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Outcomes of Delivery Room Resuscitation of Bradycardic Preterm Infants: A Retrospective Cohort Study of Randomised Trials of High vs Low Initial Oxygen Concentration and an Individual Patient Data Analysis

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Conflicts of interest: Y Rabi has patents for technology to guide oxygen titration during newborn resuscitation. He did not contribute to any aspects of the manuscript related to the targeting of oxygen saturations.

Contributor's Statement:

Dr Kapadia prepared the protocol, screened studies, abstracted data, completed risk-of-bias and Grading of Recommendations Assessment, Development and Evaluation evaluations, completed the analysis, and prepared the first draft and the final draft of the manuscript.

Dr Oei reviewed the protocol, screened studies, abstracted data, completed risk-of-bias and Grading of Recommendations Assessment, Development and Evaluation evaluations, reviewed the analysis, and prepared the first draft of the manuscript.

Steve Brown reviewed the protocol and conducted the statistical analysis. He was involved in writing and editing the manuscript.

Drs Finer, Rich, Rabi, Wright, Rook, Vermeulen, Tarnow-Mordi, Smyth, Lui, Saugstad and Vento were involved in reviewing the protocol, reviewing the analysis, and writing and editing the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract

Objective: To determine whether hospital mortality (primary outcome) is associated with duration of bradycardia without chest compressions during delivery room (DR) resuscitation in a retrospective cohort study of randomized controlled trials (RCTs) in preterm infants assigned low versus high initial oxygen concentration.

Methods: Medline and EMBASE were searched from 01/01/1990 to 12/01/2020. RCTs of low vs high initial oxygen concentration which recorded serial heart rate (HR) and oxygen saturation (SpO_2) during resuscitation of infants <32 weeks gestational age were eligible. Individual patient level data were requested from the authors. Newborns receiving chest compressions in the DR and those with no recorded HR in the first 2 minutes after birth were excluded. Prolonged bradycardia (PB) was defined as HR <100 bpm for ≥ 2 min. Individual patient data analysis and pooled data analysis were conducted.

Results: Data were collected from 720 infants in 8 RCTs. Neonates with PB had higher odds of hospital death before [OR3.8 (95% CI 1.5, 9.3)] and after [OR 1.7 (1.2, 2.5)] adjusting for potential confounders. Bradycardia occurred in 58% infants, while 38% had PB. Infants with bradycardia were more premature and had lower birth weights. The incidence of bradycardia in infants resuscitated with low (≤ 30%) and high (≥ 60%) oxygen was similar. Neonates with both, PB and SpO_2<80% at 5 minutes after birth had higher odds of hospital mortality. [OR 18.6 (4.3, 79.7)]

Conclusion: In preterm infants who did not receive chest compressions in the DR, prolonged bradycardia is associated with hospital mortality.

INTRODUCTION:

Intrauterine hypoxia or factors influencing the physiologic changes during transition can make a newborn limp, apneic or bradycardic.[1, 2] Many preterm infants experience suboptimal transition, producing bradycardia and/or apnea requiring resuscitation at birth.[3, 4] A rising heart rate (HR) is an important indicator of effective ventilation in a bradycardic newborn.[5-8] If the HR remains below 100 bpm after the initial steps, International Liaison Committee on Resuscitation (ILCOR) guidelines recommend positive pressure ventilation.[5, 7] If the HR remains below 60 bpm after attempting adequate ventilation, ILCOR guidelines recommend chest compressions[5, 7] Preterm infants who received chest compression in the delivery room (DR-CPR) have increased mortality or morbidity in survivors.[9-14] Fortunately, most preterm infants with bradycardia respond to adequate ventilation and few require DR-CPR.[4, 6] It remains unclear if the duration of bradycardia increases morbidity and mortality in preterm infants not requiring DR-CPR.

The largest clinical trial of initial oxygen (O_2) concentration for preterm resuscitation in the DR so far showed a higher incidence of bradycardia in infants whose resuscitation began with room air.[15] It was unclear if the duration of bradycardia differed between preterm infants resuscitated with low vs high O_2 concentration.[15] In a post-hoc analysis, O_2 saturation (SpO_2) < 80% at 5 minutes after birth was associated with increased mortality.[16] Along with O_2 content of blood, cardiac output is important for adequate O_2 delivery to tissues.[17] Prolonged bradycardia (PB) compromises cardiac output, causing inadequate O_2 delivery and tissue hypoxia. Intermittent bradycardia in preterm neonates during their neonatal intensive care unit (NICU) stay has been associated with decreased cerebral O_2 saturation and motor impairment.[18-20] It is unclear if prolonged bradycardia and low SpO_2 in the DR have an additive significance on adverse outcomes.

