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Sustained inflation and chest compression versus 3:1 chest compression to ventilation ratio during cardiopulmonary resuscitation of asphyxiated newborns (SURV1VE): A cluster randomised controlled trial

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ABSTRACT

Objective In newborn infants requiring chest compression (CC) in the delivery room (DR) does continuous CC superimposed by a sustained inflation (CC+SI) compared with a 3:1 compression:ventilation (3:1 C:V) ratio decreases time to return of spontaneous circulation (ROSC).

Design International, multicenter, prospective, cluster cross-over randomised trial.

Setting DR in four hospitals in Canada and Austria,

Participants Newborn infants >28 weeks' gestation who required CC.

Interventions Hospitals were randomised to CC+SI or 3:1 C:V then crossed over to the other intervention.

Main outcome measure The primary outcome was time to ROSC, defined as the duration of CC until an increase in heart rate >60/min determined by auscultation of the heart, which was maintained for 60 s. Sample size of 218 infants (109/group) was sufficient to detect a clinically important 33% reduction (282 vs 420 s of CC) in time to ROSC. Analysis was intention-to-treat.

Results Patient recruitment occurred between 19 October 2017 and 22 September 2022 and randomised 27 infants (CC+SI (n=12), 3:1 C:V (n=15), two (one per group) declined consent). All 11 infants in the CC+SI group and 12/14 infants in the 3:1 C:V group achieved ROSC in the DR. The median (IQR) time to ROSC was 90 (60–270) s and 615 (174–780) s (p=0.0502 (log rank), p=0.16 (cox proportional hazards regression)) with CC+SI and 3:1 C:V, respectively. Mortality was 2/11 (18.2%) with CC+SI versus 8/14 (57.1%) with 3:1 C:V (p=0.10 (Fisher's exact test), OR (95% CI) 0.17; (0.03 to 1.07)). The trial was stopped due to issues with ethics approval and securing trial insurance as well as funding reasons.

Conclusion The time to ROSC and mortality was not statistical different between CC+SI and 3:1 C:V.

Trial registration NCT02858583.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ 3:1 Compression:ventilation (C:V) ratio is recommended during neonatal cardiopulmonary resuscitation (CPR).
⇒ The optimal compression and ventilation approach is unknown.
⇒ Continuous chest compression (CC) superimposed by a sustained inflation (SI) significantly reduced time to return of spontaneous circulation (ROSC) in animal studies and a pilot trial in preterm infants <32 weeks' gestation compared with 3:1 C:V.

WHAT THIS STUDY ADDS

⇒ There was no statistical significant difference in time to ROSC between continuous CC superimposed by an SI and 3:1 C:V.
⇒ There was no statistical significant difference in survival between continuous CC superimposed by an SI and 3:1 C:V.
⇒ The trial suffered inherent difficulties as several institutional review boards postponed their approval until the first interim safety analysis and obtaining clinical trials insurance for a trial addressing neonatal CPR was nearly impossible.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A larger randomised trial comparing continuous CC superimposed by an SI and 3:1 C:V is warranted before this technique should be used in the delivery room.

INTRODUCTION

About 0.1% of term and up to 15% of preterm infants receive chest compression (CC) in the delivery room (DR),[1] which is associated with high mortality and short- and long-term neurological morbidity.[2 3]

Neonatal resuscitation guidelines recommend a 3:1 compression:ventilation (C:V) ratio based on expert opinion, consensus and extrapolation from animal data, rather than strong scientific evidence from clinical studies.[1 4] Animal studies have compared C:V ratios (eg, 2:1, 4:1, 9:3 or 15:2) or continuous CC with asynchronised ventilation[5–12]; however, neither resulted in shorter time to return of spontaneous circulation (ROSC) or reduced mortality. Over the last decade, we have examined continuous CC superimposed

by a high distending pressure (termed sustained inflation, SI). When CC+SI was compared with 3:1 C:V in a post-transitional piglet model, regional and systemic haemodynamic and respiratory parameters were improved, with significantly reduced time to ROSC and mortality.[13 14] In a pilot trial in infants <32 weeks' gestation, mean time to ROSC with CC+SI was significantly reduced.[15] With these encouraging results, a larger trial comparing CC+SI with 3:1 C:V during neonatal resuscitation in asphyxiated infants at birth was warranted.[16] We hypothesised that in newborn infants requiring cardiopulmonary resuscitation (CPR) in the DR, CC+SI compared with 3:1 C:V will decrease time to ROSC.

