

# Modeling cerebral palsy in rabbits

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Psychology-BNS

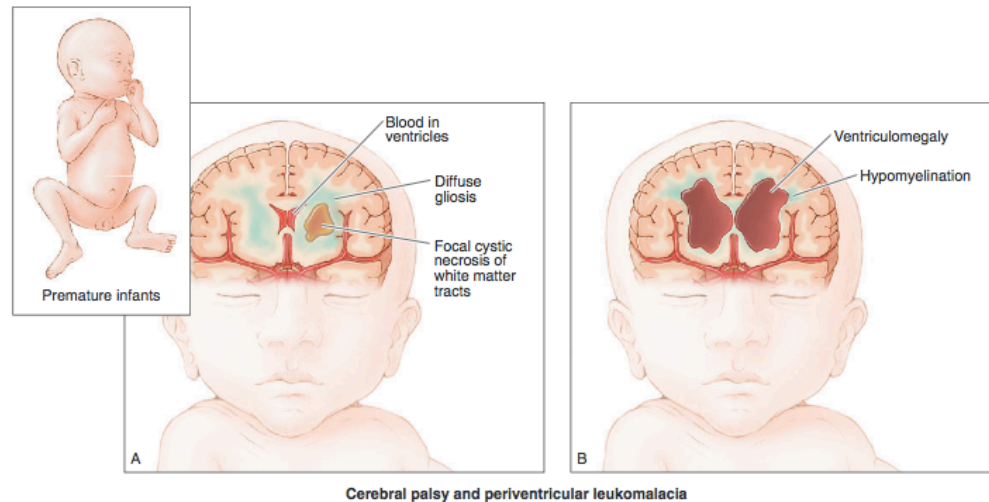
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# What is CP?

- Is a number of neurological disorders that appear in infancy or early childhood and permanently affect body movement and muscle coordination but don't worsen over time
  - Ataxia
  - Spasticity
  - Cognitive Impairments
- **Recent evidence suggest damage to the cerebral white matter is common cause of CP.**

# Rabbits as a superior model of WMI compared to rodents

- Development of spontaneous intraventricular hemorrhage with **ventriculomegaly** and **periventricular white matter loss**
- Only model that permits detailed clinicopathological correlations with neurobehavioral outcome and neuroradiological assessment



# **Human Umbilical Cord Blood Cells Ameliorate Motor Deficits in Rabbits in a Cerebral Palsy Model**

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# Human Umbilical Cord Blood Cells (HUCBC)

- Hematopoietic stem cells (CD34)
  - Under right conditions...
    - Neurons
    - Oligodendrocytes
    - Astrocytes

# Methodology

- Antenatal HI
  - In vivo global HI of fetuses was induced by sustained 40- min uterine ischemia at 22 days of gestation (70% term, embryonic day 22, E22)
    - Balloon catheter
      - left femoral artery, advancing into the descending aorta to above the uterine arteries of the dam



# Abbreviated Neurobehavioral Examination

- Locomotor functioning
- Muscle tone
- Based on the results groups were divided in two:
  - severe
  - mild

# Infusion of HUCBC

- IV injection via the external jugular or anterior abdominal vein after 4h after birth(P0)
  - Two phases:
    - High dose
      - 1.0 ml-volume containing one of the following:  $5 \times 10^6$  HUCBC cells, media or saline.
      - 1-2mins duration
    - Low dose
      - 1.0 ml-volume containing one of the following:  $2.5 \times 10^6$  HUCBC cells, media or saline.
      - 4 mins duration



# Detailed Neurobehavioral Examination

- Modified Ashworth scale
  - Tone
  - Posture
  - Locomotion
  - Righting
  - Dystonia
- Forced swimming test
  - Coordination between upper and lower joints

# MRI and PCR

- MRI
  - Whether HUCBC enters the newborn kit brain and can be detected
    - HUCBC cells were labeled with two compounds:
      - Gadofluorine (positive image contrast)
      - Feridex (negative image contrast)
- PCR
  - DNA was isolated from several rabbit kit brains at P18
  - The DNA was PCR amplified using primers derived from a portion of the human mitochondrial cytochrome b region, which shows no homology to other animal species