We therefore obtained individual patient SpO^2 and HR data from randomized controlled trials (RCT) that compared outcomes of high versus low inspired O^2 resuscitation strategies in infants <32 weeks gestational age (GA). We hypothesized that infants <32 weeks GA who are bradycardic immediately after birth and remain bradycardic for two minutes or more will be at a higher risk of the primary outcome of neonatal mortality and secondary morbidities. We also hypothesized that preterm infants whose resuscitation started with low O_2 concentration (21% - 30%) had longer bradycardia.

METHODS:

Protocol

This individual patient data analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for meta-analysis in health care interventions. [21, 22] The protocol was submitted with the Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/CRD42020216231).

Eligibility Criteria

RCTs which recorded serial HR, SpO_2, fraction of inspired oxygen (FiO_2) during resuscitation of preterm neonates <32 weeks GA, titrated FiO_2 to achieve a target SpO_2 and reported neonatal morbidities and mortality were eligible for this study. Methods of HR assessment, pulse oximeter or an ECG monitor, were noted. Individual patient data for infants <32 weeks GA were obtained directly from the authors. Neonates without HR data by two minutes or who received chest compressions in the DR were excluded as per the protocol. Patients were divided into three groups based on their HR data in the DR during the first 10 minutes from birth. 1. No bradycardia (NB): HR ≥100 bpm throughout the first 10 minutes 2. Transient bradycardia (TB): HR below 100 bpm for < two minutes 3. Prolonged bradycardia (PB): HR below 100 bpm for ≥ two minutes.

Outcomes

The primary outcome of this study was neonatal in-hospital mortality. This and the secondary outcomes of bronchopulmonary dysplasia (BPD), severe retinopathy of

prematurity (ROP), necrotizing enterocolitis (NEC), and severe intraventricular hemorrhage (IVH) were analysed in relation to the three groups of bradycardia. In-hospital mortality was defined as death before discharge from the NICU. The low O_2 strategy was defined as starting resuscitation with 21%-30% O_2 while high O_2 strategy was defined as starting with 60%-100% O_2. [23] BPD was defined as need for supplemental O_2 and/or ventilatory support at 36 weeks postmenstrual age.[24, 25] Severe IVH was defined as grade 3 or higher on any head ultrasounds unilaterally or bilaterally as per Papile criteria.[26] NEC was defined ≥ Stage 2 based on the modified Bell criteria.[27] Severe ROP was defined as Stage 3 or higher based on the international classification of retinopathy of prematurity.[28]

Search strategy and data sources (Figure 1):

Databases (Medline/PubMed, EMBASE, ClinicalTrials.gov, Cochrane controlled trial registers) and meeting abstracts (Pediatric Academic Societies, European Society of Paediatric Research, European Association of Paediatric Societies) were searched from 1990 to 1 November 2020 without language restrictions using index terms: preterm, resuscitation and O_2. Studies in full manuscript or abstract forms were acceptable. An iterative approach was used to ensure that key articles (identified by VK and JO) were found.

Study Selection and Data Extraction

Two authors (VK and JO) independently screened titles and abstracts. In the event of a disagreement during abstract screening, the full text was reviewed. They subsequently completed full-text review for eligibility independently. Final decisions were determined by consensus. The reason for exclusion was captured according to a predetermined, ordered list of exclusions.

Data Collection, Risk of Bias, and Certainty of Evidence Assessment

For each study, two authors (VK and JO) independently extracted predetermined study characteristics and outcomes and then achieved consensus. They independently evaluated the risk of bias (RoB) in individual studies using the Cochrane Risk of Bias Tool for RCTs. The two authors also assessed the certainty of evidence (confidence in the estimate of effect) for each outcome based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (GRADEpro Guideline Development Tool; McMaster University, Hamilton, Canada). Individual patient data were obtained directly from the authors including the HR and SpO_2 data downloaded from the pulse oximeter.

Data analysis

A. Individual patient data analysis: Individual patient data analysis was performed to assess the association of bradycardia with neonatal mortality and secondary morbidities. For this individual data analysis, categorical data were examined by chi-square for trend. Continuous variables were assessed by ANOVA or Kruskal Wallis test. To adjust for confounding variables, multivariate stepwise forward logistic regression was conducted, including GA, birth weight, gender, antenatal steroids, $SpO_2 < 80\%$ at 5 minutes after birth and individual studies as independent variables.

