NICHD

NEONATAL RESEARCH NETWORK

Length of Exposure to a Single Dose of Betamethasone: Infant Mortality and Morbidity Outcomes

Sanjay Chawla, Myra H. Wyckoff, Matthew A. Rysavy, Ravi Mangal Patel, Dhuly Chowdhury, Satyan Lakshminrusimha, Abhik Das, Rachel G. Greenberg, Edward F. Bell, Namasivayam Ambalavanan, Noelle E. Younge, Girija Natarajan, Seetha Shankaran, Abbot R. Laptook, Leeann R. Pavlek, Carl Backes, Krisa P. Van Meurs, Erika F. Werner, Waldemar A. Carlo
for the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network

Dedicated to the memory of Ira Adams-Chapman MD

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Disclosures

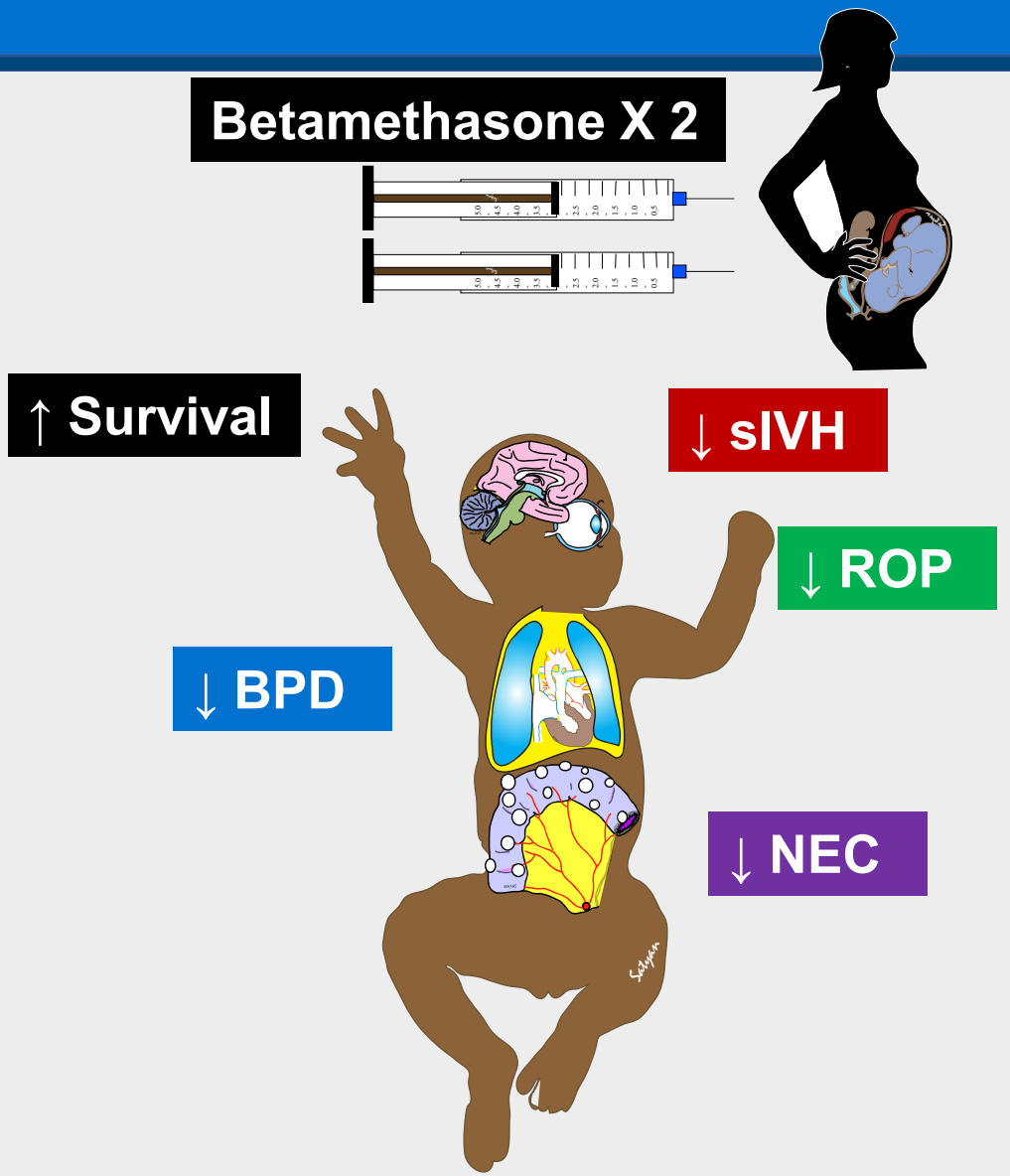
- Speaker: Sanjay Chawla
- Dr. Chawla has no financial relationships to disclose or Conflicts of Interest to resolve
- This presentation will not involve discussion of unapproved or off-label, experimental or investigational use of a drug

