

Commentary on Pilot Trial of a Novel Two-Step Therapy Protocol Using Nebulized Tranexamic Acid and Recombinant Factor VIIa in Children with Intractable Diffuse Alveolar Haemorrhage

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The cases presented here is an initiative trial in the management of diffuse alveolar hemorrhage (DAH) in a noninvasive method [1]. In the evaluation and treatment of a pediatric patient with pulmonary hemorrhage, a three step approach may be the straightest forward. The physician must prevent asphyxiation, stop the bleeding, and treat the underlying cause [2]. This study aimed at exploring the feasibility and efficacy of nebulized tranexamic acid TXA (n-TXA) and nebulized recombinant factor VIIa (n-rFVIIa) when used in a two-step therapy protocol in children with intractable DAH in a pediatric intensive care unit. In this prospective trial, n-TXA (250 mg/dose for children <25 kg and 500 mg/dose for children >25 kg) was administered to 18 children (median age 24.0 months [11.3, 58.5]) with intractable DAH. N-rFVIIa (35 µg/kg/dose for children <25 kg, and 50 µg/kg/dose for children >25 kg) was added if no or minimal response was seen after 3 to 4 doses (18 to 24 hours) of n-TXA. DAH was stopped in 10 (55.6%) children with n-TXA alone within 24 hours of therapy. In the other 8(44.4%) children, n-rFVIIa was added due to n-TXA failure. Six (75.0%) showed complete cessation of DAH, while two children failed to respond with the addition of n-rFVIIa (25.0%). None of the children who responded to therapy showed recurrence of DAH after therapy termination. Documented concomitant respiratory infection showed a significant negative association with response to n-TXA in a stepwise regression analysis (OR=0.06; 95% CI=0.01-0.74). No complications related to therapy were recorded [3-6].

Tranexamic acid (TXA), a synthetic derivative of the amino acid lysine, is an anti-fibrinolytic agent that exerts its action through binding to plasminogen preventing its binding to fibrin and hence its activation to plasmin [7]. TXA was also successful in controlling bleeding when directly administered intrapleurally [8] and into the pericardial cavity [9].

Recombinant factor VIIa (rFVIIa) is a hemostatic agent that achieves hemostasis by one of two mechanisms:

1) Activating factors X and IX at sites of tissue injury through binding to tissue factor (TF) and activated platelets resulting in thrombin generation;

2) TF-independent mechanism, in which rFVIIa directly activates factor X on the surface of activated platelets [10]. There is an increasing interest in off-label use of intravenous rFVIIa in children with clinical bleeding due to non-hemophilic reasons [11], including DAH in newborns [12] and children [13].

Recently, two case reports were published in which DAH was treated by direct intrabronchial rFVIIa instillation in children [14,15]. Several cases reported the successful use of rFVIIa locally administered through bronchoscope to adults with DAH. One case in was given rFVIIa through nebulization after failure of intravenous rFVIIa [16]. Direct intrabronchial instillation was the primary method of drug delivery in all reports [17-19].

This preliminary clinical trial confirmed the feasibility of n-TXA and n-rFVIIa when used in a two-step therapy protocol to control intractable DAH in PICU settings. The two drugs as used in this study showed an excellent risk/benefit profile that warrants further

exploration through a larger multicenter prospective double blind randomized clinical trial which we are currently planning to start.

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