B. Pooled data analysis: Pooled analysis was conducted from aggregated data per study to compare neonates with PB and those without PB using Review Manager software 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark), which does not adjust for potential confounding variables. We used the standard methods of the Cochrane Collaboration. Individual studies were weighted. Random effects models were used to account for variation within and between studies and to compute the summary odds ratio (OR). We report unadjusted summary OR and corresponding 95% confidence intervals (CIs) using the Mantel-Haenszel (MH) method for dichotomous variables. Forest plots were used for the graphical representation of ORs generated from unadjusted data. Heterogeneity between studies was evaluated with I^2 statistics and publication bias was assessed by the Egger's test and by funnel plot inspection.

RESULTS:

Literature Search and Study Selection: (Figure 1)

In total 152 records were identified. As there were no duplicates, 152 records were screened by title and abstract. Two additional articles were found via reference searches and added to the full-text screening. [29, 30] A total of 13 full text articles were assessed for eligibility. Two articles were excluded as serial HR data were not available.[30, 31] Three articles were excluded as they represented a further analysis of the previous study.[32-34] After consensus between two authors (VK and JO), eight RCTs were included in the final quantitative synthesis. [15, 29, 35-40]

Study and patient characteristics (Table 1)

In total, 720 preterm infants < 32 weeks GA were enrolled in the eight RCTs. Most infants had serial HR data in the first 2 minutes after birth except in the RCTs of Rook et al[38] (44% of infants) and Wang et al[40] (73% of infants). As pre-specified, 115 infants (16%) were excluded, as no HR were data available for the first 2 minutes after birth. In total, 605 infants (84% of the eligible infants) were included. All studies used pulse oximetry to collect HR data. Fifty eight percent of preterm infants were bradycardic when first assessed after birth. Thirty eight percent of preterm infants had PB. Amongst bradycardic preterm infants, 93% were bradycardic when first assessed.

RoB Assessment (Supplemental table 1)

All studies except Rabi et al were classified as unclear RoB.[37] Caregivers were blinded to the intervention in only three of the included RCTs.[35, 37, 38] Five RCTs reported that researchers assessing trial end points were blind to randomized group.[29, 35, 37-39] In two RCTs, many infants had no HR in the first 2 minutes after birth making them at high risk of bias because of incomplete outcome data.[38, 40] The study by Oei et al was terminated early due to low recruitment rate.[15] More infants <32 weeks GA in the RCT by Vento et al had PB compared to the average in the study (74% vs 38%) and their mean (SD) GA was 26 ± 1 weeks compared with 28 ± 2 weeks GA ($p<0.05$) in the other studies.

Individual patient data analysis (Table 2)

Bradycardic infants in the DR were more premature, with lower birth weights, than infants without bradycardia. There was no association between initial FiO_2 and bradycardia in the DR. More infants with bradycardia in the DR had SpO_2 <80% at 5 minutes after birth. They also had lower 1 minute and 5 minute Apgar scores. As the duration of bradycardia increased, the incidence of IVH, BPD and in-hospital mortality also increased. This was also true for a composite outcome of in-hospital mortality and/or IVH but not true for in-hospital mortality and/or BPD. These associations remained significant even after adjusting for GA. Even after adjusting for these potential confounders, prolonged bradycardia remained associated with in-hospital mortality, the primary outcome. [OR 1.7 (1.2, 2.5), p<0.01] (Table 3) There was an exposure response relationship between duration of bradycardia and in-hospital mortality (figure 2).

Pooled data analysis (Figure 3)

The primary outcome of in-hospital mortality was reported in eight RCTs involving 605 preterm infants (Figure 3A). The pooled data analysis found higher summary odds of in-hospital mortality for infants with PB [Summary OR 3.57, 95% CI (1.34, 9.5)]. Pre-specified sensitivity analysis was conducted by excluding two studies, which had a large number of infants with no HR recorded by 2 minutes of life. The summary odds ratio was 3.49 [95% CI (1.45, 8.44)] (Supplementary figure 1). The pooled data analysis did not find any statistical difference between the PB and no PB groups for IVH [Summary OR 1.77, 95% CI (0.62, 5.08)] or BPD [Summary OR 1.18, 95% CI (0.78, 1.79)] (Figure 3B and 3C). The summary OR of low initial FiO_2 was not different between the PB and no PB groups [Summary OR 1.28, 95% CI (0.71, 2.29)] (Supplementary figure 2A). Similarly, the summary OR of having SpO_2 < 80 % at 5 minutes was no different between the PB and no PB groups [Summary OR 1.89, 95% CI (0.82, 4.36)] (Supplementary figure 2B). The certainty of evidence was down-graded to low due to serious concerns with RoB, imprecision and plausible confounding.

