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CASE REPORT

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Intranasal breast milk for severe intraventricular hemorrhage in a preterm neonate: A case report

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Abstract: *Introduction:* Intraventricular haemorrhage is a serious complication predominantly affecting preterm neonates, particularly those with very low birth weight. Severe intraventricular haemorrhage is associated with high mortality and long-term neuro developmental impairment. While preventive measures such as antenatal steroids and delayed cord clamping exist, their application is often limited by the unpredictability of preterm birth. Emerging therapies such as intranasal breast milk administration offer promising neuroprotective potential in these infants

Case Presentation: We report a preterm male infant born at 25 weeks gestation age who required positive pressure ventilation at birth, surfactant and continuous positive airway pressure after birth for respiratory distress syndrome and antibiotics for presumed sepsis. The infant was found to have grade 1 intraventricular haemorrhage on day 2 of life that worsened to grades 2 and 3 by day 13 of life. Freshly expressed breast milk was given intranasal using syringe for 8 weeks. Subsequent cranial scan revealed complete resolution of intraventricular haemorrhage and normal neurodevelopmental assessment at 20 weeks corrected age

Conclusion: The resolution of intraventricular haemorrhage could have been multifactorial but intranasal administration of breast milk may have played a role in positive neuro-developmental outcomes in the infant following its complete resolution. Further studies of a controlled nature are warranted to confirm the therapeutic role of intranasal breast milk for intraventricular haemorrhage. This intervention could provide a safe, low cost and readily accessible therapeutic treatment option for preterm infants with intraventricular haemorrhage

Keywords: Preterm, Intraventricular haemorrhage, Intranasal breast milk, Resolution of intraventricular haemorrhage, Positive neurological outcomes

Résumé: *Introduction:* L'hémorragie intraventriculaire constitue une complication grave touchant principalement les nouveau-nés prématurés, en particulier ceux de très faible poids de naissance. Les formes sévères sont associées à une mortalité élevée et à un risque important de séquelles neurodéveloppementales à long terme. Bien que des mesures préventives telles que la corticothérapie anténatale et le clampage tardif du cordon ombilical soient disponibles, leur application reste limitée par le caractère imprévisible de la naissance prématurée.

Des approches thérapeutiques émergentes, telles que l'administration intranasale de lait maternel, présentent un potentiel neuroprotecteur prometteur chez ces nourrissons.

Observation: Nous rapportons le cas d'un nouveau-né de sexe masculin né à 25 semaines d'âge gestationnel, ayant nécessité une ventilation en pression positive à la naissance, l'administration de surfactant et une ventilation en pression positive continue (CPAP) pour un syndrome de détresse respiratoire, ainsi qu'une antibiothérapie probabiliste pour suspicion de sepsis.

Une hémorragie intraventriculaire de grade 1 a été diagnostiquée au deuxième jour de vie, avec aggravation aux grades 2 puis 3 au treizième jour de vie. Du lait maternel fraîchement exprimé a été administré par voie intranasale à l'aide d'une seringue pendant une durée de huit semaines.
L'échographie transfontanellaire ultérieure a montré une résolution complète de l'hémorragie intraventriculaire. L'évaluation neurodéveloppementale à 20 semaines d'âge corrigé était normale.
Conclusion: La résolution de l'hémorragie intraventriculaire est probablement multifactorielle. Toutefois, l'administration intranasale de lait maternel pourrait avoir contribué à l'évolution neurologique favorable observée après la disparition complète de l'hémorragie.
Des études contrôlées supplémentaires sont nécessaires afin de confirmer le rôle thérapeutique potentiel du lait maternel administré par voie intranasale dans la prise en charge de l'hémorragie intraventriculaire. Cette intervention pourrait représenter une option thérapeutique sûre, peu coûteuse et facilement accessible pour les prématurés atteints d'hémorragie intraventriculaire.

Mots-clés: Prématuré ; Hémorragie intraventriculaire ; Lait maternel intranasal ; Résolution de l'hémorragie intraventriculaire ; Évolution neurologique favorable.

Introduction

Intraventricular Haemorrhage (IVH) is a devastating complication that preterm neonates may encounter. It occurs in 10–20% of preterm infants and severe IVH (grades 3 and 4)occur in 35–45% of neonates born with birth weight of < 750 grams[1]. Besides gestational age and birth weight, other risk factors for IVH include hemodynamically significant patent ductus arteriosus (HsPDA), 5-minute Apgar score ≤ 5, prolonged intubation, use of vasoactive drugs and sepsis[2,3,4].