METHODS

Study design and participants

The SURV1VE-Trial was an international, multicenter, prospective, cluster cross-over randomised controlled trial in asphyxiated infants at birth conducted at four level III neonatal intensive care units (NICUs) (two each in Austria and Canada). Research ethics committees approved the trial (Edmonton: #Pro00066739, Graz: #30-368ex17/18, Vienna: #1750/2018, Halifax: #1024910). All sites had approval for deferred consent; some (Edmonton, Vienna) had a waiver of consent if the infant died in the DR. Research staff approached parents after intervention for written informed consent for data collection. The protocol appears in online supplemental file 1, the statistical analysis plan in online supplemental file 2. The trial is reported according to Consort 2010 statement: extension to cluster randomised trials,[17] and Neonatal Utstein Style (online supplemental file 3).[18]

Participants

The initial protocol included term and preterm infants[16]; however, after the Sustained Aeration of Infant Lungs (SAIL) trial,[19] inclusion criteria were changed to infants >28 weeks' requiring CC in the DR. Exclusion criteria were congenital abnormalities with adverse effect on breathing or ventilation (eg, congenital diaphragmatic hernia), congenital heart disease requiring intervention, or if parents did not provide consent.

Randomisation and cross-over

Hospitals were randomised 1:1 (computer-generated allocation sequence) to CC+SI or 3:1 C:V for Period 1 (12 months), and then crossed over to the other intervention during Period 2 (12 months). A 2-month washout period occurred after Period 1, to allow for personnel retraining and assessment of adherence to the new intervention.

Blinding

Owing to the nature of the intervention, only the statistician was blinded by reporting data as groups A and B until the data were locked.

Sample size and power calculation

Primary outcome was time to ROSC. We hypothesised that time of CC to ROSC would be reduced with CC+SI compared with 3:1 C:V. A review of data from Edmonton over a 2-year period identified a mean time to ROSC of 420 s. We calculated a sample size of 208 infants (104/group) would detect a 33% reduction (282 vs 420 s) in time to ROSC using Cox proportional hazards regression with 80% power and a two-tailed alpha error of 0.05. To account for cluster