Interaction between SpO_2 and Bradycardia (Supplementary table 2)

For this analysis, the group of preterm infants who neither had bradycardia nor had SpO_2 <80% at 5 minutes was used as the reference group. Compared to this reference group, preterm infants who had PB without SpO_2 <80% at 5 minutes were 10 times more likely to die before discharge. [OR 10.2, 95% CI (2.1, 48.4)] If preterm infants had both, PB and SpO_2 < 80% at 5 minutes after birth, the odds of in-hospital mortality were 18 times higher. [OR 18.6, 95% CI (4.3, 79.7)] This positive additive interaction between SpO_2<80% at 5 minutes and PB in the DR for mortality persists after controlling for GA.

DISCUSSION:

In this study, thirty-eight percent of preterm infants < 32 weeks GA experienced prolonged bradycardia, which was associated with increased mortality and severe IVH. To focus on PB not receiving chest compressions, infants receiving chest compressions were excluded from the study. There was no association between duration of bradycardia and low vs high O_2 strategy. Neonates who were bradycardic were more likely to have SpO_2 < 80 % at 5 minutes after birth. There was an exposure response relationship between duration of

bradycardia and mortality. The highest odds of in-hospital mortality were in preterm infants with PB and SpO_2 < 80 % at 5 minutes after birth.

Studies have shown that infants who receive higher intensity of resuscitation have a higher incidence of adverse outcomes.[41-43] A recent study showed that low 5 minute and 10 minute Apgar scores are associated with an increased risk of mortality in preterm infants.[44] Apgar score at 5 minutes < 3 has been linked with higher mortality in term infants.[8, 10] None of these studies have examined the association between the duration of bradycardia and neonatal mortality. Intermittent hypoxemia in the NICU has been associated with adverse outcomes. Study by Walter et al showed that in preterm infants admitted to the NICU, bradycardic episodes were associated with clinically significant cerebral desaturations.[20] This effect was more prominent in preterm infants < 32 weeks GA. Interestingly, post hoc analysis of a large randomized controlled trial by Poets et al showed percentage time with bradycardia was associated with motor impairment at 18 months of age, but it did not add any significant prognostic information when added in the model with exposure to intermittent hypoxemia.[19] We have shown in our previous publication that HR < 100 bpm at 5 minutes is associated with mortality and infants who have SpO2 <80% at 5 minutes are more likely to have bradycardia too.[16]

The current study was designed to examine the association between duration of bradycardia in preterm infants not needing CPR and adverse outcomes The PB may reflect in-utero insult and perhaps in some cases, inadequate resuscitation. In the fetus, HR is the most important determinant of cardiac output.[17, 45] In a depressed preterm neonate at birth, PB can interfere with O_2 delivery and may contribute to tissue hypoxia, which in turn may cause adverse outcomes. Alternatively PB may just be a surrogate marker for severity of intrauterine insult or a neonate with significantly impaired transition at birth. Similarly, the additive interaction between SpO_2< 80% at 5 minutes and PB for mortality could reflect severe tissue hypoxia or suggest severity of illness. Low SpO_2 and bradycardia may not be independent of each other. Given its retrospective nature, this study cannot prove causation. Even so, this study shows that HR is the most important vital sign during neonatal resuscitation. It remains to be seen if DR interventions that decrease duration of bradycardia improve clinical outcomes.

This study, analyzed individual data on 605 preterm infants in 8 RCTs using pre-specified, uniform definitions for bradycardia and outcomes. Its strengths include use of individual patient data analysis, pooled data analysis[46, 47] and inclusion of a biostatistician as a co-author.[48] To our knowledge, this is the only study of the association between duration of bradycardia in the DR and adverse outcomes in infants < 32 weeks who did not need CPR. As one objective was to explore the interaction between PB and low SpO_2, only trials collecting serial FiO_2, HR and SpO_2 data were included. The study demonstrates an exposure response relationship between duration of bradycardia and mortality, which strengthens the association between PB and mortality. Also, pre-specified confounders were included in the logistic regression to reduce bias.

This study has several limitations. All RCTs used pulse oximetry to record HR data. Pulse oximeters frequently underestimate HR in the first few minutes after birth, likely due to

