were randomized to receive immediate cord clamping (<10 seconds) or delayed cord clamping (≥60 seconds). Echocardiography and cardiorespiratory data were collected at 3, 9, and 24 hours after birth. The primary outcome was mean lowest superior vena cava (SVC) flow.

Results Of 266 infants enrolled, 133 were randomized to immediate cord clamping and 133 to delayed cord clamping. The 2 groups were similar at baseline, including mean gestation (immediate cord clamping 28 weeks vs delayed cord clamping 28 weeks) and birth weight (immediate cord clamping 1003 g vs delayed cord clamping 1044 g). There was no significant difference between groups in the primary outcome of mean lowest SVC flow (immediate cord clamping 71.4 mL/kg/min [SD 28.1] vs delayed cord clamping 70.2 mL/kg/min [SD 26.9]; $P = .7$). For secondary outcomes, hemoglobin increased by 0.9 g/dL at 6 hours in the group with delayed cord clamping (95% CI 3.9, 14.4; $P = .0005$, adjusted for baseline). The group with delayed cord clamping had lower right ventricular output (–21.9 mL/kg/min, 95% CI –39.0, –4.7; $P = .01$). Rates of treated hypotension, ductus arteriosus size and shunt direction, and treatment of the ductus arteriosus were similar.

Conclusions Delayed cord clamping had no effect on systemic blood flow measured as mean lowest SVC flow in the first 24 hours in infants <30 weeks' gestation. *(J Pediatr 2016;178:81-6).*

Trial registration Australia New Zealand Clinical Trials Registry: ACTRN12610000633088.

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Survival of infants born at <30 weeks' gestation has improved; however, a significant proportion develop neurodevelopmental disability.[1] A recent systematic review[2] of placental transfusion by either delayed cord clamping or cord milking in infants born at <30 weeks' gestation found placental transfusion was associated with short-term benefits, including improved blood pressure and hemoglobin (Hb) concentration, fewer blood transfusions, and reduced late-onset sepsis, with no significant effects on other morbidities. No difference was found in rates of disability or death (3 trials, 96 infants). Appropriately designed, large randomized controlled trials (RCTs) to assess short- and long-term outcomes are needed to inform practice in extremely preterm infants. The Australian Placental Transfusion Study (APTS) was designed to establish whether delayed cord clamping in infants born at < 30 weeks' gestation improves health outcomes compared with immediate cord clamping. The primary outcomes were death and/or major morbidity at 36 weeks' postmenstrual age.

The mechanism of reported benefit of delayed cord clamping may be related to an increase in circulating blood volume at birth. In the first day, when shunts frequently occur across the adapting heart, cardiac input (superior vena cava [SVC] flow) as a measure of systemic blood flow has been reproducibly reported to predict mortality, organ injury including necrotizing enterocolitis and intraventricular hemorrhage, and impaired neurodevelopmental outcome.[3-6]

APTS	Australian Placental Transfusion Study
Hb	Hemoglobin
Hct	Hematocrit
RCT	Randomized controlled trial
RVO	Right ventricular output
SVC	Superior vena cava
UCM	Umbilical cord milking

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In a cohort of infants with low SVC flow born at < 30 weeks' gestation who had their cords clamped early, a normal saline bolus of 10 mL/kg was associated with a transient 55% increase in mean SVC flow with no change in blood pressure.[7] The primary hypothesis of the APTS echocardiography substudy was that delayed cord clamping would be associated with greater systemic blood flow in the first 24 hours. The objective is to determine whether delayed cord clamping decreases or increases the risk of low systemic flow, measured by echocardiography on the first day, in babies born at <30 weeks' gestation.

Methods

This is a substudy of a multicenter, 2-arm parallel, open-label RCT (APTS) (Australia New Zealand Clinical Trials Registry: ACTRN12610000633088). The echocardiography substudy was conducted in 5 tertiary neonatal intensive care units in Australia. Approval was obtained from respective local ethics committees. The sample size at 242 babies was estimated to yield 90% power, assuming 2-sided significance of 5% and 20% noncompliance. This was to detect a relative increase of 27% in mean lowest SVC flow, from a predicted 55 mL/kg/min from recently reported data[8] in infants with immediate cord clamping to 70 mL/kg/min in infants with delayed cord clamping (variance on log scale 0.21). The sample size subsequently was adjusted, given a study noncompliance rate of 28% overall, requiring 262 babies to yield 86% power to detect the same difference.