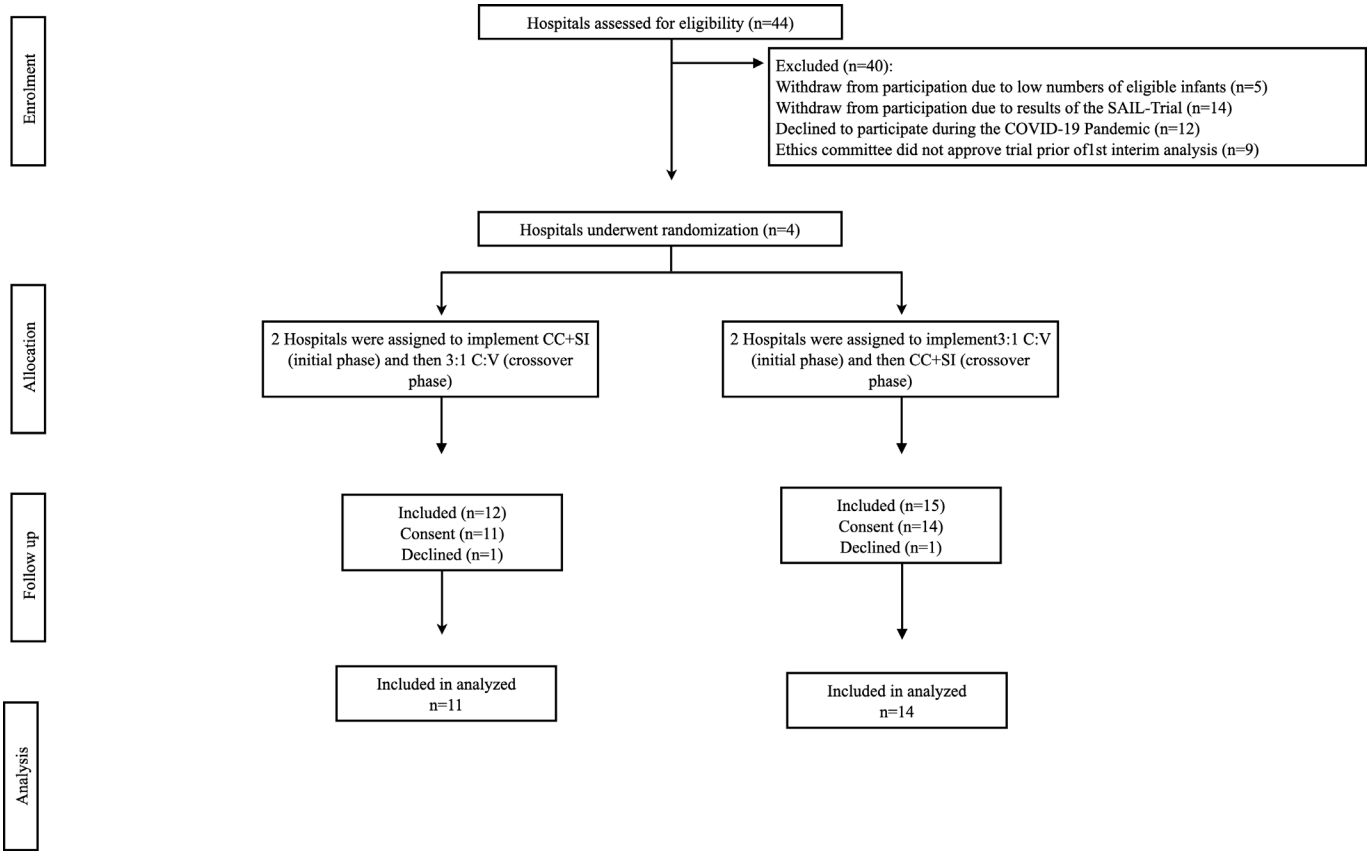

Figure 1 CONSORT diagram: screening, eligibility and randomisation.

randomisation, the sample size was multiplied by design effect of 1.045 (intracluster correlation coefficient, from pilot data), with a total sample size of 218 infants (109/group).

Intervention

CC was performed using the two-thumb encircling hands technique at 90/min, using a compression depth of 1/3 of the anterior–posterior chest diameter.[20–22] CPR quality metrics were not assessed, as there is currently no available technology for newborn infants.

Study interventions

3:1 C:V group

In the 3:1 C:V group, infants received CC at 90/min and ventilations at 30/min in a 3:1 C:V ratio with heart rate (HR) re-evaluated every 60 s.[20–22]

CC+SI group

In the CC+SI group, infants received SIs with a peak inflation pressure (PIP) of 25–30 cmH_2O during continuous CC at 90/min. SI was delivered over 20 s, followed by a positive end expiratory pressure (PEEP) of 5–8 cmH_2O for 1 s. Then the next 20 s SI was started while CCs continued, then PEEP for 1 s, then another SI for 20 s. After 3×20 s CC+SI (a total of 60 s), HR was assessed. If HR remained <60/min, CC+SI was continued in 60-second intervals (3×20 s CC+SI) with HR assessment every 60 s.

Revert to standard of care rule for CC+SI

If CPR was ongoing for 5 min with CC+SI, the clinical team converted to 3:1 C:V ratio.

Outcomes

Primary outcome

The primary outcome was time to ROSC, defined as duration of CC until HR increased >60/min, determined by auscultation, which was maintained for 60 s.

