

# Effect of mesenchymal stem cell treatment on retinopathy of prematurity in patients with bronchopulmonary dysplasia: experience of a tertiary center

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## ABSTRACT

**Background.** Retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) share overlapping mechanisms involving oxidative stress, inflammation, and aberrant angiogenesis. Mesenchymal stem cell (MSC) therapy has shown promise in the treatment of BPD through paracrine modulation and anti-inflammatory effects, but its influence on retinal vascular development remains uncertain.

**Case Presentation.** This retrospective case series included five extremely low birth weight (ELBW) infants (<1000 g) who received allogeneic umbilical cord-derived MSC therapy for severe BPD between October 2021 and May 2023. Each infant received intravenous ( $2 \times 10^6$  cells/kg) and intratracheal ( $1 \times 10^7$  cells/kg) MSC administration in a single session. ROP screening and treatment were conducted in accordance with national guidelines. Clinical data and ocular outcomes were analyzed descriptively.

**Conclusions.** The mean gestational age was  $26^{2/7}$  weeks (range,  $25$ – $28^{3/7}$ ) and the mean birth weight was 810 g (580–1060 g). MSC therapy was given between postnatal days 36–126 (mean, 74 days). No systemic or ocular complications occurred during hospitalization or follow-up. One infant had no ROP, one developed Type 2 ROP with spontaneous regression, and three developed Type 1 ROP requiring intravitreal bevacizumab. All treated cases achieved complete regression after a single intravitreal bevacizumab injection, without recurrence, repeat injection, or need for laser therapy. MSC therapy appeared clinically safe in ELBW infants with BPD, with no adverse ocular effects. However, ROP developed in most infants despite MSC treatment, suggesting that MSCs do not prevent disease onset. The potential modulatory role of MSCs on retinal angiogenesis warrants further investigation through larger, controlled trials.

**Key words:** bronchopulmonary dysplasia, mesenchymal stem cells, retinopathy of prematurity.

Retinopathy of prematurity (ROP) is a major cause of childhood blindness worldwide and remains a significant challenge among surviving preterm infants despite major advances in neonatal care. The global pooled prevalence of ROP has been reported as 31.9%, with severe ROP accounting for 7.5% (6.5–8.7%) over the past four decades.<sup>1</sup> Standard treatment options include laser photocoagulation and

intravitreal anti-vascular endothelial growth factor (VEGF) injections.<sup>2,3</sup> Bronchopulmonary dysplasia (BPD) and ROP share common pathogenic pathways, including inflammation, oxidative stress, and dysregulated neovascularization.<sup>4-8</sup> Both disorders involve aberrant vascular development in the retina and lungs. Although preventive agents such as glucocorticoids, vitamin A, and caffeine

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have demonstrated benefits in BPD, their long-term efficacy is limited, and adverse effects are considerable.<sup>9,10</sup> In recent years, mesenchymal stem cell (MSC) therapy has emerged as a promising intervention for neonatal diseases, including hypoxic-ischemic encephalopathy and BPD.<sup>11-13</sup> Evidence from preclinical and clinical studies suggests that the therapeutic benefits of MSCs are primarily mediated through paracrine signaling and exosome release, rather than direct engraftment.<sup>14-16</sup> MSC-derived secretomes contain bioactive molecules such as VEGF, insulin-like growth factor 1 (IGF-1), transforming growth factor beta (TGF- $\beta$ ), fibroblast growth factor (FGF), and interleukin-10, which together modulate angiogenesis, apoptosis, and inflammation.<sup>14</sup> Given these multifaceted effects, MSC therapy for BPD could theoretically influence retinal vascularization and ROP development either beneficially or adversely. However, no clinical data currently evaluate the ocular outcomes of MSC therapy in extremely low birth weight (ELBW) preterm infants.

Our study reports on the ROP course in five preterm infants who received MSC therapy for BPD and discusses whether MSC administration may affect ROP progression.

## Case Presentation

### Patient selection

Our study was approved by the Ondokuz Mayıs University local ethics committee (approval number B.30.2.ODM.0.20.08/407-549) and conducted in accordance with the Declaration of Helsinki. Clinical data were retrospectively reviewed. Informed consent for participation was obtained from the child's legal parent or guardian. Between October 2021 and May 2023, 52 of the 1,500 infants treated in the neonatal intensive care unit (3.47%) were diagnosed with BPD. BPD diagnosis was established according to the Jensen criteria.<sup>17</sup> Five preterm infants (9.6%) were treated with MSCs for BPD. Demographic and clinical

characteristics—including gestational age, birth weight, ventilation mode, fraction of inspired oxygen (FiO<sub>2</sub>), and postnatal support type were recorded.