Background

- Exposure to antenatal steroids (ANS) is associated with lower risk of mortality and neonatal morbidities

- Nearly 25% of extremely preterm infants are born after exposure to an incomplete course of ANS
  - *Chawla S. JAMA Pediatrics; 2016*

- Preterm neonates may be born shortly after initiation of ANS due to
  - Insufficient time from hospital admission to delivery or
  - Maternal/fetal indications for expedited delivery



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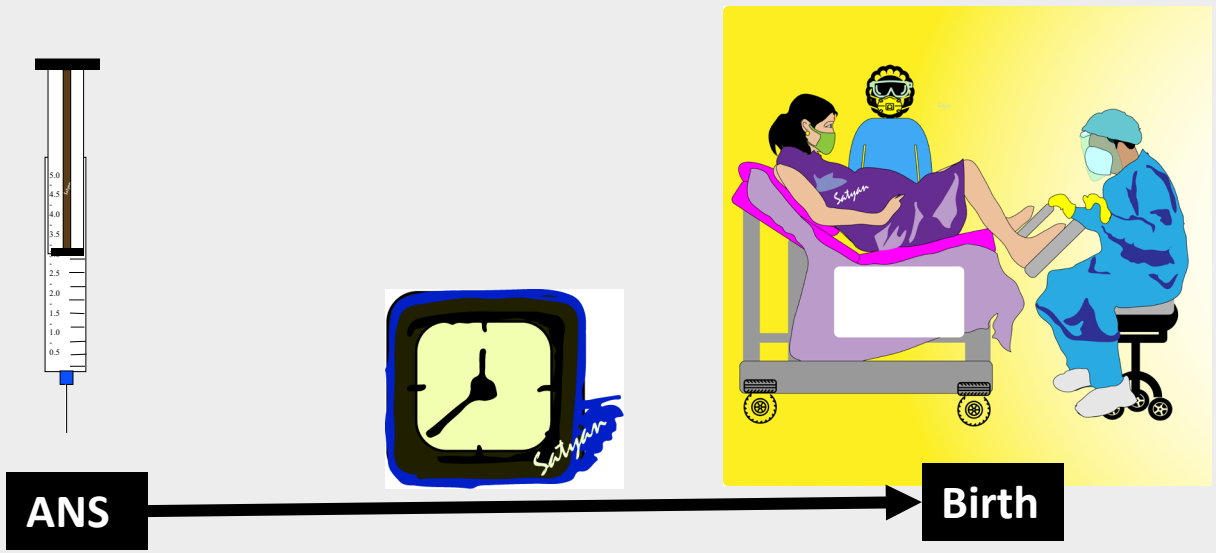
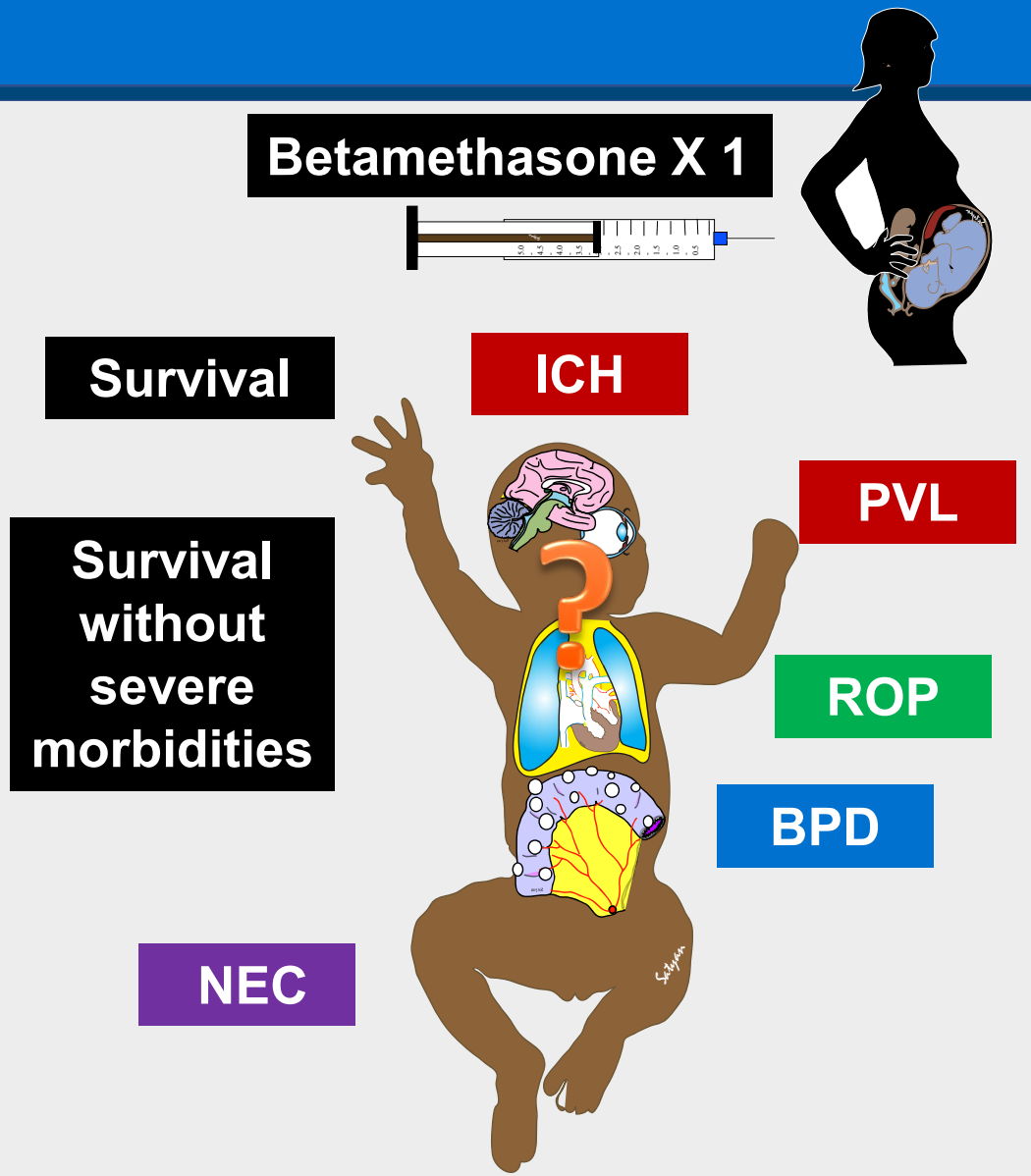


- The minimum protective time interval between ANS administration and birth is unknown
- Recently, NIH and Care Excellence Guideline Development Committee noted the lack of available evidence on the optimal timing of administration of ANS in relation to the time of birth
  - *Preterm Labor and Birth. National Institute for Health and Care Excellence Clinical Guidelines.; 2015*

Objective

- To evaluate the association between duration of in utero exposure to single dose of antenatal betamethasone and the risk of adverse outcomes among extremely preterm infants



