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Short Communication

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Is Low Molecular Weight Heparin the Treatment of choice for Neonatal Thrombosis?

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Clinical Scenario

A borderline preterm baby is born with an emergency caesarean section. The baby is found to have an unprovoked occlusive thrombosis in the left renal vein and inferior vena cava. There are no obvious risk factors for thrombosis. The baby is commenced on un-fractionated heparin (UFH) followed by a prolonged course of low molecular weight heparin (LMWH) based on the guidelines adopted from adult evidence. You wonder if this is reasonable to treat neonates as per adult guidelines given the great differences between adult and neonatal clotting parameters.

Structured Clinical Question

In term and preterm neonates with venous thrombosis is Low Molecular Weight Heparin better in terms of safety and efficacy as compared to un-fractionated heparin?

Searches

MEDLINE was searched via the PubMed interface from 1996-2018 using the following terms. LMWH AND versus Un-fractionated Heparin AND (neonatal OR neonates) AND (thrombosis OR venous thrombosis). The Search was limited to English. 467 possible articles were identified out of which 31 articles were read in detail. I selected 4 papers finally which I found potentially suitable to address this clinical question. The Cochrane database of systematic reviews was searched using the following keywords: Neonatal AND (thrombosis OR venous thrombosis). It did yield 90 articles, none of which was relevant to this clinical question.

Summary

Table 1 Results of the relevant literature search:

Citation	Study group	Study type	Outcome	Key result	Comments
Massicotte et al (2003)	Children ≥3 months and ≤ 16 years diagnosed with DVT and/or PE; n = 70. 36 children received LMWH and 40 received UFH/OA.	Multicentre Open label RCT (Level 1B)	Efficacy outcome (recurrent VTE/death during 3 months of treatment and 3 months of follow up period) Safety outcomes (major bleed, minor bleed, death in 3 months of treatment and 3 months of follow up period)	Recurrent VTE: In LMWH arm 2/36 (5.6%); in UFH/OA arm 5/40(12.5%). RR =0.41; 95% CI (0.04 - 2.76) P=0.435 Death: No VTE related death in either arm Major bleed: In LMWH arm: 2/36 (5.6%), in UFH/OA arm: 5/40(12.5%) RR=0.41; 95% CI (0.04-2.76) P=0.435 Minor bleed: In LMWH arm 32/36 (88.9%), in UFH/OA arm 27/40 (67.5%) Death: No VTE related death in either arm	There is 1 death in UFH/OA group which is due to IVH. It is not clear why author says this is not related to treatment. Author believes study is underpowered due to premature closure and small population size. This is not mentioned what assay is used for anti-factor Xa level to measure, however therapeutic target was 0.5-1.0 for LMWH treatment.

Streif W et al (2003)	62 newborn babies treated with LMWH; enoxaparin for TE events including arterial and venous thrombosis. Gestational age <37 weeks (n=15), ≥37 weeks (n=47)	Prospective cohort study; single arm study (Level 2B)	Efficacy outcomes (complete or partial resolution of thrombus, recurrent TE, clot extension,) Safety outcomes (major bleed, minor bleed, death) Secondary outcomes(time and dose required to achieve therapeutic anti-factor Xa range of 0.5-1.0)	59% babies had complete or partial resolution , 4.8% had recurrent TE, 4.8% had clot extension 4/62 babies had major bleed, 4/62 had minor bleeding. 1/62 died due to clot extension. Preterm babies required 6 days; full term babies required 2 days to achieve target range. (p<0.001) Preterm babies required 1.9mg/kg, term babies required 1.6mg/kg dose to achieve target range (p 0.009)	There is variation in duration of treatment in different subgroups and the criteria to stop treatment are not clearly defined. All babies are followed up 3 months after completion of treatment or until full resolution of clot. Anti-factor Xa level measured with Stachrom assay with therapeutic target 0.5-1.0;
Masicotte et al 1996	25 patients treated with enoxaparin for VTE events including neonates; n= 9	Single arm cohort study (Level 2B)	Primary outcome: therapeutic dose finding study to achieve target anti-factor Xa level of 0.5-1.0 Secondary outcomes: Recurrent VTE events, bleeding	Neonates required average dose of 1.64mg/kg/bid and rest of the children needed 1.0 mg/kg/bid No new VTE events seen during treatment. 2 children bled of already recognised peptic ulcers without any complication	Median duration of therapy was 14 days. It's a small cohort of 9 newborn babies and conclusions cannot be made due to small size.
O'Brien SH et al (2013)	18 patients (6 months to 19 year) treated with LMWH; dalteparin. Infants (<12 months) n=3; children (1-12 years) n= 7); adolescents (13-18 years) n= 8)	Multicentre cohort prospective study (Level 2B)	Safety efficacy and dosage of dalteparin in children to achieve therapeutic anti-factor Xa level	No recurrence of thrombosis, major or minor bleed noted in any patient; 13/18 patients had CTR. Therapeutic dosage: Infants 180 IU/kg, children 125 IU/kg, adolescents 100 IU/kg	Target anti-factor Xa level was 0.5-1.0 and measured with Stachrom assay.