Secondary outcomes

Secondary outcomes among others included neonatal mortality (death <28 days), brain injury rates (reported on MRI or head

Table 1 Demographics

	CC+SI (n=11)	3:1 C:V (n=14)	P value
Gestational age (weeks)*	35.4 (31.9–39.1)	35.6 (30–40.3)	0.938
Birth weight (g)*	2100 (1720–3000)	2835 (1270–3700)	0.537
Male/female	7/4	7/7	0.689
Multiple	1 (9%)	2 (14%)	1.000
Mode of delivery			
Vaginal delivery	–	4 (29%)	
Instrumental vaginal delivery	–	1 (7%)	
Caesarean section	11 (100%)	10 (71%)	0.230
Labour			
No labour	7 (64%)	4 (29%)	
Spontaneous labour	1 (9%)	7 (50%)	
Induced labour	3 (27%)	3 (21%)	
Maternal hypertension	1 (9%)	2 (14%)	1.000
Maternal diabetes	–	2 (14%)	0.487
Antepartum haemorrhage	4 (36%)	1 (7%)	0.133
Uterine rupture	1 (9%)	–	
Shoulder dystocia	–	3 (21%)	
Fetal distress or FHRA	10 (91%)	7 (50%)	
COVID-19 during pregnancy	–	1 (7%)	
Antenatal steroids	2 (18%)	3 (21%)	1.000
Meconium-stained amniotic fluid	–	4 (29%)	0.105
Apgar Score at 1 min*	0 (0–1)	0 (0–1)	0.398
0–3	11 (100%)	14 (100%)	
Apgar Score at 5 min*	3 (1–5)	1 (1–2)	0.091
0–3	7 (64%)	12 (86%)	
4–6	4 (36%)	2 (14%)	
Apgar Score at 10 min*	6 (3–7)	2 (1–3)	0.376
0–3	5 (45%)	12 (86%)	
4–6	2 (18%)	1 (7%)	
7–10	4 (36%)	1 (7%)	
Arterial cord gas			
pH*	7.15 (6.99–7.17)	7.09 (6.86–7.26)	0.808
pCO_2 (mm Hg)*	63 (53–74)	60 (48–100)	0.922
Base excess (mmol/L)*	−8.9 (−5.1 to −12.2)	−8.4 (−7.2 to −13.6)	0.572

Data are number (percentages), unless indicated.
pCO_2 - partial pressure of carbon dioxide
FHRA - fetal heart rate abnormalities
*Median (IQR).
CC+SI, chest compression+sustained inflation; 3:1 C:V, 3:1 chest compression:ventilation ratio.

ultrasound), DR interventions, therapeutic hypothermia, pneumothorax, infection/sepsis, intraventricular haemorrhages (IVHs) and bronchopulmonary dysplasia.

Data collection and statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Alberta.[23 24] A study specific DR record was used to record all interventions including duration of CC. Data were analysed on an intention-to treat basis and included all randomised participants. A survival analysis was done to analyse the difference in time to ROSC between groups. To account for cluster randomisation, Cox proportional hazards regression with time to ROSC as an outcome and allocation group as an independent variable was created. Centres were entered as clusters in the model and statistical significance of allocation group variable was evaluated. Clinical characteristics and outcomes were compared using Student's t-test for parametric and Mann-Whitney U-test for non-parametric comparisons of continuous variables, and χ^2 for categorical variables. For safety and selected secondary outcomes, OR and 95% CIs were estimated. Data are presented as mean (SD) for normally distributed continuous variables and median (IQR) when the distribution was skewed. All p-values are two-sided and $p<0.05$ was considered statistically significant. Statistical analysis was performed using SAS V.9.4 (SAS Institute) or later.

Data and Safety Monitoring Board

Prior to trial commencement, a Data and Safety Monitoring Board (DSMB) was appointed, consisting of two neonatologists with resuscitation expertise. A priori stopping rules were established and interim safety analyses were planned at 10%, 25% and 50% of enrolment. Stopping rules included: (1) 25% increase in mortality, pneumothorax, or IVH with CC+SI and (2) Bayesian posterior probability of CC+SI being better <0.5 or >0.98. If this probability was <0.5, the trial would be stopped for futility. If the posterior probability was >0.98, the DSMB could consider stopping for superiority.

