Mass General Brigham

HARVARD MEDICAL SCHOOL

Effect of implementing a clinical practice guideline for prophylactic indomethacin on reduction of severe IVH in extremely preterm infants

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14th International Newborn Brain Conference

BRIGHAM INFANT BRAIN STUDIES B.I.B.S

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Literature review

I. Severe intraventricular hemorrhage (SIVH) → impaired neurodevelopmental outcome

II. Indomethacin prophylaxis might reduce the incidence of IVH

III. TIPP trial: Prophylactic indomethacin in extremely preterm infants has been associated with reduction of SIVH (aOR 0.6, 95%CI 0.4–0.9) but no improvement in neurodevelopmental outcome

- **Secondary analysis** : The relative treatment effect of indomethacin did not vary based on the baseline risk of severe IVH. **In highest risk quartile the absolute risk reduction was 9 % with a NNT of 11.**

III. Meta- analysis:

- No significant difference in the risk of any grade IVH
- The rate of severe IVH decreased in infants with prophylactic indomethacin

Al-Matary, A., et al., Front Pediatr, 2022.; Schmidt, B., et al., N Engl J Med, 2001.; Foglia, E.E., et al., Neonatology, 2018. 2

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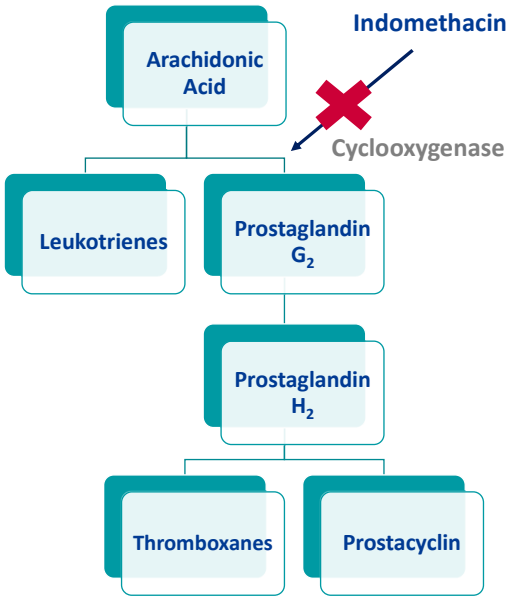
Prophylactic indomethacin

Blocks the enzyme cyclooxygenase that inhibits prostaglandin synthesis

Benefits:

- Decreases baseline cerebral blood flow
- Inhibits the formation of free radicals
- Accelerates the maturation of micro-vessels of the germinal matrix

Routine use of prophylactic indomethacin has been controversial with variable utilization in clinical practice

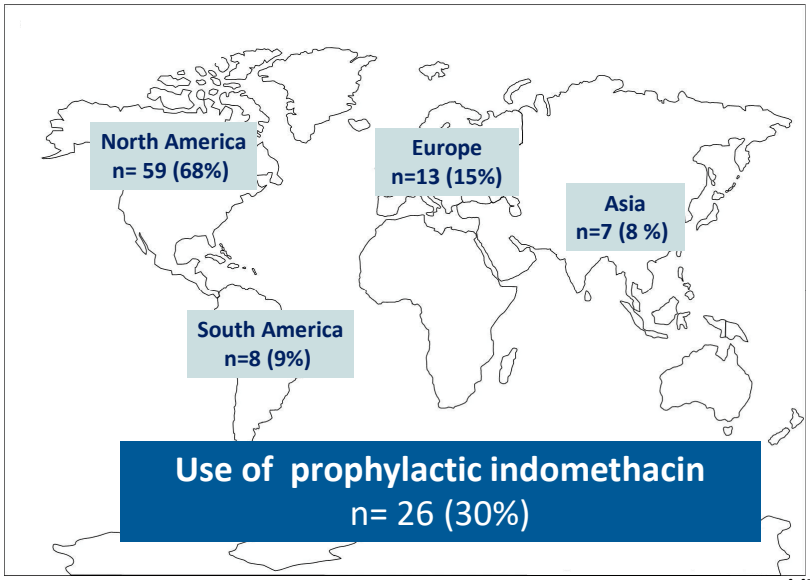


Edwards AD et al., *Lancet* 1990.; Coombs RC et al., *Archives of Disease in Childhood* 1990. Cifuentes RF, et al., *Journal of Pediatrics* 1979.