DVT, deep venous thrombosis; PE, pulmonary embolism; TE, thromboembolism; VTE, venous thromboembolism; CTR, complete thrombus resolution

Discussion

The incidence of venous thrombosis in children is highest in neonates (less than 28 days) and infants (less than 1 year of age). The preterm neonates are at much higher risk in neonatal subgroup as compared to the term babies. The incidence of neonatal thromboembolic (TE) events is variable, ranging from 2.4 to 6.8 events per 1000 neonatal intensive care unit (NICU) admissions or 5.1 events per 100,000 live births [1]. The Italian Registry of Thrombosis in Children shows an overall mortality rate of 15% with cerebral sinovenous thrombosis having the worst outcome [5]. The incidence of symptomatic thrombosis is approximately 5.1 in 100,000 live births from the German Thrombosis Registry. The incidence of asymptomatic thrombosis associated with indwelling catheters is probably much higher and has been estimated between 10 and 20 % [6].

The most important risk factor is the presence of an indwelling central venous catheter with other clinical risk factors being septicaemia, dehydration, maternal diabetes, surgical procedures and therapeutic cooling for hypoxic ischaemic encephalopathy. The most frequent inherited thrombophilic defects including deficiencies of Antithrombin, protein C, and protein S, Factor V Leiden and Prothrombin Mutation (G20210A Mutation) are associated with an increased tendency to develop venous thrombosis [1-4].

Heparin is widely used in neonatal ICU settings (NICUs) to treat patients with thrombosis and incidence of thrombosis is increasing in the neonatal population particularly due to the higher incidence of central venous catheter (CVC) related thrombosis [7]. Oral anticoagulation with warfarin is problematic in children as this need to be stopped for procedures and frequent dose adjustments are required. Current treatment strategies are extrapolated from adult evidence notwithstanding marked differences of neonatal haemostatic system, epidemiology and drug pharmacokinetics. In term neonates the concentration of several procoagulant proteins, particularly the vitamin K dependent factors is reduced when compared with adult values. The naturally occurring inhibitors of

coagulation like antithrombin, protein C, and protein S, are also reduced at birth. The fibrinolytic system also appears different in newborn babies with plasminogen concentrations almost half of the adult values. These differences are more pronounced in the preterm infant [8]. This scientific information provides the basis for reasoning that the treatment of neonatal thrombosis as per adult guidelines may not be justified. Conducted dose finding studies for enoxaparin and dalteparin in children including neonates [10, 11, 12].

Massicotte found that neonates require 1.6 times higher dose of enoxaparin than older children to achieve target anti-factor Xa level. Streif W found that preterm babies, when compared to the term babies, require longer duration (6 versus 2 days) and approximately 20% higher dose of enoxaparin to achieve target anti-factor Xa. O'Brien showed that infants require 1.8 times higher dose of dalteparin than adolescents to achieve therapeutic level of anti-factor Xa. There is no completed or ongoing randomized controlled trial (RCT) in the neonatal population to compare safety and efficacy of LMWH and UFH. In children (not including neonates) however, the first RCT was conducted in 2003 by focussed on the safety and efficacy of LMWH [9]. It established that 3 months of treatment with LMWH; reviparin-sodium is a safe and effective form of treatment of thrombosis in children. It also showed that reviparin-sodium tend to show fewer recurrences and less bleeding than UFH.

The first study to see the efficacy and safety of LMWH in neonatal population exclusively was carried out on a cohort of 62 newborn babies [10]. It showed that administration of enoxaparin in newborn infants appears to be an acceptable alternative for treatment than standard heparin with a relatively low risk of bleeding. Streif found adverse effects in less than 5% of patients. Studied safety and efficacy outcomes for LMWH; enoxaparin in children including neonates (n=9) and found no recurrence or extension of VTE, death or significant bleeding during the treatment period [11]. In conclusion, despite limited evidence and no RCT, LMWHs tend to show better outcome, safety and efficacy in treating neonatal thrombosis. Since the reported incidence of thrombosis in neonates is approximately 2.4-6.8/100,000 live births, a two-arm randomised clinical trial evaluating the superiority of LMWH in comparison to Un-fractioned Heparin would require at least 1774 patients to achieve 80% power to detect a 50% relative risk reduction of symptomatic thrombosis, which can be considered clinically meaningful.

Clinical Bottomline

- More favourable outcome and less adverse effects are seen with LMWHs as compared to UFH in the treatment of thrombosis in neonatal population. Grade C
- Preterm babies require higher dose and more time to achieve therapeutic anti-factor Xa level. Grade C

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