RESULTS

Patient recruitment occurred between 19 October 2017 and 22 September 2022 and initially included infants born between 23 and 42 weeks' gestation. However, when the steering committee became aware of the SAIL-trial results,[19] the SURV1VE-trial was temporarily stopped, to adjust inclusion criteria in discussion between steering committee and DSMB. The trial was restarted with adjusted inclusion criteria (≥28 weeks' gestation) and finally stopped due to funding constraints. At stoppage, 12 infants in the CC+SI group and 15 infants in the 3:1 group (figure 1) were included (Edmonton n=14, Graz n=5, Halifax n=2, Vienna n=4.) Parents of one infant in both groups declined consent. The demographics of both study groups are presented in table 1.

Primary outcome

All 11 infants in the CC+SI group achieved ROSC, while 2/14 infants in the 3:1 C:V group did not achieve ROSC and died in the DR. The CC times of these two infants were 13 min and 33 min. Two infants in the CC+SI group had CC ongoing for >5 min and were switched to 3:1 C:V per protocol, but analysed within the CC+SI group. Three infants (one infant with CC+SI and two infants with 3:1 C:V) achieved ROSC, but had a second episode of CC, before achieving ROSC and admission to the NICU.

The median (IQR) time to ROSC with CC+SI was (174–780) s with 3:1 C:V (p=0.0502, log rank, and p=0.16, cox proportional hazards regression). Figure 2 shows the Kaplan-Meier curve of ROSC; in both groups, the two infants who did not achieve ROSC were censored at the end of their CC time only for the Kaplan-Meier curve.

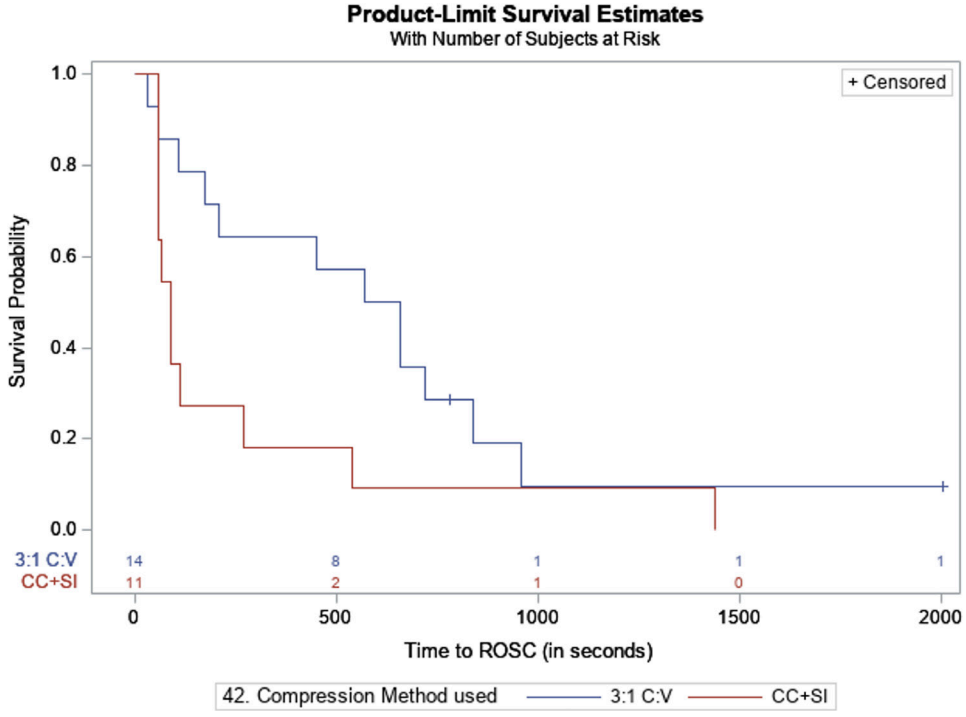

Figure 2 Kaplan-Meier graph of time to return of spontaneous circulation. CC+SI, chest compression+sustained inflation; 3:1 C:V, 3:1 compression:ventilation ratio; ROSC, return of spontaneous circulation.