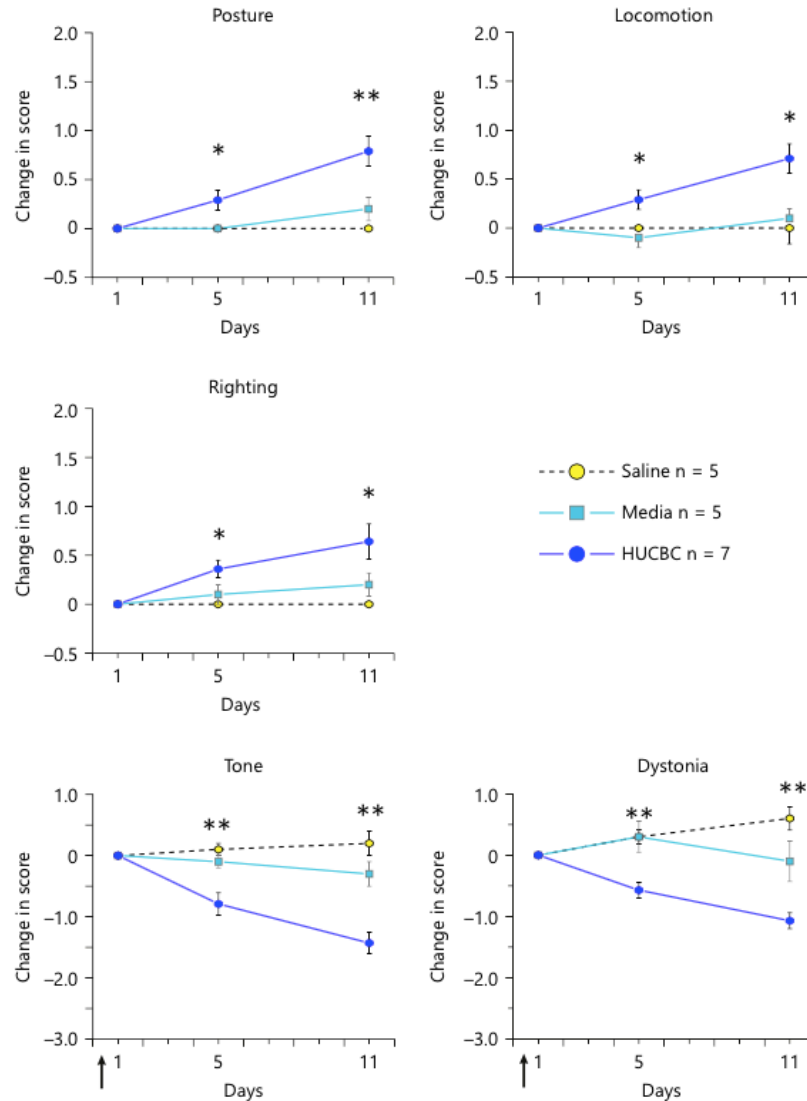
# Results

# Detailed neurobehavioral examination at P1

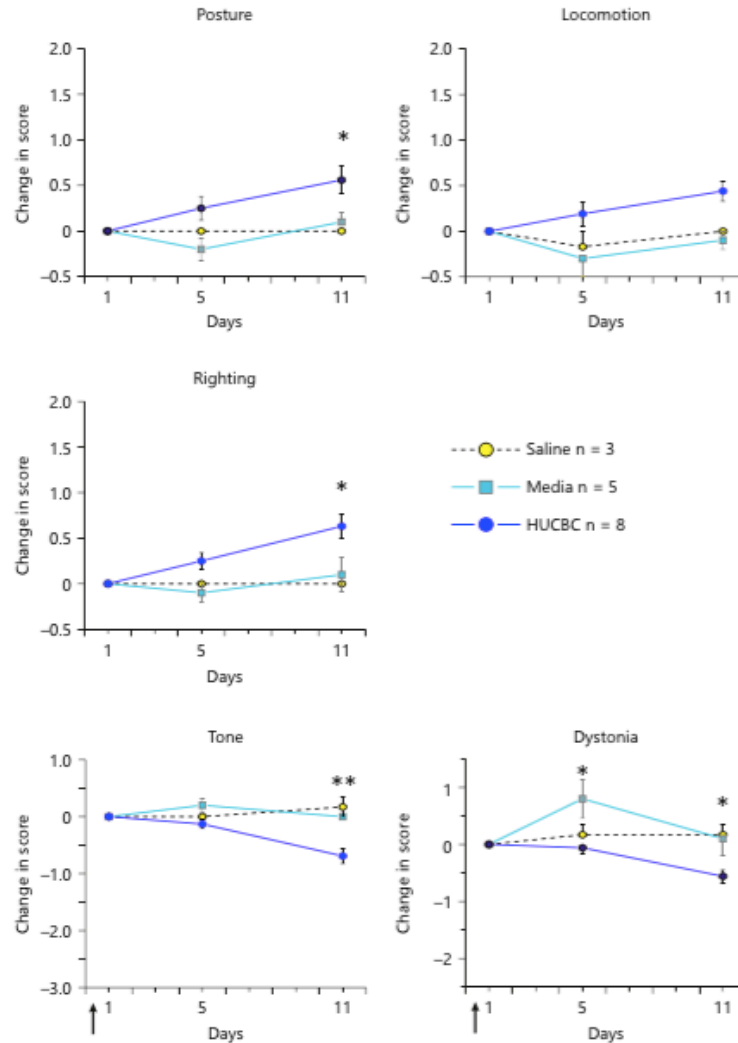
	Severe P1			Mild P1		
	saline (n = 5)	media (n = 5)	HUCBC (n = 7)	saline (n = 3)	media (n = 5)	HUCBC (n = 8)
Posture	1.4±0.2	1.7±0.2	1.5±0.1	2.5±0.0	2.6±0.1	2.4±0.1
Righting	1.4±0.2	1.7±0.2	1.6±0.1	2.5±0.0	2.6±0.1	2.3±0.1