### Clinical protocols

Standard BPD management in our unit included mechanical ventilation, systemic low-dose dexamethasone, and caffeine therapy (maintenance dose 5 mg/kg/day), which was initiated on the 28th postnatal day while the infants were still receiving ventilatory support. A second corticosteroid course was administered if extubation failed after the first course. ROP screening was performed by an experienced ophthalmologist according to the guidelines of the Turkish Neonatal Society and the Turkish Ophthalmology Association.<sup>18</sup> The first examination was performed by indirect ophthalmoscopy between 4 and 6 weeks after birth. The ophthalmologic findings determined examination intervals. All infants were re-examined before MSC transfer, and ROP treatment, if needed, was performed by a retina specialist using intravitreal bevacizumab (IVB) (0.25 mg/0.01 mL).

### MSC therapy protocol

Allogeneic umbilical cord tissue-derived MSCs were prepared in an accredited laboratory and delivered under sterile conditions. Each infant received MSCs intravenously ( $2 \times 10^6$  cells/kg) and intratracheally ( $1 \times 10^7$  cells/kg) during the same session. Infants were closely monitored for hemodynamic instability, desaturation, or other adverse events. Weekly laboratory evaluations continued until discharge and during follow-up visits to detect potential complications. After discharge, all infants were followed monthly at the neonatal outpatient clinic for at least six months. The retina specialist maintained ophthalmologic follow-ups.

The mean birth weight was 810 g (range, 580–1060 g), and the mean gestational age was 26<sup>2</sup>/<sub>7</sub> weeks (range, 25–28<sup>3</sup>/<sub>7</sub> weeks). MSC therapy was administered between postnatal

days 36 and 126 (mean, 74 days). Clinical characteristics are summarized in Table I. No systemic complications were observed during hospitalization or during the six-month post-discharge follow-up.

One infant received MSC therapy at 38 weeks postmenstrual age (PMA); retinal vascularization was in Zone 2 without any

ROP signs. No ROP developed, and complete vascularization was achieved at 68 weeks PMA.

Another infant received MSC therapy at 43 weeks PMA, with preexisting Zone 2 Type 2 ROP. ROP regressed spontaneously after MSC therapy, and complete vascularization occurred at 85 weeks PMA.

**Table I.** Clinical characteristics of infants receiving mesenchymal stem cell therapy.

Parameter	Infant I	Infant II	Infant III	Infant IV	Infant V
Antenatal condition	Preeclampsia	Preeclampsia	PPROM	Oligohydramnios	IVF triplet pregnancy
Gestational age (weeks)	26 <sup>0</sup> / <sub>7</sub>	25 <sup>0</sup> / <sub>7</sub>	26 <sup>4</sup> / <sub>7</sub>	25 <sup>1</sup> / <sub>7</sub>	28 <sup>3</sup> / <sub>7</sub>
Sex	Female	Male	Female	Female	Male
Birth weight (g)	750	740	920	580	1060
Delivery mode	Cesarean	Cesarean	Vaginal	Cesarean	Cesarean
Postnatal clinical data	RDS, LOS	RDS, LOS, Surgical PDA ligation	RDS, LOS, PDA, Grade II IVH	RDS, Surgical PDA ligation, Osteopenia of prematurity	RDS, LOS, Pneumothorax
Systemic corticosteroid therapy for BPD	2 courses	2 courses	2 courses	2 courses	2 courses
Postnatal day at MSC administration	69	126	36	90	49
Postmenstrual age at MSC administration (weeks)	31 <sup>2</sup> / <sub>7</sub>	43 <sup>0</sup> / <sub>7</sub>	32 <sup>0</sup> / <sub>7</sub>	38 <sup>0</sup> / <sub>7</sub>	35 <sup>4</sup> / <sub>7</sub>
Respiratory status at MSC transfer	Mechanical ventilation (PSV) (FiO <sub>2</sub> 45%)	Mechanical ventilation (PSV) (FiO <sub>2</sub> 45%)	Mechanical ventilation (PSV) (FiO <sub>2</sub> 45%)	High-frequency oscillation (HFO) (FiO <sub>2</sub> 50%)	Mechanical ventilation (PSV) (FiO <sub>2</sub> 45%)
Days from MSC transfer to extubation	25	3	13	47	25
Length of hospital stay (days)	145	190	81	185	118
Postmenstrual age at discharge (weeks)	46 <sup>3</sup> / <sub>7</sub>	52 <sup>0</sup> / <sub>7</sub>	38 <sup>0</sup> / <sub>7</sub>	51 <sup>4</sup> / <sub>7</sub>	54 <sup>0</sup> / <sub>7</sub>
Discharge weight (g)	3160	3800	2400	2990	2010
Respiratory support at home	CPAP for 21 days	CPAP	Low-flow oxygen	Low-flow oxygen	Low-flow oxygen
Time to discontinue supplemental oxygen (chronological age)	3.5 months	2 months	40 weeks	4 months	5 months