Study Population

- Inclusion Criteria:
  - Infants born between $22^{0/7}$-$27^{6/7}$ weeks' GA from January 2016 to February 2021 at centers participating in the National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN)
- Exclusion criteria:
  - No intensive care
  - Major anomalies
  - Receipt of antenatal dexamethasone
  - Complete course of ANS (2 doses of antenatal betamethasone)
  - Missing data on dose or timing of antenatal betamethasone

Methods

- Primary outcome
  - *Survival to hospital discharge*

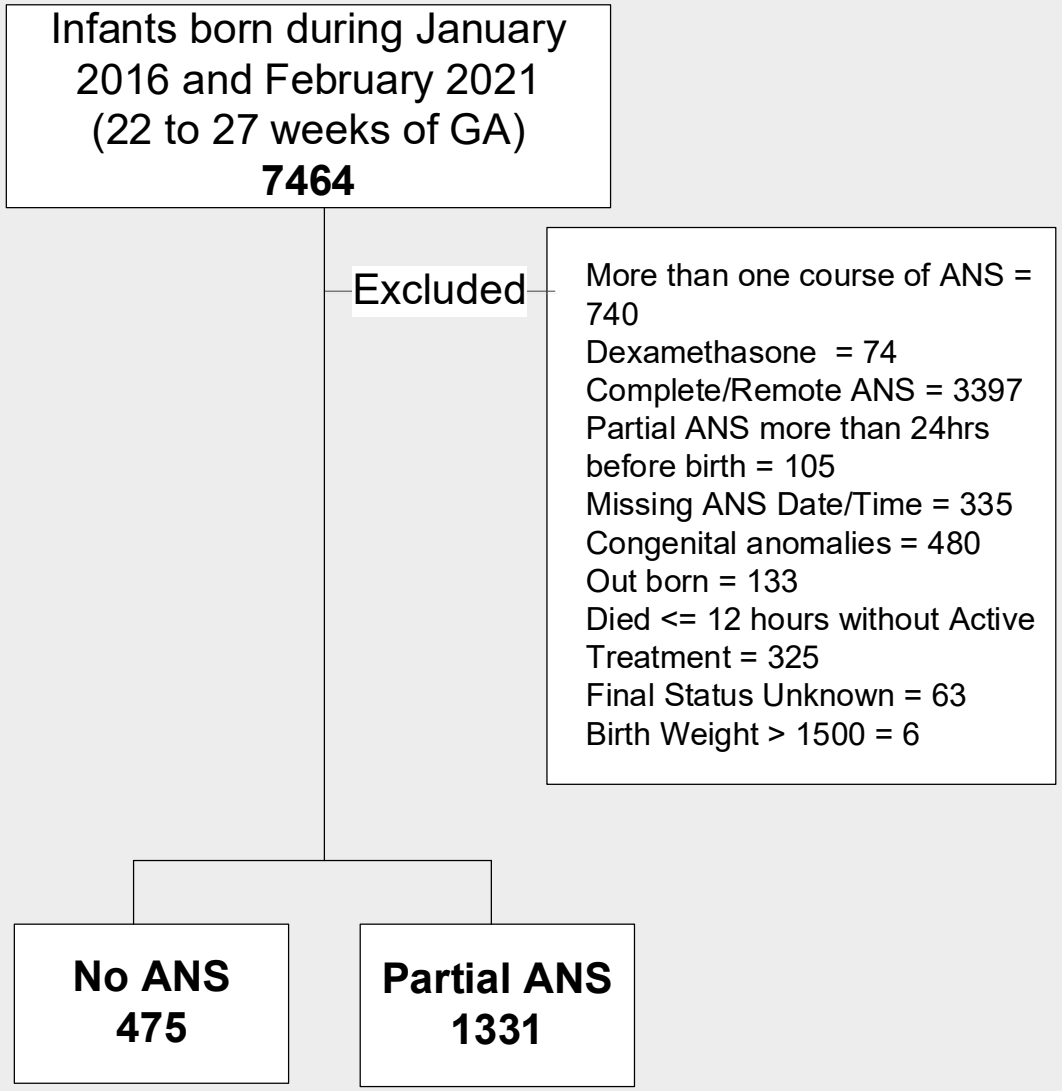
- Secondary outcomes
  - *Survival without severe neonatal morbidity* including severe intracranial hemorrhage (ICH), cystic periventricular leukomalacia (cPVL), surgical necrotizing enterocolitis (NEC), severe bronchopulmonary dysplasia (BPD) and severe retinopathy of prematurity (ROP) requiring treatment
  - *Individual severe morbidities*
  - *Composites of individual severe morbidities or death*