Table 2 Delivery room interventions

	CC+SI (n=11)	3:1 C:V (n=14)	P value
Deferred cord clamping	–	2 (14%)	
Duration of cord clamping (s)		20 (14) (in two patients)	
Cord milking	–	2 (14%)	
Number of cord milking	–	3 (0)	
Oxygen			
At starting of resuscitation*	21 (21–30)	21 (21–21)	0.960
Maximum concentration*	100 (0)	100 (0)	
During chest compression	100 (0)	100 (0)	
Positive pressure ventilation (PPV)			
Highest PIP during PPV (cm H_2O)	25 (24–30)	25 (24–28)	1.000
MR. SOPA			
Mask reposition	10 (91%)	10 (71%)	
Reposition of head	10 (91%)	11 (79%)	
Suction	10 (91%)	10 (71%)	
Open mouth	10 (91%)	9 (64%)	
Increase PIP	5 (45%)	7 (50%)	
Intubation			
Intubation prior to chest compression	5 (46%)	9 (64%)	0.453
Intubation attempts*	1.1 (0.3)	1.7 (1.4)	0.217
Duration of intubation attempts (s)	43 (20–89)	25 (10–30)	0.077
Epinephrine			
Umbilical venous catheter	3 (27%)	7 (50%)	0.505
Doses*	2.3 (1.5)	2 (14%)	0.505
Endotracheal tube	2 (18%)	7 (50%)	1.000
Doses*	1.5 (0.7)	1.2 (0.8)	1.000
Intraosseous	–	1 (7%)	
Doses*	–	2 (0)	
Peripheral intravenous	–	3 (21%)	
Doses*	–	3.6 (1.5)	
Volume bolus			
Normal-saline 0.9%	6 (55%)	13 (93%)	0.350
Packed red blood cells	3 (27%)	2 (14%)	0.290

Data are number (percentages), unless indicated.
*Mean (SD).
CC+SI, chest compression+sustained inflation; 3:1 C:V, 3:1 compression:ventilation ratio; PIP, peak inflation pressure.

Secondary outcomes

Exploratory secondary outcomes included DR interventions (table 2), NICU outcomes (table 3) and initial neurological examination at 1–6 hours after birth (online supplemental table 4). Twelve MRI exams were performed (six per group), which showed injuries related to hypoxic ischaemic encephalopathy (HIE). No infant was diagnosed with infection/sepsis, necrotising enterocolitis, bronchopulmonary dysplasia or retinopathy of prematurity.

Safety outcomes

The main safety outcome was mortality, which was 2/11 (18%) with CC+SI versus 8/14 (57%) with 3:1 C:V, p=0.10 (Fisher's exact test) and OR (95% CI) 0.17 (0.03 to 1.07). In the CC+SI group, two infants died after NICU admission (care withdrawal for severe HIE (n=1) and severe IVH (n=1)). In the 3:1 C:V group, two infants died in the DR and six further died after NICU admission (care withdrawal for severe HIE (n=4), acute myocardial ischemia (n=1) and cardiorespiratory failure (n=1)). Care was withdrawn between 0 and 8 days after birth in both groups.

Additional safety outcomes included IVH and air leaks. IVH occurred with CC+SI (1/11, Grade 4 IVH) and with 3:1 C:V (2/14, 1× Grade 4 and 1× Grade 3) (OR (95% CI) 0.60 (0.05 to 7.63)). Pneumothorax was diagnosed in 1/11 with CC+SI, and 2/14 (one pneumothorax and one pneumomediastinum) with 3:1 C:V, neither of which required treatment (OR (95% CI) 0.60 (0.05 to 7.63)). There were no tension pneumothoraces.

DISCUSSION

Annually, ~3 million infants worldwide receive CPR with devastating outcomes including mortality and severe neurological disabilities. The approach of 3:1 C:V ratio during neonatal CPR is based on expert consensus rather than clinical evidence.[1 4] Over the last decade, we have shown that CC+SI significantly improved haemodynamic and respiratory parameters, resulting in significantly reduced time to ROSC and mortality.[13–15] In this phase-2 cluster trial, we compared CC+SI with 3:1 C:V in infants >28 weeks requiring CC in the DR. The results can be summarised as follows: CC+SI reduced time to ROSC and improved survival, although both were not statistically significant, and CC+SI was not associated with adverse events.