BPD: Bronchopulmonary Dysplasia, CPAP – Continuous Positive Airway Pressure, FiO<sub>2</sub> : fraction of inspired oxygen; HFO: High-Frequency Oscillation, IVH: Intraventricular Hemorrhage, IVF: In Vitro Fertilization, LOS: Late-Onset Sepsis, MSC: Mesenchymal Stem Cell, PDA: Patent Ductus Arteriosus;; PSV: Pressure support ventilation, RDS: Respiratory Distress Syndrome.

Three infants developed Type 1 ROP after MSC therapy. In these cases, retinal vascularization was in Zone 1 prior to MSC administration. A single IVB injection induced rapid regression of ROP without complications, repeat injections, or laser photocoagulation. During long-term follow-up, complete vascularization in Zone 3 was achieved in all cases. In summary, one infant showed no ROP, one had spontaneously regressed Type 2 ROP, and three developed Type 1 ROP that regressed after a single anti-VEGF treatment. The detailed course of ROP examinations is shown in Table II.

**Discussion**

In our case series, we investigated the progression of ROP in 10 eyes of five infants following MSC treatment BPD. The coexistence of BPD and ROP is well documented in many

studies, and this association is largely attributed to their overlapping risk profiles, as ELBW infants born at very early gestational ages are at the highest risk for both conditions.<sup>19-22</sup> Infants with BPD experience more hypoxemic/hyperoxemic episodes, longer oxygen exposure, and prolonged positive pressure ventilation (PPV) and continuous positive airway pressure (CPAP) use, all of which contribute to the development and severity of ROP. Prolonged PPV has been reported as an independent risk factor for ROP, and prolonged CPAP has been shown to predict severe or treatment-requiring disease.<sup>21,22</sup>

In our study, the average birth weight was 810 g and the gestational age was 26<sup>2</sup>/<sub>7</sub> weeks. Remarkably, two infants (40%) did not require ROP treatment, which may be interpreted as a favorable outcome given the high baseline risk of this population. Although MSC treatment

**Table II.** Course of retinopathy of prematurity (ROP) in infants receiving mesenchymal stem cell therapy.

Parameter	Infant I	Infant II	Infant III	Infant IV	Infant V
First ROP examination (PMA, weeks)	29 <sup>3</sup> / <sub>7</sub>	29 <sup>0</sup> / <sub>7</sub>	30 <sup>4</sup> / <sub>7</sub>	29 <sup>1</sup> / <sub>7</sub>	32 <sup>2</sup> / <sub>7</sub>
Initial findings (both eyes)	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I	Incomplete vascularization to Zone I
Maximum ROP stage (PMA, weeks)	36 <sup>3</sup> / <sub>7</sub>	41 <sup>0</sup> / <sub>7</sub>	35 <sup>5</sup> / <sub>7</sub>	–	37 <sup>3</sup> / <sub>7</sub>
Maximum stage (both eyes)	Aggressive posterior ROP (Type 1)	Stage 2, posterior Zone II (Type 2)	Stage 2, posterior Zone II (Type 1)	No ROP	Aggressive posterior ROP (Type 1)
Plus disease	Bilateral plus	Bilateral pre-plus	Bilateral plus	–	Bilateral plus
Bevacizumab treatment (PMA, weeks)	36 <sup>3</sup> / <sub>7</sub>	–	35 <sup>5</sup> / <sub>7</sub>	–	37 <sup>3</sup> / <sub>7</sub>
Outcome after Bevacizumab	Regression	–	Regression	–	Regression
Final ROP examination (PMA, weeks)	82	85	99	68	79
Final retinal status	Complete vascularization	Complete vascularization	Complete vascularization	Complete vascularization	Complete vascularization
PMA at MSC administration (weeks)	31 <sup>2</sup> / <sub>7</sub>	43 <sup>0</sup> / <sub>7</sub>	31 <sup>4</sup> / <sub>7</sub>	35 <sup>4</sup> / <sub>7</sub>	38 <sup>0</sup> / <sub>7</sub>

MSC – Mesenchymal Stem Cell, PMA – Postmenstrual Age, ROP – Retinopathy of Prematurity.