Statistical Analysis

- The association of antenatal betamethasone administration-to-birth interval following a single dose and neonatal survival and morbidity was evaluated using logistic regression

- Model was adjusted for
  - GA
  - Sex
  - Race
  - Mode of delivery
  - Multiple birth
  - Prolonged rupture of membranes
  - Maternal education
  - Small for gestation status
  - Center of birth

Patient Cohort



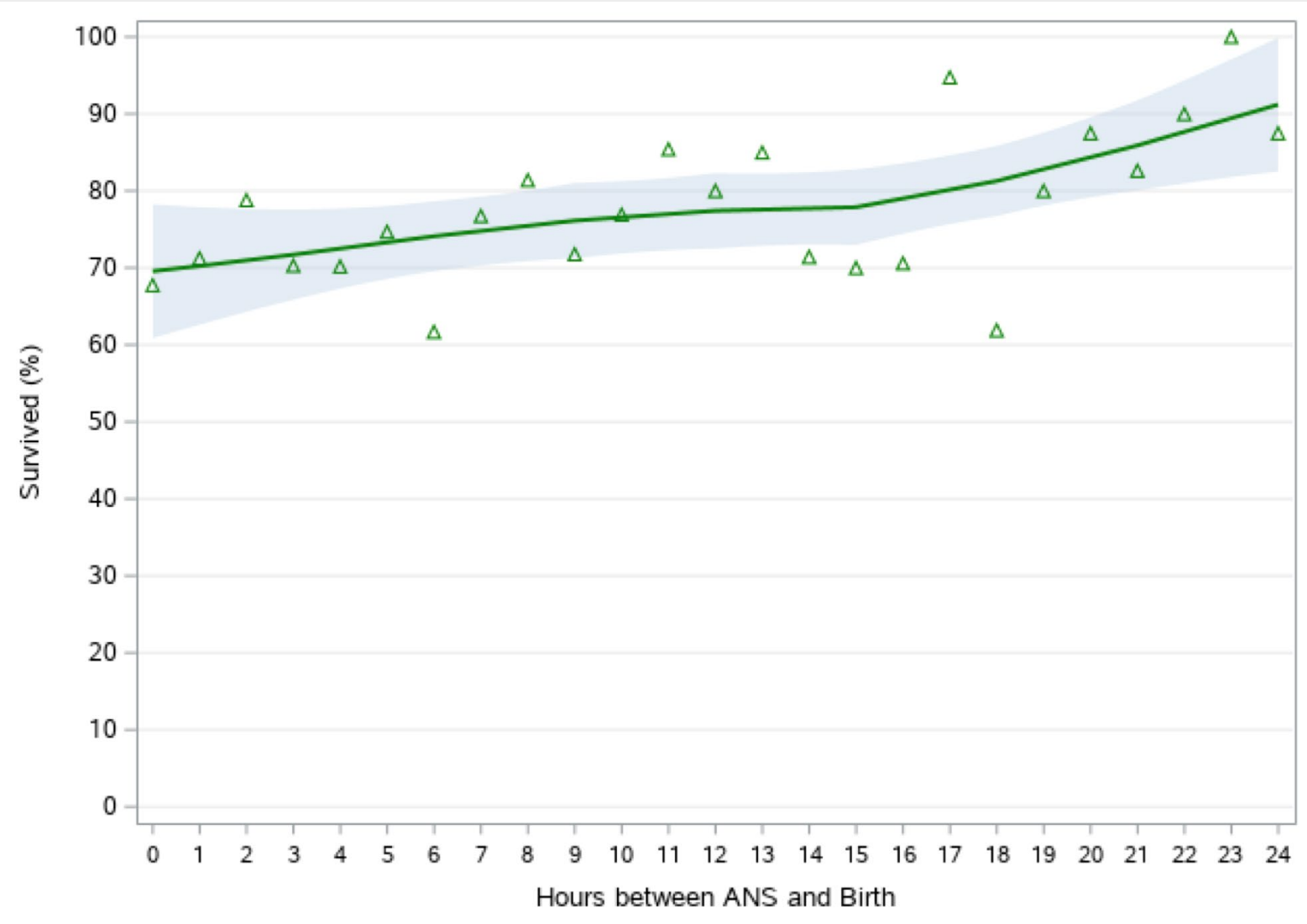
Results

- A total of 1806 infants were included
- 475 with no betamethasone
- 1331 after exposure to a single dose of betamethasone: Classified into quartiles
  - **Quartile 1:** ≤1.4 hours, n=337
  - **Quartile 2:** 1.5-3.8 hours, n=335
  - **Quartile 3:** 3.9-9.5 hours, n=328
  - **Quartile 4:** >9.5 hours, n=331

Results

- There were no significant difference in race, birth weight and sex of neonates among all groups
- Median GA was 25 weeks for patients in all groups (p=0.65)
- The median administration-to-birth time interval for patients born after a single dose of betamethasone was 3.9 hours

Association Between ANS Administration-to-Birth Interval and Neonatal Survival



Each hour increase in the administration-to-birth interval exposure was independently associated with 1% higher rate of survival