Tone	3.5±0.4	2.8±0.5	3.4±0.3	1.0±0.0	0.8±0.1	0.9±0.1
Locomotion	1.2±0.4	1.7±0.2	1.6±0.2	2.5±0.0	2.5±0.0	2.3±0.1
Dystonia	1.8±0.3	1.9±0.4	2.3±0.1	1.5±0.3	0.9±0.2	0.9±0.1

**no significant difference in motor deficit scores  
between the treatment and control groups in  
either the severe or mild groups**

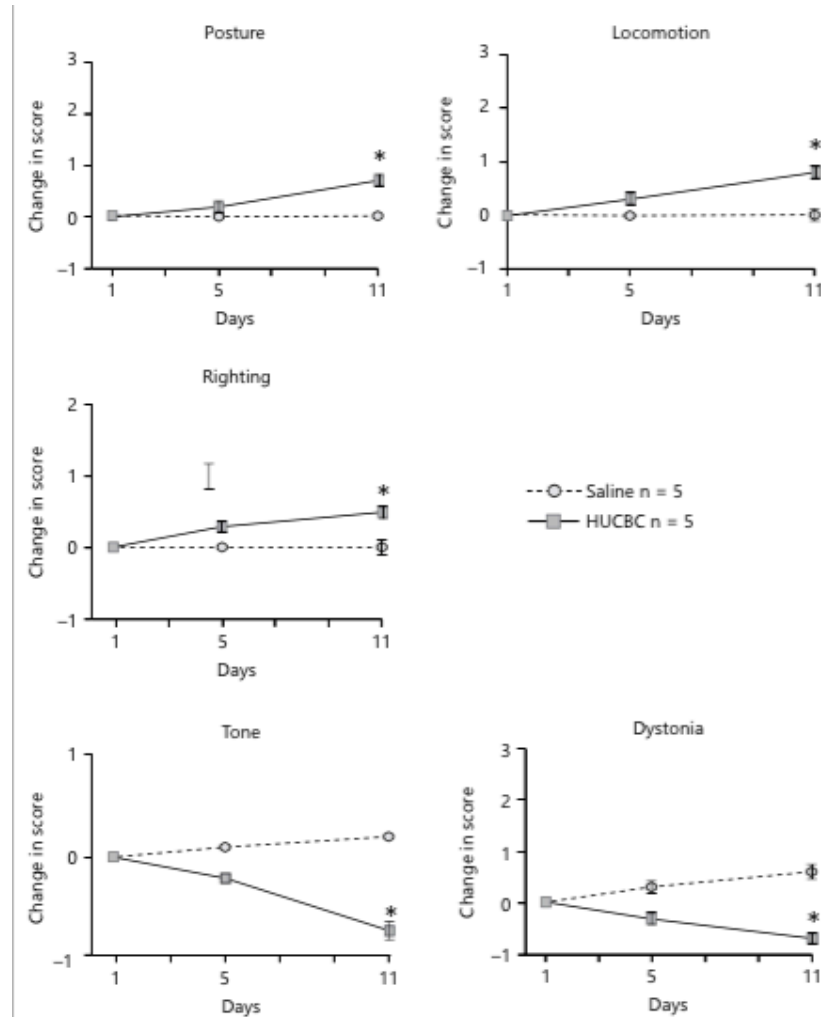
# High-Dose HUCBC Infusion in severe group (P5-P11)