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Survey, 87 level- III NICUs from 17 countries



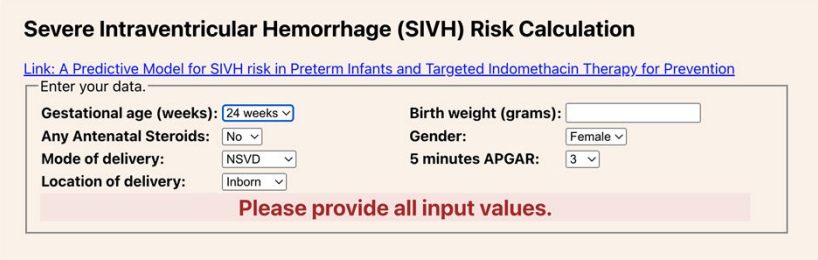
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non Published- NNCC-SIG survey

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Clinical practice guideline (CPG)

- January 2016, Brigham and Women's Hospital (BWH) has implemented a CPG for prophylactic indomethacin to reduce the rate of SIVH in extremely preterm infants
- BWH has utilized an online calculator to identify infants who are at high risk of severe IVH
- Those at a risk of >15%, receive indomethacin



Singh, R., et al., Sci Rep, 2013.
https://www.neoqicma.org/sivh

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Objectives

1. To compare the predicted rate and actual incidence of IVH utilizing the online risk calculator
2. To evaluate the association between the use of prophylactic indomethacin and the occurrence of SIVH

We hypothesized that the implementation of the indomethacin CPG would be associated with reduction of severe IVH.

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Retrospective cohort study BWH-NICU (2010-2021)

Extremely preterm infants
(23- 28 weeks of gestation)

- **Pre-group**
  Before indomethacin
  Jan 2010-Dec 2015
- **Post-group**
  After indomethacin
  Jan 2016-Dec 2021

- **Data collection**: demographics, clinical data, rate of IVH, **the use of indomethacin for any reason** from Vermont Oxford Network (VON) Registry.
- **Statistical Methods:** Mann Whitney U, T-tests, Chi-square test. Multivariate logistic regression to evaluate the association between SIVH and indomethacin.

Risk categories

Low risk	Moderate risk	High risk
<15%	≥ 15% to <25%	≥25%

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Demographics and clinical data

	Total cohort, n= 749		
	Pre-group n = 424	Post group n = 325	p-values
Gestational age (week)	26 (± 2)	26 (± 2)	0.768
Birth weight (g)	885 (± 276)	877 (± 254)	0.704
Male, n (%)	213/424 (50%)	167/325 (51%)	0.768
Inborn, n (%)	417/424 (98%)	312/325 (96%)	0.066
Antenatal Steroids, n (%)	370/423 (88%)	306/325 (94%)	**0.002**
Apgar at 1 min, median [IQR]	5 [3; 7]	4 [2; 6]	**<0.001**
Apgar at 5 min, median [IQR]	7 [6; 8]	7 [5; 8]	**<0.001**
Chest compressions during IR, n (%)	18/421 (4%)	24 /325 (7%)	0.078
ET tube ventilation during IR, n (%)	322/398 (81%)	236/260 (91%)	**0.001**
Surfactant, n (%)	370/424 (87%)	287/325 (88%)	0.736
Indomethacin for any reason, n (%)	172/390 (44%)	119/192 (62%)	**<0.001**

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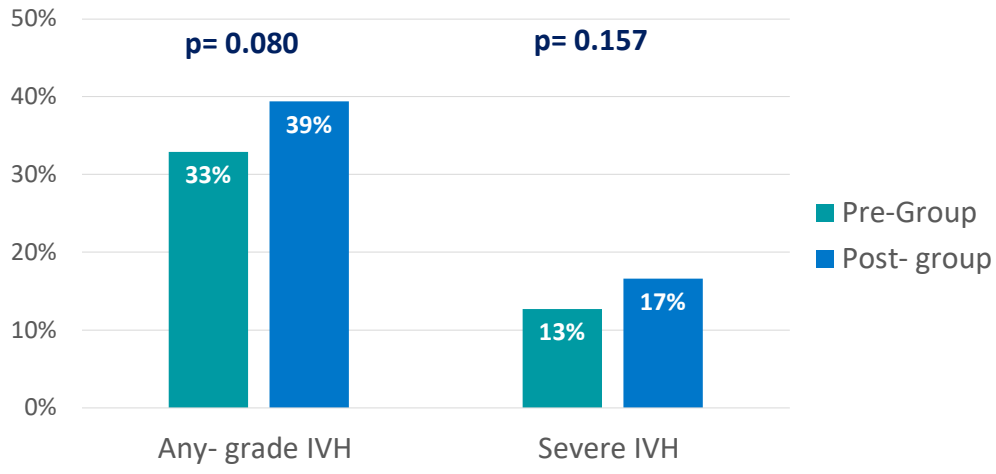
Short term outcomes and mortality