Bleeding into the ventricles may cause obstruction to cerebrospinal fluid (CSF) flow while bleeding in the periventricular area may cause ischemia, oedema and liquefaction with cystic formation (Periventricular Leukomalacia (PVL))[5]. Additionally, free haemoglobin in the brain vicinity is speculated to cause brain injury through activating cytotoxic, oxidative, and inflammatory pathways[5]. Severe grades of IVH are associated with mortality or life-long morbidity among survivors[1].
Despite several measures undertaken to minimize IVH including antenatal corticosteroids, delayed cord clamping and gentle ventilation; some preterm neonates miss these opportune measures due to the unpredictable nature of preterm delivery, hence the need for further research into alternative neuroprotective tools beyond these.

There is growing interest in the neuro-therapeutic potential of intranasal human breast milk for preterm brain injury with the transfer of neurotropic factors and stem cells derived from human breast milk being postulated as the potential mechanism[6]. Nasal vascularity and the permeability of neonatal blood-brain barrier potentially allow stem cells to be delivered to the brain tissue following intranasal administration[6].
Following a study on mice demonstrating the potential to minimize brain injury with intranasal administration of epidermal growth factor[7], a retrospective study in preterm human neonates with IVH revealed that intranasal breast milk lowered the incidence of severe porencephalic defects, ventricular dilatation and surgery for post-haemorrhagic hydrocephalus. This study hypothesized that intranasal application of breast milk could have beneficial effects on neurodevelopment in preterm infants following IVH[8].

Additionally, erythropoiesis stimulating agents have also been used in preterm infants with IVH and has shown to reduce the risk of severe IVH[10] and poor outcomes such as death and neurological disability[9]. These agents are thought to exert their neuroprotective effects by reducing inflammation, oxidative stress and apoptosis and by promoting the regeneration of neuronal stem cells and blood vessels[9].
We report a case of a preterm infant with severe IVH whom we gave intranasal breast milk which may have contributed to complete resolution of IVH with good neurological outcomes.

Case report

Apreterm infant was referred to our facility with recurrent apnoea at 12 days of age. He was conceived via in vitro fertilization (IVF) and delivered at 25 weeks of gestation by emergency caesarean section due to severe oligohydramnios following pre-labour rupture of membranes. He had APGAR scores of 2, 5, and 6 at the 1st, 5th and 10th minutes respectively; requiring positive pressure ventilation and he weighed 750 grams.
He received 4mls of surfactant, continuous positive airway pressure (CPAP) and caffeine for respiratory distress syndrome and was initiated on antibiotics for presumed sepsis. He was initiated on expressed breast milk and reached full enteral feeds by day 7 of life. Cranial scan done at day 2 of life showed grade 1 IVH.
On day 11 of life, he developed apnoea and a complete blood count showed low haemoglobin for which he was transfused with packed red blood cells (20mls/kg). The apnoea settled only to increase in frequency on the subsequent day after which he was transferred to our hospital.

On arrival at the emergency department; he was alert, having mild lower chest wall in- drawing, capillary refill<2 seconds, heart rate-158beats/min, respiratory rate-45breaths/min, SPO2-98% on CPAP with Fio2 50%, Positive end expiratory pressure (PEEP) 5 and Positive inspiratory pressure (PIP)6, body temperature-36.2C, weight-710grams and random blood glucose-7.7mmol/L.

Arterial blood gas was done which showed pH-7.437 (reference values 7.31-7.41), PCO2-41.6mmHg (reference values 41-51mmHg), PO2-66mmHg (reference values 80-105mmHg), HCO3-28.1mmol/L (reference values 23-28mmol/L) suggesting a normal result.

Laboratory investigations showed an elevated white cell count of 38.77*10^9/L (reference values 7.5-22*10^9/L), with predominance of neutrophil absolute count of 27.69*10^9/L (reference values 1.8-12.4/L), haemoglobin of -10.9g/dL (reference values 10.8-18.5g/dL), platelet count of 510*10^9/L (reference values 110-543*10^9/L), C-reactive protein of 0.53mg/L (reference values 0.5-5mg/L).

Cefotaxime (50mg/kg every 8 hours) and Amikacin (15mg/kg daily) were given in view of probable sepsis prior to which a blood culture sample was drawn which subsequently showed no bacterial growth. The infant continued with caffeine citrate and expressed breast milk given via feeding tube.

