LETTER TO THE EDITOR

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Intravesical Ozone Therapy for Refractory Hemorrhagic Cystitis Following Allogeneic Hematopoietic Stem Cell Transplantation: A Report of Two Pediatric Cases

Allojenik Hematopoetik Kök Hücre Nakli Sonrası Gelişen Refrakter Hemorajik Sistit Olgularında İntravezikal Ozon Tedavisi: İki Pediatrik Olgu Sunumu

Burcu Tufan Taş[1], Rabia Emel Şenay[1], Nurşah Eker[1], Savaş Şencan[2], Ahmet Koç[1]

[1]Marmara University Pendik Training and Research Hospital, Department of Pediatric Hematology and Oncology, İstanbul, Türkiye
[2]Marmara University Pendik Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Division of Algology, İstanbul, Türkiye

To the Editor,

Hemorrhagic cystitis (HC) is a well-recognized and potentially severe complication following allogeneic hematopoietic stem cell transplantation (HSCT), particularly in pediatric patients. HC may occur early, typically within 48-72 hours after conditioning therapy due to alkylating agents such as cyclophosphamide/ifosfamide, or later in the post-transplant period due to viral reactivation, most notably BK polyomavirus (BKPyV), adenovirus (ADV), or cytomegalovirus (CMV) [1]. Clinical manifestations range from microscopic hematuria to life-threatening hemorrhage requiring transfusion, bladder irrigation, and even surgical interventions. Standard management includes hyperhydration, diuretics, bladder irrigation, analgesia, and targeted antiviral therapy such as cidofovir or ganciclovir and hyperbaric oxygen therapy. However, in some patients, hematuria persists despite optimal supportive and pharmacological treatment, necessitating alternative interventions [2]. Here, we report two cases of HC following HSCT that were successfully treated with intravesical ozone therapy after the failure of conventional options.

Case 1: A 5-year-old boy with acute myeloid leukemia received HSCT with 9/10 HLA-matched unrelated donor peripheral blood; the conditioning regimen included busulfan and cyclophosphamide. On day +64 after the transplant, he developed macroscopic hematuria. Blood and urine BKPyV and CMV polymerase chain reaction (PCR) tests were negative, while blood ADV PCR was positive. The platelet count was within the normal range and coagulation parameters were unremarkable. Urinary ultrasound showed bladder wall thickening and clots. Despite 4 weeks of bladder irrigation, hyperhydration, diuretics, and ganciclovir and 6 weekly doses of cidofovir (intravenously 4 times at 1 mg/kg/week), symptoms persisted. Intravesical hyaluronic acid instillations provided no improvement. Therefore, intravesical ozone therapy with 25 µg/mL ozonated saline was initiated weekly for 4 sessions. Complete remission of hematuria was achieved with no recurrence during follow-up.

Case 2: An 11-year-old boy with relapsed acute lymphoblastic leukemia underwent HSCT from a 9/10 HLA-matched unrelated donor; the conditioning regimen included total body irradiation therapy and etoposide. On day +20 after the transplant, he developed gross hematuria. Viral urine and blood PCR results were negative. After failure of conventional measures including hyaluronic acid and supportive care, two sessions of intravesical ozone therapy were administered. Gross hematuria resolved rapidly. However, microscopic hematuria persisted until intravenous foscarnet was initiated for CMV colitis confirmed by colonoscopy. Complete resolution was observed thereafter.

Ozone is a triatomic molecule with potent antimicrobial, anti-inflammatory, immunomodulatory, and tissue-regenerative effects [2]. It has been used in urological practice, particularly in chronic cystitis and radiation-induced HC, as well as for limited pediatric indications such as anal fissures, stomatitis, and urinary tract infections [2,3]. Intravesical ozone therapy is believed to act by increasing tissue oxygenation, enhancing epithelial repair, and modulating local oxidative stress. In comparison to hyperbaric oxygen therapy, ozone therapy is more accessible, cost-effective, and less invasive, making it suitable for pediatric patients [4]. Although generally well tolerated, ozone therapy is contraindicated in patients with G6PD deficiency, active hemorrhage, or severe coagulopathies. Possible side effects include transient bladder irritation, dysuria, and urgency. Nonetheless, in carefully selected patients, it offers a promising adjunctive treatment [2,5]. In conclusion, intravesical ozone therapy may be an effective

and safe option in the management of refractory HC following HSCT in children. Larger prospective studies are needed to establish the optimal dosing, duration, and long-term outcomes of this novel therapeutic modality.

Keywords: Allogeneic transplantation, Hemorrhagic cystitis, Intravesical ozone

Anahtar Sözcükler: Allojenik nakil, Hemorajik sistit, İntravezikal ozon

Ethics

Informed Consent: Informed consent was obtained from the patient and their legal guardian.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.T.T., R.E.Ş., N.E., S.Ş., A.K.; Concept: B.T.T., R.E.Ş.; Design: B.T.T., R.E.Ş.; Data Collection or Processing: B.T.T.; Analysis or Interpretation: B.T.T., N.E.; Literature Search: B.T.T., R.E.Ş., A.K.; Writing: B.T.T.

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Address for Correspondence/Yazışma Adresi: Burcu Tufan Taş, M.D., Marmara University Pendik Training and Research Hospital, Department of Pediatric Hematology and Oncology, İstanbul, Türkiye
E-mail: drburcutufan@hotmail.com **ORCID:** orcid.org/0000-0003-4614-124X

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