Mothers at high risk of delivering before 30 weeks' gestation were approached and randomization occurred if informed consent had been obtained. Inclusion criteria were birth before 30 weeks' gestation with informed consent. The exclusion criterion was "no indication or contraindication to placental transfusion in the view of parent or doctor." For example, contraindications included fetal hemolytic disease, fetal hydrops, and major malformations considered incompatible with survival.

Randomization was performed when delivery was considered imminent at an estimated gestational age of <30 weeks via the use of an interactive voice response system. The computerized randomization system was developed by an independent statistician at the National Health and Medical Research Council, Clinical Trials Centre, University of Sydney. The randomization for the main study was by minimization within strata: institution and gestational age (<27 weeks; ≥27 weeks). Each infant of a multiple birth was randomized separately. Randomization into the echocardiography substudy was a further stratification factor.

Intervention

The mother and infant were randomized to either immediate or delayed cord clamping group. For infants allocated to the group with immediate cord clamping, the cord was clamped 6 cm from the umbilicus within 10 seconds of delivery. For infants allocated to the group with delayed cord clamping, a birth attendant held the baby as low as possible below the level of the introitus or placenta for ≥60 seconds before the cord was clamped 6 cm from the umbilicus. The timing of parenteral administration of uterotonic or the use of plastic wrap to warm the baby was according to existing local protocol. Variation from the recommended procedures was undertaken whenever this was judged necessary by the responsible clinician(s), acting in the interests of the mother or baby. Compliance to the intervention was defined as a delay of ≤10 seconds for immediate cord clamping and a delay of ≥60 seconds for delayed cord clamping, with no milking of the umbilical cord allowed in either group.

Assessments

Infants had blood collected for Hb and hematocrit (Hct) at birth from the umbilical cord (where this was not possible, blood was collected at admission) and at 6 hours of age. Echocardiographic assessment was performed at 3-6 hours, 6-12 hours, and 20-28 hours. The measurements were performed at each study center by the research fellow in batches blind to infant identity and treatment. If the research fellow was unavailable, the measurements were performed by clinicians accredited to perform ultrasound scanning. Measures of SVC flow, right ventricular output (RVO), ductal arteriosus diameter, and direction of flow were obtained at each examination. For SVC flow and RVO, an average of measurements over 5 consecutive cardiac cycles was taken; for patent ductus arteriosus diameter, the average of measurements over 3 consecutive cardiac cycles was performed. Flow measures were calculated as previously described with the following formula[9,10]: output (mL/kg/min) = heart rate × (π × diameter^2 / 4) × velocity time integral/weight (kg). A blinded independent reviewer evaluated echocardiography sets for the first 10 babies from each of 4 centers to calculate interobserver variability.

Cardiorespiratory variables collected at the time of echocardiography included mean blood pressure (invasive if arterial line in situ, otherwise noninvasive), heart rate, type of respiratory support, mean airway pressure, inspired oxygen, and use of inhaled nitric oxide. The arterial blood gas closest to the echocardiographic measurement was recorded. Total intravenous fluid intake, use and type of volume expanders, and inotropes administered in the first 6 hours and the first 24 hours were recorded.

Outcomes

The primary outcome of the echocardiography substudy was the mean lowest systemic blood flow for each group defined as lowest recorded SVC flow (mL/kg/min) of 3 measurements at 3, 9, and 24 hours. Secondary outcomes included SVC flow (mL/kg/min), RVO (mL/kg/min), ductal size, and shunt direction at 3, 9, and 24 hours; change in Hb and Hct between baseline and 6 hours; medical or surgical treatment of the ductus arteriosus; incidence of persistent hypotension; and incidence of hypotension treated with volume expansion or inotropes or corticosteroids. Low SVC flow was defined as ≤55 mL/kg/min from recently reported data[8] and low RVO as ≤150 mL/kg/min.[11] Hypotension was defined as a mean blood pressure (mm Hg) below the gestation in weeks for at least 15 minutes.