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4. Characterization of F(ab')₂ and Fab crotalidae antivenom single and combination therapy 2018-2020: retrospective analysis of the North American Snakebite Registry

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Background: Equine F(ab')₂ crotalidae antivenom became available in the United States in late 2018. Previous studies have evaluated this F(ab')₂ therapy in comparison to ovine Fab crotalidae antivenom as single agents, but the utilization of combination antivenom therapy is not well described. This study investigates the utilization and effectiveness of this combination of antivenoms for rattlesnake envenomation in comparison to single agent therapy.

Methods: Hospital visits for identified rattlesnake envenomations with complete data were extracted from the 2018-2020 Toxicology Investigators Consortium North American Snake Bite Registry. Data were divided into four therapy groups: Fab-only, F(ab')₂-only, Fab-first, and F(ab')₂-first. Descriptive statistics were utilized, and comparisons performed with chi-squared, t-test or Wilcoxon tests when appropriate. Dosing equivalents (DE) are recorded as a 10:5 vial correction for F(ab')₂ and Fab antivenoms.

Results: The registry contained 279 patients given antivenom. Fab-only therapy occurred in 100%, 43.6%, and 27.5% of cases in 2018, 2019, and 2020, respectively. Only 4 states utilized F(ab')₂ (AZ, NM, CO, CA). Combination therapy accounted for 30.9% and 32.5% of 2019 and 2020 cases. Only 6 cases of F(ab')₂-first combination therapy were identified and 3 had early adverse reactions. 159 Fab-only, 60 F(ab')₂-only, and 54 Fab-first cases were identified with median (IQR) durations of antivenom therapy 14.5 (0-26), 6.9 (0-17.3), and 16.1 (8.7-23.1) hours, respectively. The duration of F(ab')₂-only therapy was significantly shorter than either Fab-first ($p < 0.01$) or Fab-only ($p < 0.03$) with 38 patients getting maintenance dosing in the Fab-only group. Hospitalization was less than 48 hours in 69.9% of patients but this was not significantly different between groups. Signs of post-hospitalization serum sickness occurred in 3.2% of Fab-only, 6.7% F(ab')₂-only, and were not recorded in Fab-first. Post-hospitalization antivenom was given in 5 cases, all in the Fab-only group. Rehospitalization occurred in 3.1% of Fab-only, 3.3% of F(ab')₂-only, and 7.4% of Fab-first. Median DE (IQR) required for initial hospitalization were 2.4 (1.2-3.6) Fab-only, 1.8 (1-2.5) F(ab')₂-only, 2.8 (2.2-3.8) Fab-first. Adverse reactions occurred in 13.0% of Fab-first cases vs 2.5% of Fab-only and 3.33% F(ab')₂ only ($p < 0.01$). Outside hospital transfers were reported in 72.2% of the Fab-first group vs 37.7% Fab-only ($p < 0.01$), and 61.7% F(ab')₂-only. Late thrombocytopenia (platelets < 0.001) and 9.3% of Fab-first ($p < 0.05$). Late coagulopathy (prothrombin time > 15 sec) and hypofibrinogenemia (fibrinogen < 170 mg/dL) were present more frequently in Fab-only therapy than both other groups.

Conclusion: In the 2018-2020 North American Snake Bite Registry combination therapy with F(ab')₂ and Fab was more likely associated with early adverse events and outside hospital transfers though characterization was limited by the rarity of F(ab')₂-first therapy. F(ab')₂-only therapy was associated with fewer dose equivalents, and shorter duration of antivenom therapy. No significant differences were detected in the rate of hospitalization under 48 hours. Fab-only therapy was more closely associated with antivenom required at follow up, late thrombocytopenia, coagulopathy, and hypofibrinogenemia.