

COAGULOPATHY

Supporting information

This guideline has been prepared with reference to the following:

Chalmers E, Williams M, Brennand J, et al. Guideline on the management of haemophilia in the fetus and neonate. *Br J Haematol* 2011;154:208-15

<http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08545.x/full>

What are normal coagulation parameters in the newborn?

Normal values for term infants are as follows, with values for premature infants in brackets:

- Platelet count: 150-400,000 (ditto)
- Prothrombin time (sec): 11-15 (12-16)
- Partial thromboplastin time (sec): 30-40 (30-80)
- Fibrinogen (mg/dL): 175-350 (150-325)
- Fibrin split products (mcg/mL): <10 (ditto)
- Thrombin time (sec): 15-20 (17-25)
- Adult coagulation reference ranges, especially for PT and APTT, cannot be applied to newborns and young infants (Lippi, 2007).

Buchanan GR. Coagulation disorders in the neonate. *Pediatr Clin N Am* 1986;33:203-220

Lippi G, Salvagno GL, Rugolotto S, et al. Routine coagulation tests in newborn and young infants. *J Thromb Thrombolysis* 2007;24:153-5

Evidence Level: V

Is there any causative relationship between deranged coagulation and intraventricular haemorrhage (IVH) in the newborn? If so, does treating abnormal coagulation prevent IVH in preterm infants?

A single centre retrospective, observational cohort study of infants born at less than 28 weeks gestation found that of 109 infants, 26 developed IVH (Williams, 2019). Elevated International normalized ratio (INR) was associated with increased risk of a severe IVH (odds ratio [OR] 6.50; 95% confidence interval [CI], 1.65 to 25.62) adjusted for gestation, birth weight, and sex. INR was significantly associated with severe IVH in infants who did not receive blood products (OR, 64.60; 95% CI, 1.35 to 3081.25), but not in those who did (OR, 2.93; 95% CI, 0.67 to 12.71).

In a study of 106 preterm infants of 34 weeks' gestation (Beverley, 1984), 25 (23.5%) developed intraventricular haemorrhage in the first 48 hours of life. Although coagulation parameters appeared normal at birth, differences had appeared by 48 hours, with the IVH group showing a prolonged activated partial thromboplastin time and reduced factor II, VII, and X activity. The authors postulated that, although the aetiology of IVH is multifactorial, early correction of coagulation anomalies may prevent progression to more severe grades of haemorrhage. Survivors of grade III or IV IVH have a 40% risk of permanent brain damage (Krishnamoorthy, 1979).

Another study, in 58 VLBW infants (Setzer, 1982), found that 32 (55%) developed IVH. The affected infants had lower mean platelet count and platelet aggregation response and prolonged mean bleeding time compared to those unaffected.

A study of 54 preterm infants <35 weeks' gestation (Amato, 1988) found peri-intraventricular haemorrhage (PIVH) in 21 (38%). The affected infants showed lower fibrinogen levels than unaffected infants and significant correlation between platelet count and degree of PIVH.

One prospective study in 49 infants (Van de Bor, 1986) found no difference in coagulopathy between 20 who developed PIVH and 29 who did not, apart from lower levels of factor V in the affected group. A prospective, randomised trial in 100 infants <32 weeks' gestation and <1500 gm in weight (Morales, 1988) compared those whose mothers had received 10 mg vitamin K1 i.m. 5 days prior to delivery with a similar number who had not received the vitamin. Infants in the "intervention" group showed significant reduction in the prothrombin time (12.7 vs 15.2 seconds) and partial thromboplastin time (42.6 vs 58.9 seconds). These infants also experienced a lower incidence of total (16% vs 36%) and severe (0% vs 11%) grades of IVH.

A single maternal dose of 10 mg vitamin K1 i.m. 4 hours before delivery may be sufficient to provide significant protection against IVH (Pomerance, 1987).

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One randomised prospective study in 98 infants (Kazzi, 1989) found no improvement in coagulopathy or incidence of IVH when mothers received 10 mg vitamin K1.
See also following question on FFP.

Amato M, Fauchere JC, Hermann U. Coagulation abnormalities in low birth weight infants with peri-intraventricular hemorrhage. *Neuropediatrics* 1988;19:154-7

Beverley DW, Chance GW, Inwood MJ, et al. Intraventricular haemorrhage and haemostasis defects. *Arch Dis Child* 1984;59:444-8
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1628492/pdf/archdisch00734-0058.pdf>

Kazzi NJ, Ilagan NB, Liang KC, et al. Maternal administration of vitamin K does not improve the coagulation profile of preterm infants. *Pediatrics* 1989;84:1045-50

Krishnamoorthy KS, Shannon DC, DeLong GR, et al. Neurologic sequelae in the survivors of neonatal intraventricular haemorrhage. *Pediatrics* 1979;64:233-7

Morales WJ, Angel JL, O'Brien WF, et al. The use of antenatal vitamin K in the prevention of early neonatal intraventricular hemorrhage. *Am J Obstet Gynecol* 1988;159:774-9

Pomerance JJ, Teal JG, Gogolok JF, et al. Maternally administered antenatal vitamin K1: effect on neonatal prothrombin activity, partial thromboplastin time, and intraventricular hemorrhage. *Obstet Gynecol* 1987;70:235-41