technical limitation.[49-52] It is unclear if HR measured by ECG, based on cardiac electrical activity, or by pulse oximetry, based on the peripheral pulse, is a better measure of a cardiac contraction and circulation of blood to peripheral tissues. Our findings should be confirmed by observations where ECG is used for HR measurement. Similarly, individual studies do not describe if delayed cord clamping was practiced on vigorous preterm infants. Studies have shown that immediate cord clamping results in bradycardia.[45] Healthy newborns who underwent delayed cord clamping had lower HRs and higher SpO_2 in the delivery room.[53, 54] Our findings should be confirmed in preterm infants who have undergone delayed cord clamping as recommended by current guidelines.[5, 7, 55] Inadequate ventilation during neonatal resuscitation may lead to prolonged bradycardia. Details of respiratory interventions during neonatal resuscitation were not available for the individual patient data analysis. Future studies should include the amount of DR respiratory support provided and its duration. None of the RCTs were designed to investigate the duration of bradycardia and adverse neonatal outcomes. Despite collecting individual patient data from 8 RCTs, the sample size is relatively small. The studies included in this study were heterogeneous and used different O_2 strategies, which may have affected results. The random effect model was used for the pooled analysis to account for this. In addition, the study did not find any association between starting FiO_2 and incidence of PB. Due to missing HR data for the first 2 minutes after birth, 16% of eligible infants were excluded from the analysis based on the pre-specified study protocol. Although this seems to be missing data at random, a sensitivity analysis of the primary outcome by excluding these two studies was conducted. Although Forest Plots are increasingly used in observational analyses like ours, we used them as only graphic representation of the unadjusted pooled data analysis.[56]. Even though logistic regression was performed to control for known confounders, it is possible that some variables, which may have influenced mortality and intraventricular hemorrhage in this population, are unaccounted for.

In conclusion, PB in the DR was associated with mortality and IVH in preterm infants < 32 weeks GA. PB and low SpO_2 in the DR increased the odds of mortality. The quality of evidence was judged to be low due to risk of bias and imprecision. Future studies involving resuscitation in preterm infants should report duration of bradycardia and 5 minute SpO_2 as an outcome. Larger prospective studies should be done to evaluate the association between PB and adverse outcome in neonates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BPD	Bronchopulmonary Dysplasia

DR	Delivery Room
DR-CPR	Chest compressions and/or epinephrine use in the DR
FiO2	Fraction of inspired oxygen
GA	Gestational age
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Heart rate
ILCOR	International Liaison Committee on Resuscitation
IVH	Intraventricular Hemorrhage
NB	No bradycardia
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
O_2	Oxygen
PB	Prolonged bradycardia
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT	Randomized controlled trial
RoB	Risk of bias
ROP	Retinopathy of prematurity
SpO_2	Oxygen saturation
TB	Transient bradycardia

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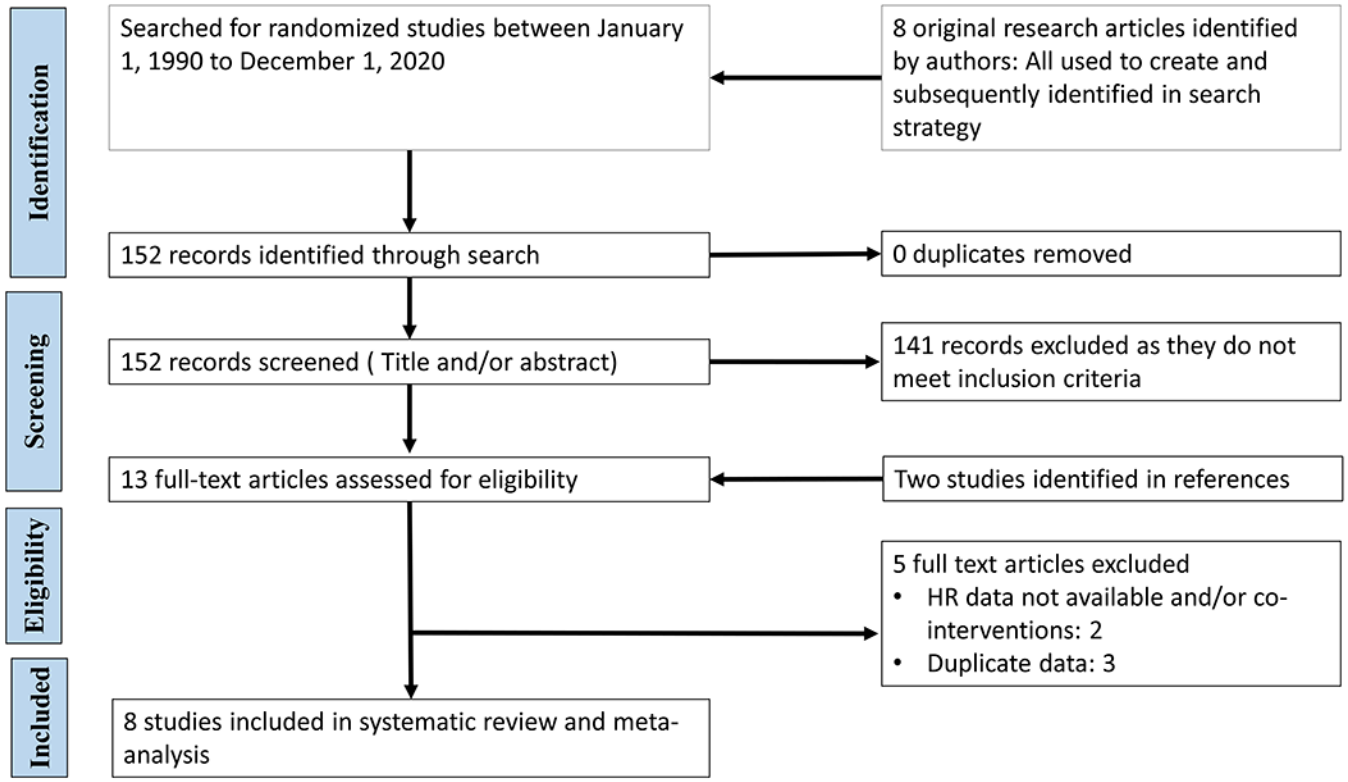