Given the clinical presentation, worsening of IVH was suspected and on the next day (13th day of life), a cranial scan was done that showed bilateral IVH, grade 2 on the right and grade 3on the left side with mild dilatation of the lateral ventricle as shown in figure 1. Echocardiography was also done and ruled out presence of a significant patent ductus arteriosus.

A subsequent cranial scan done after one week at day 19 of life, showed bilateral persistent IVH with cystic changes as seen in figure 2 and he was initiated on freshly expressed breast milk 0.1mls instilled in each nostril every 8 hours using syringe for a period of 8 weeks after discussion and obtaining consent from the parents.

Additionally, subcutaneous darbepoietin 10ug/kg thrice a week for 2 weeks was started on the 28th day of life because of recurrent anaemia requiring frequent blood transfusions (four times). Repeat cranial scan on this day showed no changes from previous study.

On day 48 of life, the infant was screened for retinopathy of prematurity (ROP) which was negative and cranial scan revealed same findings as previous study. On day 68 of life, repeat screening for ROP was negative and the infant was discharged with minimal support of oxygen and a weight of 1.8 kg.

On follow-up clinic on day 90 of life, cranial ultrasound showed resolution of IVH as shown in figure 3. Since he was a high risk infant, neuromotor assessment was also done by developmental specialist at corrected age of 20 weeks with normal neuromotor findings in the infant as below:

Gross Motor findings: Symmetrical lie when supine, prone elbow support, pulls to sit-no head lag - corresponds to age of 4-6months

Fine Motor findings: Follows through 180, four part sequence- reach, grasp, retrieve to mouth, crumples paper - corresponds to age of 5-7months

Communication skills: Coos and chuckles, initiates vocalization, giggles and laughs –corresponds to age of 4-6months

Social skills: Obvious pleasure at being handled, tries to hold bottle, friendly towards strangers –corresponds to age of 4-6months

Fig 1: : Cranial ultrasound done on 13th day of life showing right grade II (blue arrow) and left grade III (white arrow) germinal matrix haemorrhages

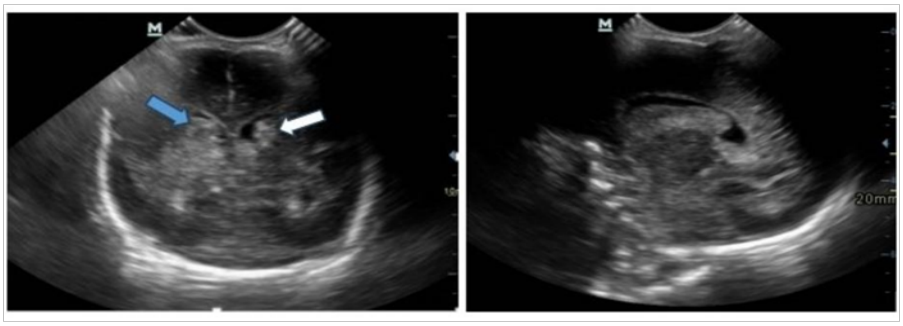

Fig 2: Cranial ultrasound done on 19th day of life showing bilateral persistent Intraventricular Haemorrhage with periventricular cystic changes (white arrows)

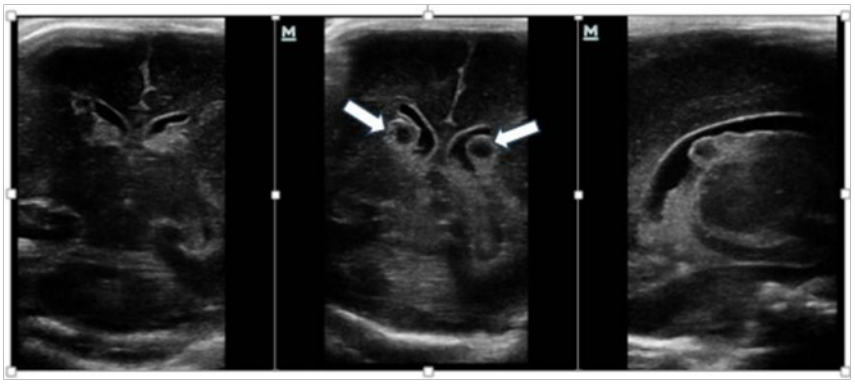

Fig 3: Cranial ultrasound showing complete resolution of the germinal matrix haemorrhages on both sides