Setzer ES, Webb IB, Wassenaar JW, et al. Platelet dysfunction and coagulopathy in intraventricular hemorrhage in the premature infant. *J Pediatr* 1982;100:599-605

Van de Bor M, Briet E, Van Bel F, et al. Hemostasis and periventricular-intraventricular hemorrhage of the newborn. *Am J Dis Child* 1986;140:1131-4

Williams AG, Odd D, Bates S et al. Elevated International Normalized Ratio (INR) is Associated With an Increased Risk of Intraventricular Hemorrhage in Extremely Preterm Infants. *J Pediatr Hematol Oncol*. 2019;41:355-60

Evidence Level: III

What are the indications for giving fresh frozen plasma (FFP)?

The main use of FFP in the neonate is to replace single coagulation deficiencies (factors V, VII, X, XI and XIII), where a specific or combined factor concentrate is unavailable (Contreras, 1992). This is essentially a "second best" solution, as very large volumes are often needed in order to reach sufficiently high plasma levels (Muntean, 2002).

A prospective study in 33 neonates (Hyytiainen, 2003) found that FFP had an acute thrombin-reducing effect in those infants with the highest pretransfusional thrombin formation. The authors stress that FFP has poorly-defined effects on coagulation and unproven clinical efficacy.

One randomised study in 73 preterm infants (Beverley, 1985) found that 15 (41%) of control patients sustained intraventricular haemorrhage compared with 5 (14%) of 36 patients given FFP 10ml/kg on admission and at 24 hours of age.

An earlier controlled trial of the same regimen in 66 infants (Hambleton, 1973) had found no evidence of a protective effect for FFP on IVH. Similarly negative results were obtained in a later and larger trial in 776 infants (Anon, 1996). Osborn and Evans (2009) performed a meta-analysis of randomized trials of early volume expansion in neonates using different volume expanders (including FFP). This meta-analysis concluded that there were no benefits associated with the early administration of FFP to preterm neonates, in terms of improving blood pressure, decreasing rates or severity of IVH, decreasing mortality, or improving neurodevelopmental outcomes.

Anon. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. Northern Neonatal Nursing Initiative Trial Group. *Lancet* 1996;348:229-32

Beverley DW, Pitts TT, Congdon PJ, et al. Prevention of intraventricular haemorrhage by fresh frozen plasma. *Arch Dis Child* 1985;60:710-3
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1777434/pdf/archdisch00719-0022.pdf>

Contreras M, Ala FA, Greaves M, et al. Guidelines for the use of fresh frozen plasma. British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. *Transfus Med* 1992;2:57-63

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http://www.bcshguidelines.com/documents/Use_of_fresh_frozen_plasma_1992.pdf

Hambleton G, Appleyard WJ. Controlled trial of fresh frozen plasma in asphyxiated low birthweight infants. Arch Dis Child 1973;48:31-5

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1647801/pdf/archdisch00869-0033.pdf>

Hyytiainen S, Syrjala M, Fellman V, et al. Fresh frozen plasma reduces thrombin formation in newborn infants. J Thromb Haemost 2003;1:1189-94

Muntean W. Fresh frozen plasma in the pediatric age group and in congenital factor deficiency. Thromb Res 2002;107(Suppl 1):S29-32

Osborn DA, Evans NJ. Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Database of Systematic Reviews 2004, Issue 2.

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002055.pub2/pdf/standard>

Evidence Level: I (for no evidence in favour of FFP for IVH)

What is the role of Vitamin K in abnormal coagulation in the newborn?

Vitamin K is administered to prevent haemorrhagic disease of the newborn (HDN). A Cochrane review of 13 RCTs (Puckett, 2000) concluded that a single dose (1.0 mg) of intramuscular vitamin K after birth is effective in the prevention of classic HDN. Either intramuscular or oral prophylaxis improved biochemical indices of coagulation status at 1-7 days. Neither route of administration has been tested in RCTs for effect on late HDN (week 2-12), and the oral route has also not been tested for effect on classic HDN (day 1-7).

The American Academy of Pediatrics has consistently recommended vitamin K in its guidelines since 1961 (Anon, 2003).

There is no evidence that vitamin K deficiency bleeding is commoner in preterm babies (Hey, 2003), or that cancer risk is raised in infants given intramuscular vitamin K (Roman, 2002).

Anon. Controversies concerning vitamin K and the newborn. Policy statement. American Academy of Pediatrics. Committee on Fetus and Newborn. Pediatrics 2003;112:191-2

<http://pediatrics.aappublications.org/content/112/1/191.long>

Hey E. Vitamin K – what, why, and when. Arch Dis Child Fetal Neonatal Ed 2003;88:F80-3

<http://fn.bmj.com/content/88/2/F80.1.long>

Puckett RM, Offringa M. Prophylactic vitamin K for vitamin K deficiency bleeding in neonates. The Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD002776

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002776/full>

Roman E, Fear NT, Ansell P, et al. Vitamin K and childhood cancer: analysis of individual patient data from six case-control studies. Br J Cancer 2002;86:63-9

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2746550/>

Evidence Level: I

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