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Bai-Horng Su, Kang-Hsi Wu, Hsiang-Yu Lin, Ming-Hsia Lin, Ching-Tien Peng, Chris Tsai, (Dr. Su and Dr. Wu are contributed equally to this work) (21 January 2011)

Umbilical Cord-derived Mesenchymal Stem Cells for Severe Bronchpulmonary Dysplasia

21 January 2011

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Popova et al presented a study on the tracheal aspirates from 84 premature infants requiring mechanical ventilation for respiratory distress and concluded that isolation of lung mesenchymal stem cells (MSCs) within the first week of life predicts the development of bronchpulmonary dysplasia (BPD) [1]. Their results revealed that MSC isolation negatively correlated with gestational age at birth. There was also a significant positive correlation between postnatal age and MSC yield. The history of maternal chorioamnionitis was

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higher in the MSC group. Their findings possibly implied that the more immature lung and the longer duration of the lung disease was, the more likely the MSC isolation yield within the first week of life.

In the animal model studies, the depletion of putative distal lung progenitor cells in the developing lung is associated with arrested lung development [2,3]. Resident MSCs migrate preferentially toward injured lung, suggesting that MSCs contribute to attenuate lung injury. However, after prolonged hyperoxia the circulating and lung resident MSC population was reduced. The possible interpretation is that chronic hyperoxia overwhelms the repair capacity of the developing lung, causing a depletion of resident progenitor cells that results in the irreversible arrest of alveolar development [4], features described in experimental BPD models [5] and in humans [6,7].

Collectively, the findings of Popova et al may reflect the early manifestation of the MSCs migration toward injured lung. These MSCs finally were depleted by prolonged hyperoxia and/or inflammation that resulted in the alveolar growth arrest, a characteristic feature described in experimental BPD. These findings formed the rationale for exogenous MSC administration to prevent BPD.

Recent studies reported that intratracheal delivery of bone marrow- derived mesenchymal stem cells (bmMSCs) [4] or umbilical cord blood- derived MSCs (cbMSCs) [8] prevent alveolar growth arrest in experimental BPD. Umbilical cord-derived MSCs (ucMSCs) have been found easier to acquire [9]. We present our findings from intratracheal instillation of ucMSCs as a rescue treatment for severe BPD in an extremely preterm infant for whom conventional therapies had failed.

The infant's mother was transferred to China Medical University Hospital because of rupture of membrane for 4 days and failure in tocolysis. The mother had received 2 doses of betamethason and antibiotics. A female infant was born at 24 gestational weeks with birth weight 800 g via vaginal delivery, the Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. She received nasal continuous positive airway pressure with 5 cmH2O and FiO2 0.25 immediately after birth, and initial chest X-ray revealed no respiratory distress syndrome. However, she developed respiratory distress and became worse by day 2 and chest X-ray revealed diffuse linear-reticular infiltration. She was intubated and received intermittent mechanical ventilation. A patent ductus arteriosus was closed by 3 doses of oral ibuprofen within 88 hours after birth. At the age of 100 days, she still depended on IMV and required a very high setting to maintain SpO2 at around 80%. Her oxygenation index was always >40. She did not receive surfactant or glucocorticoids at all. Therefore, we decided to propose the protocol of ucMSC treatment to the institutional review board (IRB) of the hospital. The IRB approval was acquired after many disputes and finally the MSC treatment was applied at age of 168

days after parental written informed consent.

All procedures for ucMSC processing complied with good manufacturing practices (GMPs) requirements and the ucMSCs are clinical grade [10,11]. The MSCs suspension in 6 ml (3x 10^6 cells per kg of the patient's weight) were divided into 4 aliquots for 4 positions as the way of giving surfactant at age of 168 days and weighed 2680 g. Bronchoalveolar lavages (BAL) were performed before and after the MSC treatment. The concentrations of proinflammatory cytokines including interleukin-6 (IL-6), IL-8, and tumor necrosis factor (TNF)-alpha were measured using commercial enzyme- linked immunosorbent assay (ELISA) kits from Research and Diagnostic Systems (Minneapolis, MN, USA). Echocardiographic assessment of pulmonary arterial pressure (PAP) was performed as our previous report [12] on the day BAL was performed. The time to peak velocity (TPV) and right ventricular ejection time (RVET) were measured and the heart rate-corrected TPV/RVET(c) is inversely related to PAP. The patient did not undergo treatment for pulmonary hypertension, such as sildenefil or prostacyclin, prior to MSC treatment. The mean values of oxygenation, mean airway pressure and oxygenation index were also recorded on the days when lavages were performed. The severity score of BPD on the chest radiographs was graded [13].

Dramatic reduction in FiO2 requirement, improvement of PaO2, fall in oxygenation index and significant improvement of PAP as evidenced by TPV/RVET(c) followed by extubation on day 7 after treatment is noted. The proinflammatory cytokine levels in lavage fluid reduced progressively by day 7 to less than one tenth of the level before treatment. The clinical improvement and reduced PAP were significantly related with the reduced proinflammatory cytokines levels. The severity score of BPD improved disproportionately less than the reduction in proinflammatory cytokine levels initially, but much improved by 60 days after treatment. The patient is breathing room air 73 days after MSC treatment, and now is well 7 months after treatment.

Inflammation may predispose the premature newborn to pulmonary hypertension [14]. Previous animal studies have shown that intratracheal administration of MSCs ameliorated pulmonary hypertension [15]. We have demonstrated clinically that intratracheal MSC are capable of reducing PAP as evidenced by echocardiography in this patient. The dramatic clinical improvement and the disproportionately less initial improvement in the x- ray implicate that the initial beneficial effects of ucMSC treatment might be mediated mainly by its anti-inflammatory effects. We assume that the improvement of chest x-ray 60 days after treatment is due to the late effect of ucMSC treatment.

In summary, the overall effects attributed to MSC treatment in this patient could be potentially derived from the reduced pulmonary inflammation and hence the reduced pulmonary hypertension. The draw back is

the uncertainty when darwing conclusions from a single case. However, this satisfactory initial outcome shows the feasibility and potential of intratracheal instillation of ucMSCs as a rescue treatment for severe BPD in extremely preterm infants. More patients and experience should be accumulated and restricted to rescue treatment for severe BPD until we have much improved understanding on the role of MSC and their long-term safety.

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hypertension and endothelial dysfunction. Am J Physiol Heart Circ Physiol. 2007;292(2):H1120-1128.

Conflict of Interest:

None declared