Figure 1:
PRISMA flow diagram of study selection

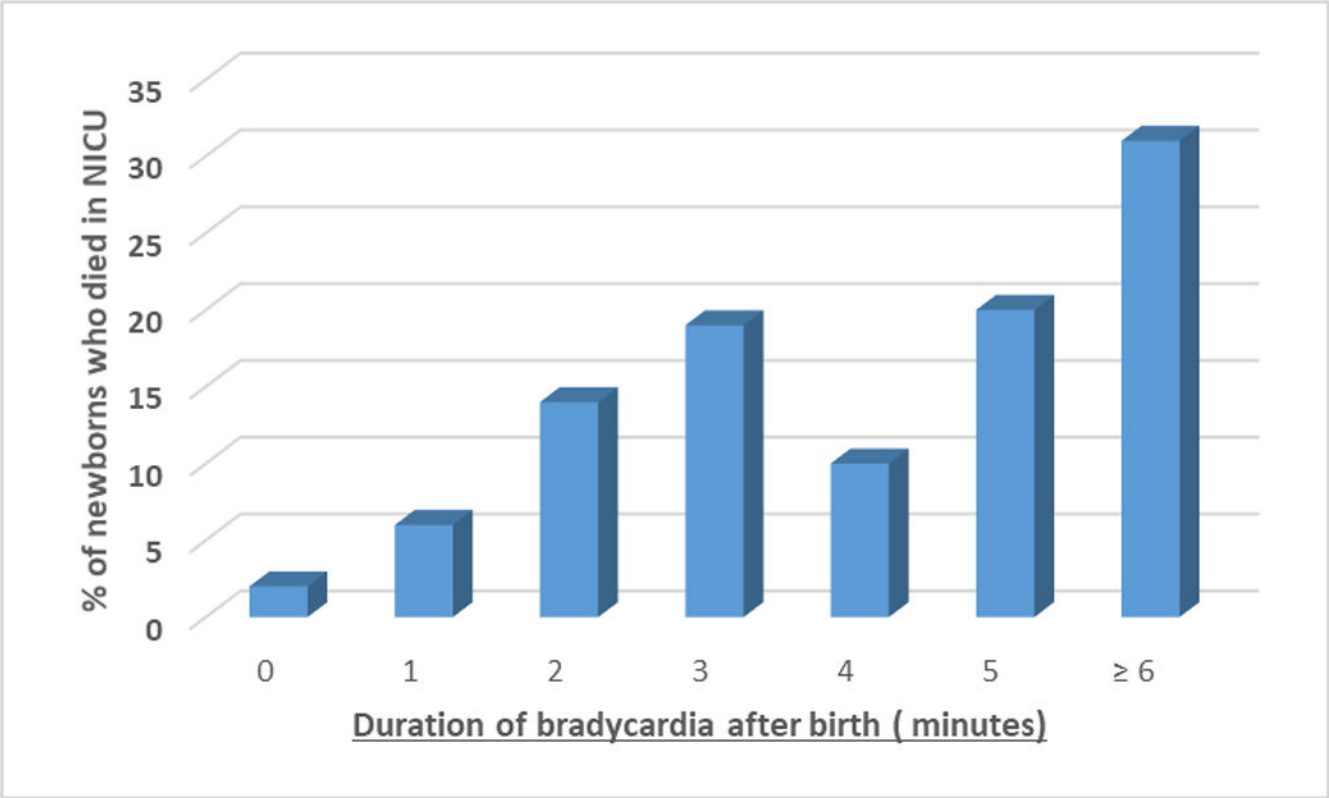
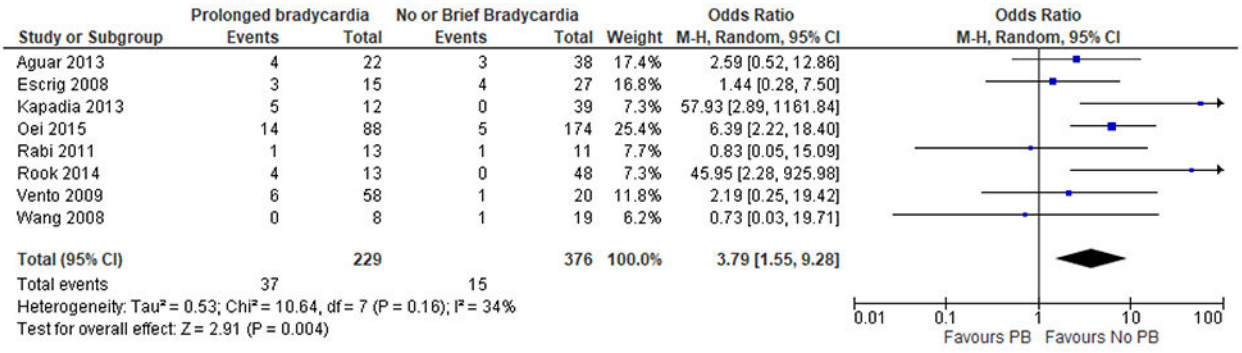
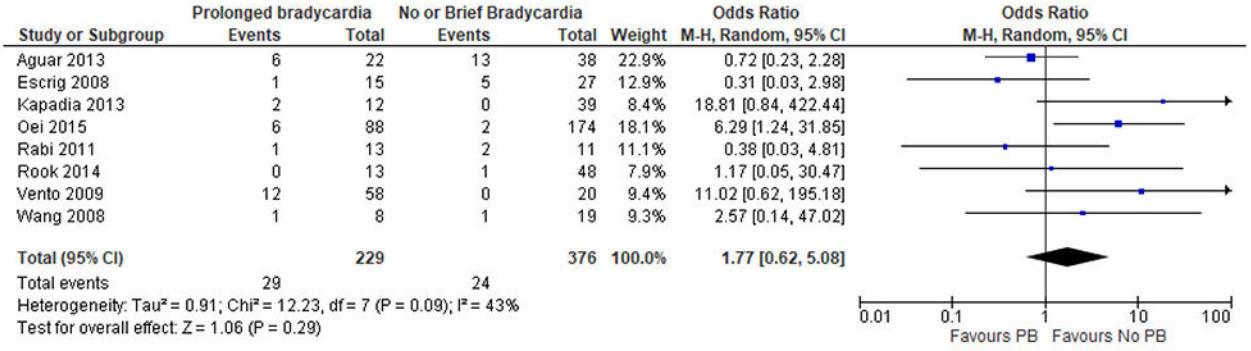