	Pre-group n = 424	Post group n = 325	p-values
Bacterial sepsis and/ or meningitis ≤ day 3	11/411 (3%)	5/318 (2%)	0.446
PDA, n (%)	239/414 (58%)	155/319 (49%)	**0.017**
NEC, n (%)	20/413 (5%)	28/319 (9%)	**0.036**
GI perforation, n (%)	10/414 (2%)	12/319 (4%)	0.383
Surgery for suspected NEC or bowel perforation, n (%)	7/413 (2%)	19/319 (6%)	**0.002**
Mortality rates			
Death in delivery room, n (%)	10/372 (3%)	6/129 (5%)	0.260
Death any time, n (%)	50/424 (12%)	64/ 325(20%)	**0.004**

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Rate of any- grade IVH and severe IVH

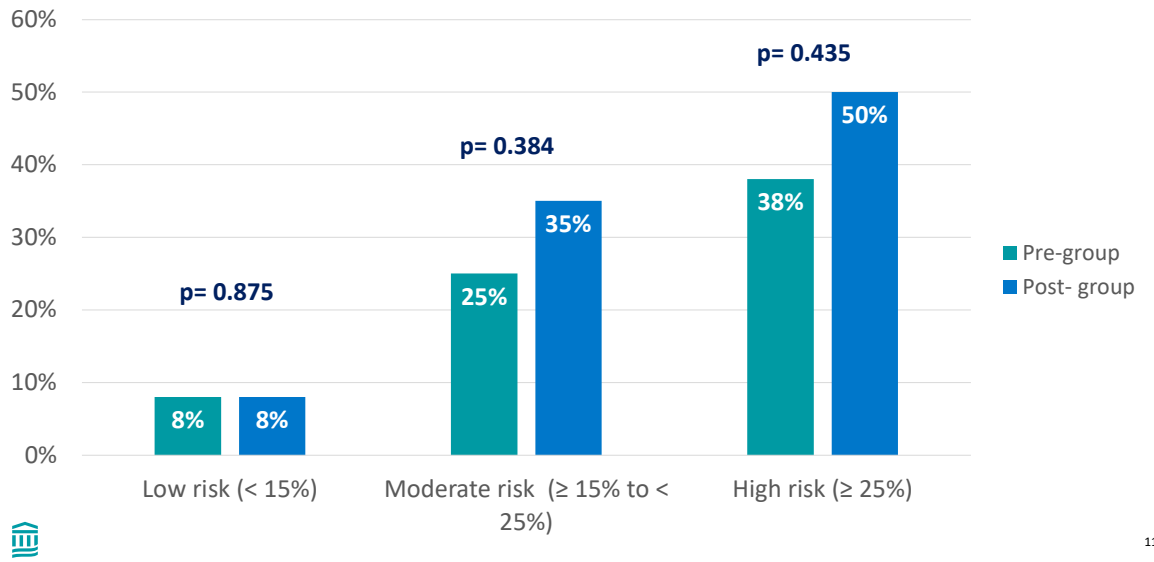


- 52 infants do not have IVH data

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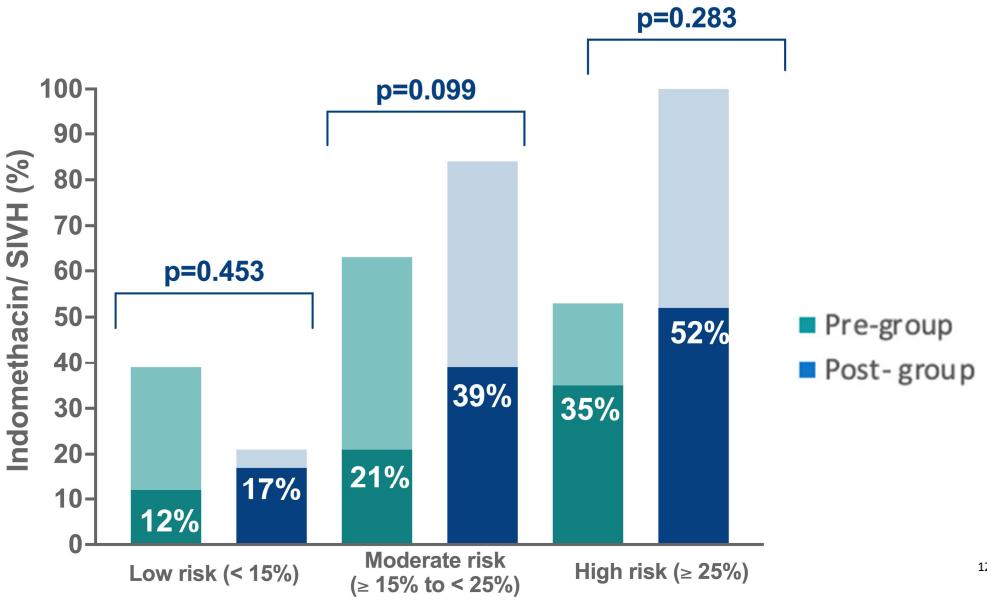
Rate of infants with SIVH within each risk category



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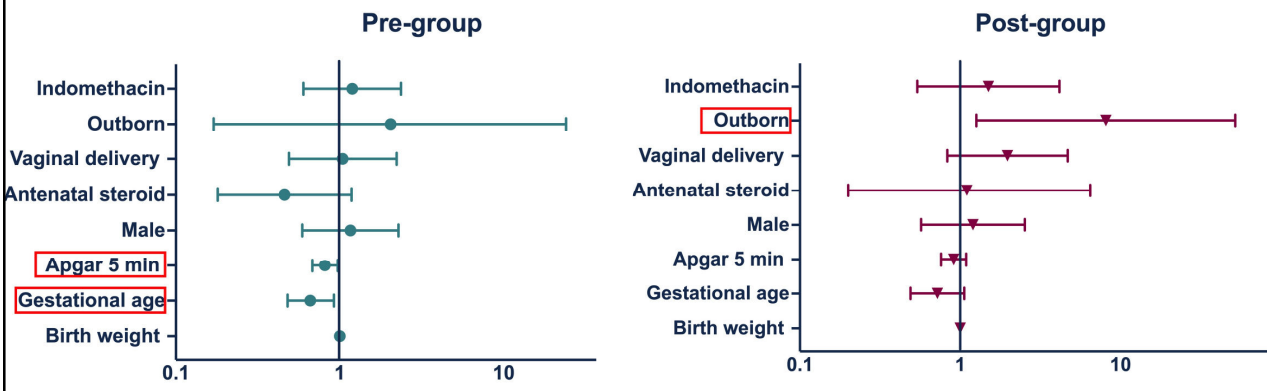
Rate of infants with SIVH out of those who received indomethacin



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Association between SIVH and the use of indomethacin



Indomethacin: aOR 1.2 (95% CI 0.6-2.4), p=0.624

aOR 1.5 (95% CI 0.5-4.2), p=0.238

- Covariates were based on the online IVH calculator utilized by BWH.
- There was no association between the use of indomethacin and development of SIVH

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Conclusions

- **The implementation of CPG for prophylactic indomethacin** in extremely preterm infants **was not associated with reduction in the incidence of severe IVH**.
- **No association was found between indomethacin and development of SIVH.**
- In presence of potential significant side effects, routine use of prophylactic indomethacin might not be encouraged.

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Limitations and Strengths

LIMITATIONS

I. The use of **indomethacin for any reason** was collected- **the rate of administration was high in both groups**

II. Patients in post-group were possibly in more severe condition

III. Higher rate of NEC and bowel perforation in the post-group can be the consequence of more severe condition or indomethacin administration

IV. Data about renal failure were not collected

STRENGTHS

I. Large population

II. Risk calculation for individual patients

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Thank you for listening.

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