Outcomes of Infants by Exposure to Antenatal Betamethasone at Varying Timing

Variable (%)	Partial ANS by Administration-to-Birth Quartile				Adjusted RR (95% CI) [for 1 hour increase in time difference between ANS & birth]
	Q1: ≤1.4 hrs, n=337	Q2: 1.5-3.8 hrs, n=335	Q3: 3.9-9.5 hrs, n=328	Q4: >9.5 hrs, n=331	
Survival	70%	74%	73%	81%	**1.01 (1.00 to 1.01)**
Survival without major morbidities	41%	44%	44%	54%	**1.01 (1.01 to 1.02)**
Severe ICH	32%	29%	28%	21%	**0.98 (0.96 to 0.99)**
cPVL	7%	9%	6%	4%	**0.96 (0.92 to 0.99)**
Grade 3 BPD	6%	11%	11%	12%	1.00 (0.97 to 1.03)
Surgical NEC	6%	7%	3%	5%	0.99 (0.95 to 1.03)
Severe ROP	13%	13%	12%	10%	0.99 (0.96 to 1.02)

Outcome of Infants by Exposure to Antenatal Betamethasone at Varying Time
Compared to No ANS Exposure

	Adjusted Relative Risk (95% CI)			
Variable	Q1[<1.4 hrs] vs. No ANS	Q2 [1.5-3.8 hrs] vs. No ANS	Q3 [3.9-9.5 hrs] vs. No ANS	Q4 [>9.5 hrs] vs. No ANS
Survival	1.08 (0.99-1.18)	**1.13 (1.04-1.23)**	**1.13 (1.04-1.23)**	**1.22 (1.13-1.32)**
Survival without major morbidities	1.01(0.87-1.18)	1.05 (0.91-1.22)	1.07 (0.93-1.24)	**1.29 (1.12-1.48)**
Severe ICH	0.95 (0.76-1.18)	0.85 (0.67-1.07)	0.86 (0.68-1.08)	**0.67 (0.52-0.86)**
Severe ICH or death	0.93 (0.81-1.07)	**0.83 (0.71-0.97)**	**0.87 (0.75-1.00)**	**0.70 (0.60-0.83)**