Table 3 Outcomes during NICU administration

	CC+SI (n=11)	3:1 C:V (n=12)	OR (95% CI)
Passive cooling in delivery room	3 (27%)	5 (36%)	0.53 (0.09 to 3.03)
Therapeutic hypothermia in the NICU	4 (36%)	5 (33%)	0.80 (0.15 to 4.30)
Temperature at NICU arrival	35.8 (0.4)	35.9 (0.3)	−0.10 (−0.39 to 0.19)
Glucose within the 1st hour	4.6 (2.5–7.2)	4.3 (1.4–13.6)	
Moderate/severe aEEG 1st 6 hours	6 (55%)	5 (35%)	1.68 (0.32 to 8.76)
Seizures (clinical or electrical)	5 (45%)	10 (83%)	0.17 (0.02 to 1.14)
Clinical	3 (27%)	7 (50%)	0.27 (0.05 to 1.55)
Electrical (on aEEG)	2 (18%)	3 (31%)	0.30 (0.03 to 3.43)
Mechanical ventilation			
Conventional mechanical ventilation	10 (91%)	10 (71%)	2.00 (0.16 to 25.75)
High frequency oscillation ventilation	1 (9%)	4 (29%)	0.20 (0.02 to 2.16)
Inhaled nitric oxide	1 (9%)	2 (14%)	0.50 (0.04 to 6.44)
Inotropes			
Dopamine	4 (36%)	4 (28%)	1.14 (0.21 to 6.37)
Dobutamine	8 (72%)	7 (50%)	1.90 (0.33 to 11.01)
Epinephrine	5 (45%)	5 (35%)	1.17 (0.22 to 6.08)
Norepinephrine	1 (9%)	3 (21%)	0.30 (0.03 to 3.43)
Milrinone	–	1 (7%)	

Data are presented as n (%), unless indicated.
*Median (IQR).
aEEG, amplitude-integrated electroencephalography.; CC+SI, chest compression+sustained inflation; 3:1 C:V, 3:1 chest compression:ventilation ratio; NICU, neonatal intensive care unit.

To achieve ROSC, healthcare professionals must provide high quality CC to optimise cardiac output while providing adequate ventilation to maintain lung aeration to optimise oxygen delivery. Antegrade blood flow during CPR is achieved by direct cardiac compression or by increasing intrathoracic pressure.[25] While continuous CC without rescue breaths improves ROSC and survival after adult cardiac arrest,[26] in newborns cardiac arrest is due to asphyxia with insufficiently aerated lungs, therefore a combination of ventilation and CC is necessary for ROSC. Chandra *et al* used a high PIP (60 cmH_2O) during continuous CC in an animal model and reported improved carotid flow, without compromising oxygenation.[27] Similarly, Sobotka *et al* demonstrated that SI given immediately after birth increases intrathoracic pressure without impeding blood flow.[28] CC+SI combines these interventions, resulting in improved pulmonary artery and carotid artery blood flow.[13 14]

Furthermore, the downward force applied during CC results in forced expiration while chest recoil air re-enters the lung. Tsui *et al* applied a relatively low downward force (0.16 kg) onto the chest of anaesthetised infants and reported that the tidal volumes forced out of the lungs were greater than the dead space, while the amount of air entering during recoil with a PEEP of 5 cmH_2O was minimal.[29] Similarly, in neonatal piglets, Li *et al* reported that because the air forced out during CPR is larger than the air delivered, a loss of functional residual capacity (FRC) results, which could lead to atelectasis, reduced oxygen delivery and delayed ROSC. In comparison during CC+SI, the constant high distending pressure prevents decruitment, thereby maintaining FRC,[30] improving oxygen delivery and reducing time to ROSC.