did not prevent ROP onset in all infants, it did not appear to exacerbate progression. As discussed in previous studies, the underlying pathophysiology of both BPD and ROP involves dysregulation of angiogenic factors such as VEGF, IGF-1, and TGF- $\beta$ .<sup>23,24</sup> The close relationship between angiogenic pathways in the developing lung and retina supports the hypothesis that interventions that affect pulmonary angiogenesis could simultaneously influence retinal vascular development. Initially, it was believed that MSCs repaired tissue by engrafting into damaged sites.<sup>14,15</sup> However, later studies demonstrated that their therapeutic benefit primarily derives from paracrine mechanisms, including immunomodulatory, anti-inflammatory, antibacterial, antioxidative, angiogenic, and regenerative effects.<sup>16</sup> MSCs have been successfully investigated in adult retinal degenerative diseases such as age-related macular degeneration, diabetic retinopathy, and glaucoma. Experimental studies further support their cytoprotective potential: Ezquer et al. showed that intravitreal MSCs created a cytoprotective microenvironment in diabetic mouse retina.<sup>16</sup> Noueihed et al. demonstrated that MSCs reduced vaso-oblivation by 75%, inhibited neovascularization, and migrated toward avascular zones in a mouse model of oxygen-induced retinopathy.<sup>15</sup> Similarly, Kim et al. reported that human placental amniotic membrane-derived MSCs secreted high levels of TGF- $\beta$ 1, suppressing endothelial proliferation and pathological neovascularization; importantly, injected MSCs were shown to migrate into the retina.<sup>14</sup>

Consistent with these findings, in the present study, four infants developed ROP, and three progressed to aggressive posterior ROP requiring treatment. One infant had Type 2 ROP that regressed spontaneously after MSC transfer, and one infant did not develop ROP at all. ROP regressed after a single IVB injection in all treated infants, and vascularization was completed without recurrence during follow-up. The rapid regression after anti-VEGF may indicate that the bioactive molecules

released by MSCs did not induce aberrant neovascularization and may even have contributed to stabilization of the retinal vasculature. Importantly, MSC administration did not elicit an inflammatory ocular response in any case.

When these results are compared with national and international data, our findings appear promising. In a meta-analysis by Ramaswamy et al., the incidence of ROP and ROP requiring treatment was 49% and 18%, respectively.<sup>25</sup> In a multicenter study from Türkiye, these rates were higher: 68% and 26%.<sup>19</sup> In two separate studies from our NICU, in 2013 and 2022, the incidence of ROP in infants  $\leq 1000$  g was 70.7% and 81%, respectively, and the incidence of ROP requiring treatment was 30.2% and 23.9%, respectively.<sup>20,26</sup> In our series, only two of five infants (40%) did not require ROP treatment despite ELBW and BPD. However, this rate does not appear to be lower than that reported in previous studies. Therefore, the potential contribution of MSC treatment to systemic stability and retinal outcomes should be carefully evaluated.

One critical consideration is the timing of MSC administration. Phase II trials recommend administering MSCs within 5–14 days to prevent early pulmonary injury.<sup>13</sup> However, legal requirements in Türkiye mandate that infants remain dependent on mechanical ventilation despite two courses of postnatal steroids before MSC eligibility. Additionally, parental hesitation and administrative approval processes delayed treatment. As a result, MSC infusion occurred at a median of 74 days (range 36–126). Infants who later required ROP treatment received MSCs earlier, likely reflecting worse initial lung maturity. It is possible that earlier MSC administration could have contributed to earlier lung stabilization and potentially mitigated ROP progression. Nonetheless, early intervention raises theoretical concerns, particularly because MSC-derived exosomes contain VEGF and IGF-1, which might exacerbate pathological retinal neovascularization similar

to the increased ROP risk observed with early recombinant erythropoietin therapy.<sup>27</sup> Therefore, determining the optimal timing of MSC administration remains a critical objective for future research.

Despite limitations-including small sample size, retrospective design, heterogeneous timing of MSC administration, and relatively short follow-up—our study provides one of the earliest clinical descriptions of retinal outcomes following systemic MSC therapy in ELBW infants. The absence of ocular or systemic adverse events suggests that MSC administration is clinically safe, but its protective or therapeutic effect on ROP remains uncertain.

Previous studies indicate that MSC therapy can lessen the severity of BPD in very low birth weight infants, yet its effect on ROP remains unclear. These findings raise the possibility that MSCs might influence ROP risk or contribute to a more favorable disease trajectory. However, larger studies are required to understand better whether the timing of MSC administration—early or delayed—has any meaningful impact on ROP development or severity.

### Ethical approval

The study was approved by Clinical Research Ethics Committee of the Ondokuz Mayıs University (date: 07.08.2024, number: B.30.2.ODM.0.20.08/407-549).

### Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: CS, ECC; Data collection: ECC; analysis and interpretation of results: CS, ECC, OEY; draft manuscript preparation: CS, OEY. All authors reviewed the results and approved the final version of the manuscript.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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