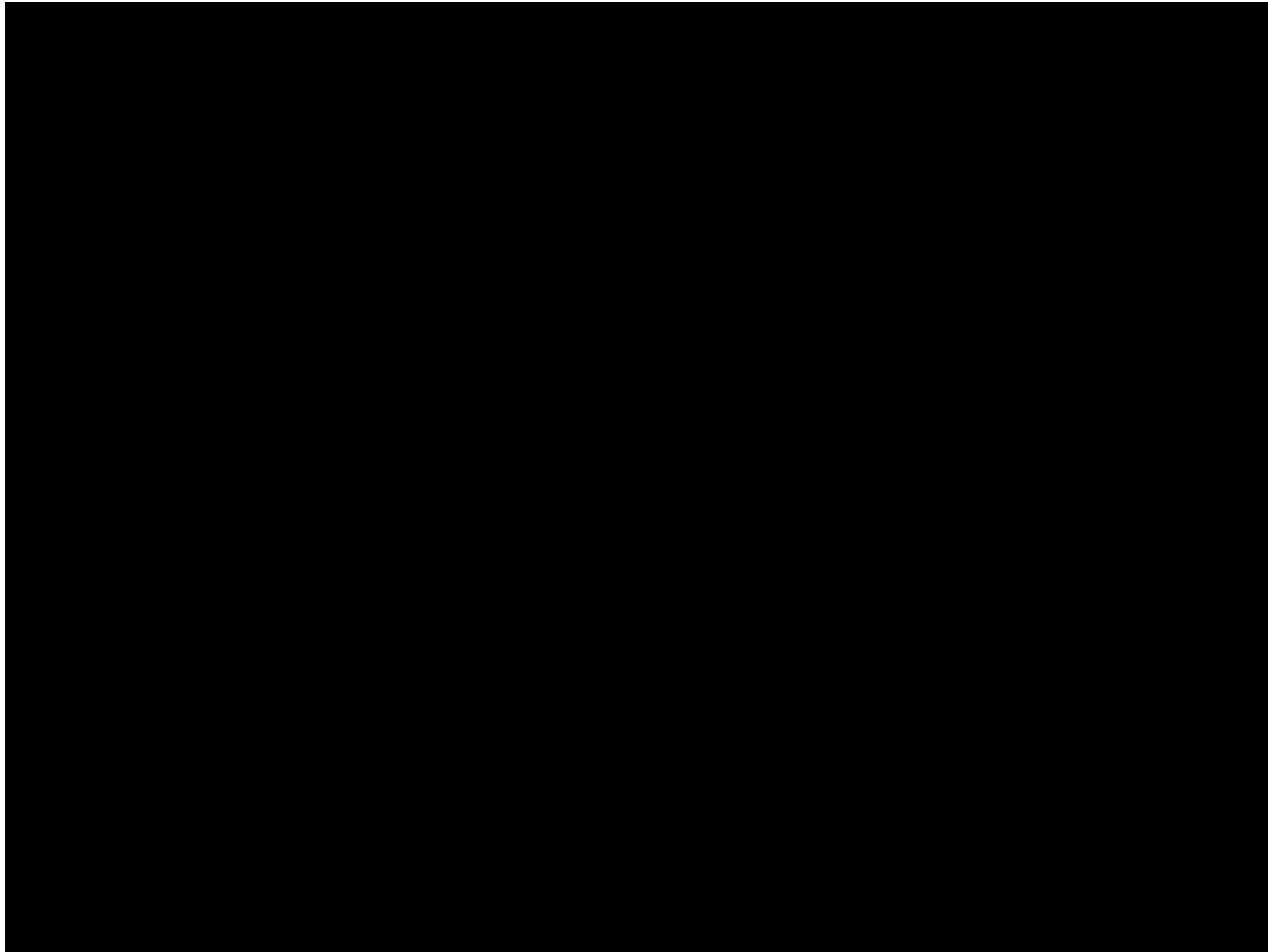
# High-Dose HUCBC Infusion in mild group (P5-P11)



