

Anticoagulation in Congenital Nephrotic Syndrome: 15 year experience from a national cohort

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Introduction: Congenital nephrotic syndrome (CNS) is an ultra-rare disease characterised by heavy proteinuria and severe oedema within 3 months of birth. Severe urinary plasma protein leakage, including loss of antithrombin III, confers a greater risk of venous thromboembolism (VTE). To mitigate this risk, prophylactic warfarin or low molecular weight heparin (enoxaparin) may be used. The evidence base for anticoagulation in CNS is limited. This study aimed to determine the time taken and doses required to achieve effective anticoagulation in patients with CNS. We hypothesised that these patients will require high doses of anticoagulants and that a long duration of treatment may be required to reach therapeutic levels.

Methods: Patients were included if CNS was diagnosed from 1st July 2005 until 1st January 2018. Eight children had a confirmed diagnosis of CNS, representing all cases nationally in that time. Data was collected prospectively by two authors, with independent retrospective verification of a cross-section by a third author. The database was locked on 1st January 2020. The primary study endpoint was effective anticoagulation, defined as three consecutive therapeutic measurements. Therapeutic 'prophylactic' levels of enoxaparin were defined as anti-factor Xa levels of 0.2-0.4mmol/l; therapeutic warfarinisation was defined as an INR between 2.0 and 3.0. Secondary endpoints were bilateral nephrectomies, transplantation or the development of end-stage renal disease (ESRD). Secondary outcomes included any clinically confirmed VTE, or any clinically significant episode of haemorrhage.

Results: Histologically, two patients had Finnish type CNS, two patients had Pierson's syndrome, three had diffuse mesangial sclerosis and one was classed as Non-Finnish type CNS. All patients initially commenced on enoxaparin, with five patients subsequently treated with warfarin. Using enoxaparin, two patients reached therapeutic anti-factor Xa levels (Time: 6-26 weeks, Dose: 4.0 – 4.79mg/kg/day) and six patients did not reach therapeutic levels (3 patients: ESRD, 3 patients: non-therapeutic levels). Whilst heparinised one patient developed a femoral vein thrombosis (Anti-factor Xa = 0.27iu/ml) and one suffered a bleeding complication (Anti-factor Xa: 1.38 iu/ml). For warfarin, three patients reached therapeutic INRs (Time: 6-19 weeks, Dose: 0.124-0.25mg/kg/day) and two patients did not reach therapeutic levels (2 patients: non-therapeutic levels). One patient was discontinued from warfarin due to two bleeding events (Bleed 1: INR 6, Bleed 2: INR 5.5). At the time of data lock three patients were successfully transplanted, three patients had died and two patients were on peritoneal dialysis.

Conclusions: Our study highlights that achieving therapeutic anticoagulation in CNS is challenging. Reasons may include phenotypic variation and clinical heterogeneity, precluding a defined therapeutic regimen to achieve optimal drug levels. More patients achieved effective anticoagulation whilst on warfarin, with variable therapeutic times and doses. Both agents had similar efficacy and safety profiles. All bleeding complications were associated with non-therapeutic measurements, highlighting the requirement for careful monitoring.