



### R<sup>3</sup>: Research, Read & Review

*Literature dissemination by the NIDCAP and Science Sub-Committee*

**April 2022**

<b>Title</b>	Intranasal Breast Milk for Premature Infants with severe Intraventricular Hemorrhage – an observation.
<b>Reference</b>	Keller T, Körber F, Oberthuer A, Schafmeyer L, Mehler K, Kuhr K, Kribs A. European Journal of Pediatrics. 2019;178:199-206. <a href="https://doi.org/10.1007/s00431-018-3279-7">doi.org/10.1007/s00431-018-3279-7</a>
<b>What is known about this topic?</b>	<ul style="list-style-type: none"> <li>• This is the first report of intranasal breastmilk as a reparative treatment for preterm brain injury, referenced in the excellent review “Neuroscience meets Nurture”, (Soni R et al., Arch Dis in Child Fetal and Neonatal Ed - 2021;0:F1-F8. doi:10.1136/archdischild-2020-319450)</li> <li>• Intraventricular hemorrhage (IVH) and parenchymal brain injury are serious complications of prematurity with long term effects on the child’s neurodevelopment and behaviour. There are no effective preventive or reparative treatments for the injury to the developing brain.</li> <li>• Animal studies have shown that intranasal stem cell administration leads to regeneration of the somatosensory cortex and hippocampus, after hypoxic-ischemic injury in a mouse model. One study states that the source of the stem cells was ‘GIBCO Mouse C57BL/6’, so was probably not mouse-milk. (Donega V et al. in Experimental Neurology 2014; 261:53-64). There are other animal (but no human) studies of intranasal administration of neuroprotective factors and Mesenchymal Stromal Cells (MSC) in the literature.</li> <li>• A recent Cochrane Review titled ‘<i>Stem cell-based interventions for the prevention and treatment of Germinal Matrix-Intraventricular Hemorrhage in Preterm Infants</i>’ (Romantsik et al., 2019) states there is no evidence that stem cell therapies lead to either benefit or harm. The review included five phase-1 studies which used MSC from umbilical cord blood, not from breastmilk. MSC were</li> </ul>

	<p>administered by autologous cord blood transfusion in 3 studies, by intra-cerebral-ventricular injection in one study, and intra-tracheally in another study. The Cochrane Review mentions one phase-2 study of intracerebroventricular injection of MSC in progress, but no results are available yet.</p>
<b>What does this paper add?</b>	<ul style="list-style-type: none"> <li>- Breastmilk is a source of MSC and other neurotrophic factors.</li> <li>- MSC and neurotrophic factors administered intranasally reach the brain.</li> <li>- Intranasal breastmilk (INB) might repair the damage caused by severe IVH/parenchymal injury and can be tested as a potential treatment.</li> </ul>
<b>A summary</b>	<p>Short background: INB was used in this study as a compassionate treatment with parental consent. The authors based the potentially beneficial effect they expected on the case of one infant diagnosed with IVH grade II/III with intraparenchymal infarction. INB was suggested in that specific case as a means of increasing neurotrophins and stem cells in the brain. They state that INB was commonly used for nasal congestion in their unit and thus they had no safety concerns about its administration. They report that IVH in this infant resolved, and that the infant's neurologic exam at discharge was "good"; however, longer term outcomes are not reported.</p> <p>This is a retrospective study of preterm infants with severe IVH. The authors report the outcome of 16 infants with IVH grades III/IV, who received 0.1 ml of fresh breastmilk into each nostril between, 3-8 times per day, starting by 5 days of age and for at least 28 days. These infants were compared to 15 historical controls. Cerebral ultrasounds were read by a radiologist blinded to the intervention; the text implies that all ultrasounds (control and treated infants) were read again for this analysis.</p> <p>There was a trend towards a lower rate of progressive ventricular dilatation, fewer surgeries for posthemorrhagic hydrocephalus, and reduced incidence of severe white matter damage for the infants treated with INB (Table 2 in the actual paper). Numbers are small and thus differences were not statistically significant. The authors conclude that their hypothesis (resolution of severe IVH with INB) warrants testing.</p> <p>No long-term neurodevelopmental outcomes are reported; the authors report that this kind of follow up was not complete, and data were difficult to interpret given use of different developmental follow up tools.</p>

<p><b>What is the relevance to NIDCAP?</b></p>	<ul style="list-style-type: none"> <li>• The use of stem cells for treatment of IVH is a novel topic in neonatology. The intervention depicted in this study has some potential for becoming a possible future treatment. Although not yet studied in a randomised controlled trial (RCT), it is a simple intervention when compared, for example, to intracerebroventricular injection of stem cells. Fresh breastmilk is an easily available source of MSC. If ultimately proven, this could become a low cost, simple treatment to prevent long term impairments resulting from severe IVH.</li> <li>• One can envision that INB could be administered by parents, with professional and sensitive guidance. The infant could be held, while gentle social interaction could precede and follow the intranasal administration of breastmilk. The rate at which the milk is dripped into the nose could be guided by the infant's behaviour, aiming at maintaining organization of the infant's neurobehavioural subsystems. The colour photo included in this paper (best seen in the online version) depicts a tiny premature infant receiving INB and might stimulate further thoughts about NIDCAP-guided treatment and interaction.</li> <li>• As NIDCAP professionals, we should be aware that within the next decade, stem cell therapies might become a preventive treatment for bronchopulmonary dysplasia (BPD), even if it does not become a treatment for severe IVH. Further information on this topic can be found in the Cochrane Review mentioned above.</li> </ul>
<p><b>Questions suggested for reflection</b></p>	<ul style="list-style-type: none"> <li>- Is INB commonly used for <i>nasal congestion</i> in your NICU, as seems to be the practice at the NICU in which this study was performed?</li> <li>- Are you aware of this practice at other NICUs?</li> <li>- Would your NICU consider participating in a RCT of INB for infants with severe IVH?</li> </ul>