# Lower-Dose HUCBC Infusion in severe group (P5-P11)

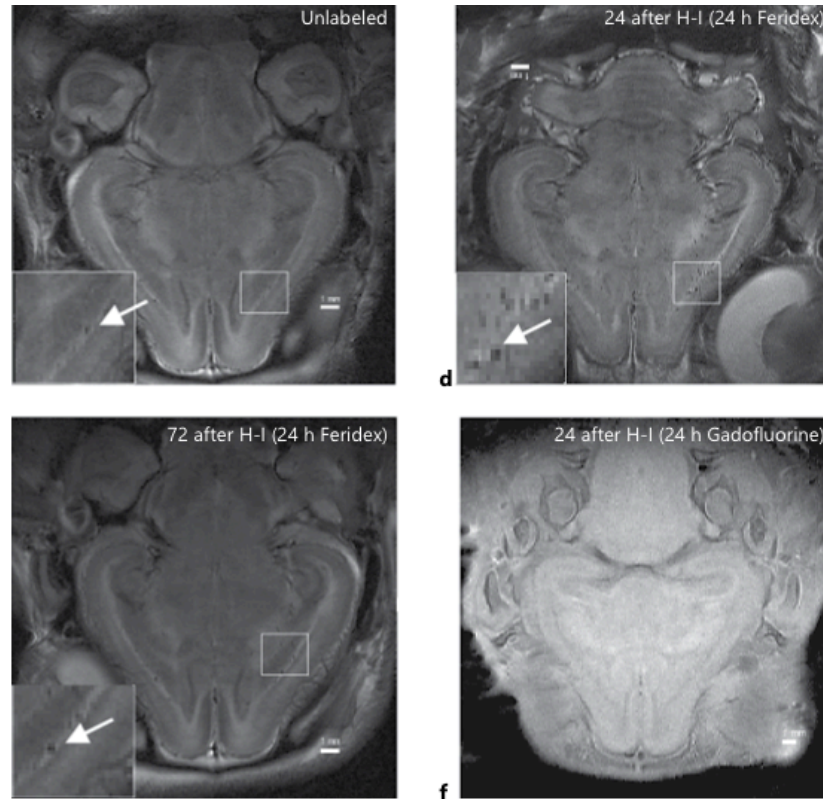


# Forced swim test (video)



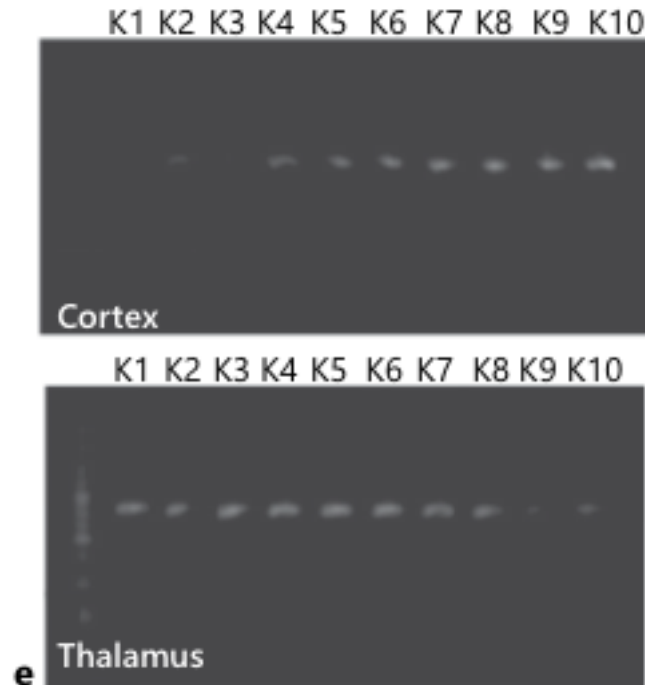


# MRI



**Absence of MRI Evidence that HUCBC enters the Newborn Brain**

# PCR



**10 brain samples; 8 cortex and 9 thalamus samples showed positive results for human DNA, with none for the saline group**

# Conclusions

- Improvement in scoring (eg. Tone, Posture, Dystonia) following HUCBC over the saline-treated group in both phases of the study
- Improvements in locomotion following HUCBC in the forced swim test
- Intravenous infusion of HUCBC may not necessarily lead to HUCBC entry into the brain tissue in appreciable numbers, since MRI demonstrated only cells in the vascular system and DNA studies showed only a very small number in the brain