Results

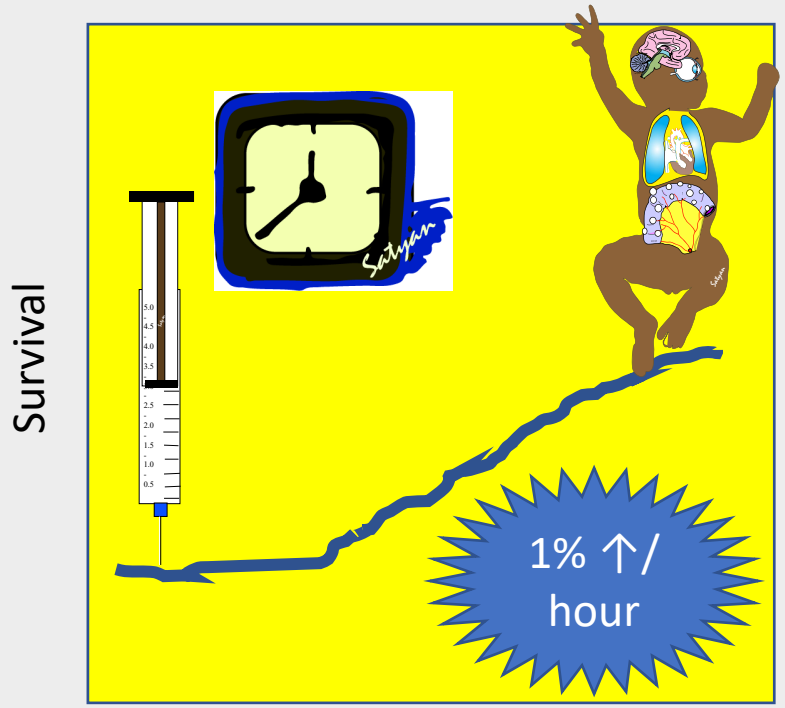
- The rate of survival was significantly higher for infants in quartile 2 [(ANS Administration-to-Birth Interval of **1.5 to 3.8 hours**) **74%**], as compared to **65%** in no ANS group, with adjusted relative risk of 1.13 (1.04-1.23)

Conclusions

- After a single dose of antenatal betamethasone, each hour increase in the administration-to-birth interval was independently associated with 1% higher rate of survival and survival without severe neonatal morbidity

- Extremely preterm infants born after as little as 1.4 to 3.8 hours after a single dose of betamethasone had a significantly higher survival compared to infants without exposure to betamethasone

- Administration of ANS even if delivery is imminent is associated with benefit to the newborn



Neonatal Research Network Centers (2016-2021)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center at Houston
- University of Utah

Questions ?

Table 3: Adjusted Relative Risk of Mortality and Morbidity of Infants by Exposure to Antenatal Steroids at Varying Time Interval Compared to No ANS Exposure

	Adjusted Relative Risk			
Variable	Q1[<1.4 hrs] vs. No ANS	Q2 [1.5-3.8 hrs] vs. No ANS	Q3 [3.9-9.5 hrs] vs. No ANS	Q4 [>9.5 hrs] vs. No ANS
Survival	1.08	1.13(1.04-1.23)	1.13(1.04-1.23)	1.22 (1.13-1.32)
Survival without major morbidities	1.01	1.05	1.07	1.29 (1.12-1.48)
Severe ICH	0.95	0.85	0.86	0.67 (0.52-0.86)
Severe ICH or death	0.93	0.83 (0.71-0.97)	0.87 (0.75-1.00)	0.70 (0.60-0.83)
Grade 3 BPD	0.74	1.09	1.07	1.09
Grade 3 BPD or death	0.87	0.83 (0.69-1.00)	0.87	0.76 (0.63-0.92)
Surgical NEC	1.08	1.27	0.58	0.87
Surgical NEC or death	0.93	0.81 (0.66-1.00)	0.79 (0.65-0.97)	0.68 (0.55-0.85)
cPVL^	0.83	1.22	0.81	0.55
cPVL or death**	0.91	0.86	0.82	0.66