In post-transitional piglets with asphyxia cardiac arrest, CC+SI resulted in improved pulmonary and carotid blood flow, improved minute ventilation from passive ventilation, and significantly reduced time to ROSC.[13] Another animal study in post-transitional piglets with asphyxia cardiac arrest also reported reduced time to ROSC.[31] This was confirmed in a pilot trial comparing CC+SI with 3:1 C:V in infants <32 weeks' gestation: The time to ROSC was 31 (9) s with CC+SI compared with 138 (72) s with 3:1 (p=0.011).[15] In the current trial, the median (IQR) time to ROSC was not statistically significant different between CC+SI with 90 (60–270) s and 615 (174–780) s with 3:1 C:V. Furthermore, in animal studies CC+SI improved survival (7/8 (87.5%) vs 3/8 (37.5%),(p=0.038)[13]); in this trial, survival was 82% with CC+SI and 43% with 3:1 C:V, not reaching statistical significance. The survival with 3:1 C:V was not different to neonatal registries, which reported survival between 34% and 60%.[2 32] Overall, enrolled patients number was too low; therefore, no conclusion should be drawn nor should CC+SI be used outside of research settings.

Any DR trial faces the uncertainty of patient recruitment with either antenatal/deferred consent or waiver of consent, and uncertainty of when a potential eligible newborn will be delivered.[33] Clinical trials examining CC have additional challenges. The rate of neonatal CPR is ~1–3/1000 births in high-risk delivery centres,[34] which suggests that many sites have three to five CC events annually. Given the low number of CC events, many sites withdrew their commitment before the trial started due to lack of potential infants and the fear that the healthcare professionals would forget about the study intervention.

While the trial was approved by four institutional review boards (IRBs), other IRBs unexpectedly postponed their approval until the first interim safety analysis. The DSMB had no safety concerns at the first interim analysis, however, as the trial was closed a few months later, we do not know if these IRBs would have approved the study.

In Canada, all clinical trials need clinical trials insurance to comply with Guideline for Good Clinical Practice regarding Investigator/Institution insurance against trial related claims. While there is an existing clinical trials insurance agreement between Canadian universities, insurance had to be purchased for international sites. Obtaining insurance for a neonatal CPR trial was nearly impossible. Risk management at the University of Alberta negotiated for 3.5 years to secure clinical trial insurance

for other sites. This duration is unacceptable and raises the question if a similar delay would occur if the trial examined CC in children or adults.

Limitations

The trial was stopped early, due to funding constraints and recruitment delays due to insurance and the COVID-19 pandemic; thus the proposed sample size was not obtained. Sustained inflation has come under scrutiny in preterm infants 23–26 weeks' gestation,[19] which led to the trial being paused to adjust the inclusion criteria to infants >28 weeks' gestation. Recruitment over 5 years was low (n=27, 25 enrolled and 2 declined) reflecting the limited available patients.

CONCLUSION

There were no statistical differences in time to ROSC and mortality between CC+SI and 3:1 C:V. The number of enrolled patients was too low, therefore no conclusion should be drawn nor should CC:SI be used outside of research settings. A larger randomised trial comparing CC+SI with 3:1 C:V is warranted.

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Contributors GMS conceptualised and designed the study, obtained funding, designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript for important intellectual content. GP conceptualised and designed the study, collected data, and critically reviewed and revised the manuscript for important intellectual content. ALS conceptualised and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content. BHYL designed the data collection instruments, collected data, and critically reviewed and revised the manuscript for important intellectual content. SM, MW and DP collected data, and critically reviewed and revised the manuscript for important intellectual content. MY conceptualised and designed the study, carried out the initial analyses, and critically reviewed and revised the manuscript for important intellectual content. P-YC conceptualised and designed the study, collected data, drafted the initial manuscript, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. GMS (guarantor) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval The research ethics committees approved the trial (Edmonton: #Pro00066739, Graz: #30-368 ex17/18, Vienna: #1750/2018, Halifax: #1024910). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Data used to generate the results reported in this study will be made available following publication to researchers who provide a methodologically sound proposal. Data will only be made available if approval is granted from the Human Research Ethics Committee Board, University of Alberta, Edmonton, Canada. Furthermore, all requesters will need to sign a data transfer agreement. Requests should be directed to the corresponding author.

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