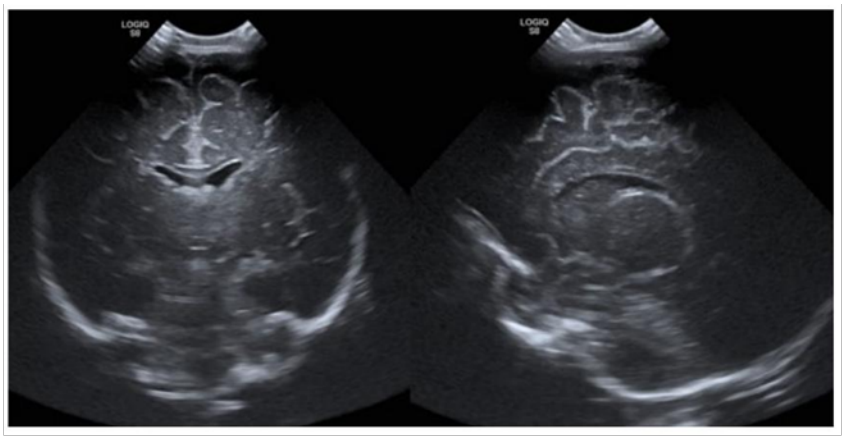

Fig 4: Showing timeline of events

Discussion

The infant in this case report developed significant IVH; he had multiple risk factors including extreme prematurity, low APGAR score at birth and needed positive pressure ventilation, all of which placed him at high risk for IVH, consistent with what is described in literature[2,3,4].
Our infant was at risk for developing post haemorrhagic hydrocephalus secondary to grade 3 IVH that he had sustained. From literature, his risk was as high as 50%, he was also at risk for cerebral palsy as high as 60% with most cases presenting early[1].

Intranasal breast milk was initiated to our infant at day of life 19 in view of IVH. In literature, two studies supported some benefit from intranasal administration of breast milk for intraventricular haemorrhage in preterm neonates[8,10]. In both studies, 0.1mls of fresh breast milk was instilled into each nostril 4-8 times a day and initiated within the first week of life.
In our study similar dose was used but was started after the first week of life. However, there is no data available on the effectiveness of late initiation of intranasal breast milk and the therapeutic window for optimal effects of intranasal breast milk on IVH is not known.
Additionally, studies have shown early administration of erythropoietin within 72 hours of diagnosis of IVH reduced its severity and improved neurological outcomes in preterm infants with IVH[9,10].

Our infant received darbepoiet in which is a long acting erythropoiesis stimulating agent at a dose of 10ug/kg thrice weekly for 3 weeks for repeated transfusion needs. However, it was started after 7 days of life. There is no data supporting initiation of erythropoiesis stimulating agents after 7 days of life for improved neurological outcomes in preterm infants with IVH. Hence, its role in the outcome of our patient is not known.
Spontaneous resolution of IVH has been described in literature[12], It is therefore plausible that the complete resolution of IVH in our patient could have happened even in the absence of our interventions.

However, intranasal administration of breast milk may have contributed positively to our infant's neurodevelopmental outcomes after the resolution of IVH, given its potential in regeneration of brain tissue, reducing inflammation and stimulating growth of new cells like oligodendrocytes[6].
This is consistent with the normal neuromotor assessment of the infant observed at 20 weeks corrected age and can further be supported from a recent experimental animal study showing that intranasal administration of colostrum could ameliorate PVL like injury in neonatal pups[13].

Conclusion

The resolution of IVH could have been multifactorial but intranasal breast milk administration may have contributed to positive neurodevelopmental outcomes after complete resolution of IVH; however, we cannot infer causality from a single case report. Further studies of a controlled nature are warranted to confirm the therapeutic role of intranasal breast milk for IVH. This intervention could provide a safe, low cost and readily accessible therapeutic treatment option for preterm infants with intraventricular haemorrhage.
Ethics approval and consent to participate: This retrospective review of patient data did not require ethical approval by the local guidelines of the Aga Khan University, Ethical Review Committee, East Africa (AKU-ERC, EA).

Informed consent for publication: Written informed consent was obtained from the parent of the infant for publication of this case report and the accompanying radiological images. A copy of the written consent is available for review by the corresponding author.

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