Figure 2:
Association of mortality with duration of bradycardia during resuscitation in preterm infants

A. Death before discharge



B. Severe intraventricular hemorrhage



C. Bronchopulmonary dysplasia

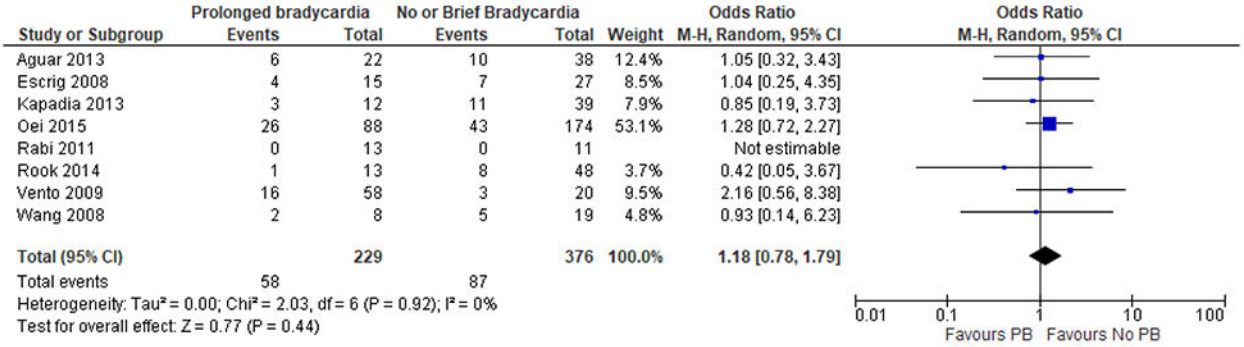


Figure 3:

Summary of results: Prolonged bradycardia versus no prolonged bradycardia at birth. The following forest plots are graphic representation of the unadjusted data. A. Death before discharge B. Severe Intraventricular hemorrhage C. Bronchopulmonary dysplasia

Table 1:

Study characteristics

Study	Enrollment period	Location	FiO_2 groups	Total eligible	Total included, N (%)	Total excluded as no HR available for the first two minutes after birth	No bradycardia	Transient bradycardia	Prolonged bradycardia
Wang et al	2005-2007	United States	0.21 vs 1.0	37	27 (73%)	10 (27%)	14	5	8
Escrig et al	2005-2007	Spain	0.3 vs 0.9	42	42(100%)	0 (0%)	2	25	15
Vento et al	2007-2008	Spain	0.3 vs 0.9	78	78 (100%)	0 (0%)	18	2	58
Rabi et al	2005-2007	Canada	0.21 vs 1.0	26	24 (92%)	4 (8%)	7	4	13
Aguar et al	2010-2012	Spain	0.3 vs 0.6	60	60 (100%)	0 (0%)	14	24	22
Rook et al	2018-2012	Netherlands	0.3 vs 0.6	139	61 (44%)	78 (54%)	44	4	13
Kapadia et al	2010-2011	United states	0.21 vs 1.0	51	51 (100%)	0 (0%)	28	11	12
Oei et al	2009-2014	Australia Malaysia Qatar	0.21 vs 1.0	287	262 (91%)	25 (9%)	127	47	88
Total				720	605 (84%)	115 (16%)	254	122	229

No bradycardia: HR ≥ 100 bpm throughout the first 10 minutes. Transient bradycardia: HR below 100 bpm for < two minutes. Prolonged bradycardia: HR below 100 bpm for ≥ two minutes.

Table 2:

Pooled data analysis: Infant characteristics and outcomes

	No Bradycardia N= 254 (42%)	Transient Bradycardia N= 122 (20%)	Prolonged Bradycardia N= 229 (38%)	*P* value	Adjusted *P* value for GA
Gestational age, wks	28 ± 2[a]	27 ± 2[b]	27 ± 2[b]	< 0.01	NA
Birth weight, gms	1152 ± 352[a]	976 ± 257[b]	980 ± 270[b]	< 0.01	NA
Male	114 (45%)	65 (53%)	113 (49%)	NS	NS
Antenatal Steroids	216 (85%)	101 (83%)	198 (87%)	NS	NS
Cesarean section	152 (60%)	64 (52%)	131 (58%)	NS	NS
Starting low FiO2	112 (44%)	58 (48%)	122 (53%)	NS	NS
SpO2 < 80% at 5 minutes	89 (35%)[a]	51 (43%)[a]	149 (65%)[b]	<0.01	<0.01
Apgar 1 min	7 (6,8)[a]	5 (3,6)[b]	5 (3,6)[b]	<0.01	<0.01
Apgar 5 min	9 (8,9)[a]	7 (7,9)[b]	7 (6,9)[b]	<0.01	<0.01
IVH	10 (4%)[a]	14 (12%)[b]	29 (14%)[b]	<0.01	0.03
NEC	4 (2%)	1 (2%)	4 (4%)	NS	NS
BPD	49 (20%)[a]	38 (32%)[b]	58 (27%)[a,b]	0.03	NS
ROP	34 (14%)	20 (17%)	37 (17%)	NS	NS
Death	6 (3%)[a]	9 (7%)[a,b]	37 (16%)[b]	<0.01	<0.01
Death or BPD	54 (22%)[a]	45 (38%)[b]	88 (41%)[b]	<0.01	NS
Death or IVH	16 (6%)[a]	23 (20%)[b]	61 (28%)[b]	<0.01	<0.01

Superscripts in columns signify pairwise comparison of columns with different letters (a or b) signify statistical difference with Bonferroni correction and similar letters are not statistically different.

Table 3:

Multiple regression analysis reporting the association of in-hospital mortality as primary outcome (dependent variable) - with seven pre-specified exposures (independent variables).

Independent variable	Odds Ratio (95% CI)	*p* value	Coefficients
Prolonged Bradycardia *	1.7 (1.2,2.5)	0.004	0.552
Gestational Age **	0.6 (0.4,0.8)	0.003	−0.513
Male gender †	2 (1,4)	0.06	0.671
Birth Weight	0.1 (0.1,1)	0.2	−0.00189
Antenatal Steroids	1 (0.2,5.2)	0.9	0.032
Individual Study	0.9 (0.8,1)	0.1	−0.111
SPO_2 < 80% at 5 minutes after birth	1.4 (0.6,3)	0.4	0.327

* Exposure to prolonged bradycardia vs non-exposure is associated with a statistically significant increase in odds of in-hospital mortality of 1.7 (95% CI 1.2 to 2.5)

** Each increase in gestation of one week is associated with a statistically significant reduction in the odds of hospital mortality of 0.6 (95% CI 0.4 to 0.8).

† Relative to being female, being male is associated with a non-statistically significant twofold increase in the odds of hospital mortality