

# Does the Heparin Infusion Decrease the Risk of Catheter Related Thrombosis in Neonates with Central Venous Catheters?

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### Clinical Scenario

A preterm newborn baby needs a peripherally inserted central venous catheter (PICVC) for the administration of parenteral nutrition (PN), intravenous (IV) fluids and medications. Echocardiogram is performed on this baby to ascertain the presence of PDA. Echocardiogram shows an incidental finding of inferior vena cava (IVC) thrombosis that is partially blocking the IVC. Here the question arises whether administration of continuous infusion of heparin through the central venous catheters including the umbilical venous catheters (UVC) or peripherally (percutaneous) inserted central venous catheters, commonly referred as long lines can reduce the incidence of catheter related thrombosis in neonates.

### Structured Clinical Question

In term and preterm neonates does continuous heparin infusion as compared to no heparin infused through the central venous catheters decrease the risk of catheter related thrombosis?

### Searches

MEDLINE was searched via the Pubmed interface from 1996-2019 using: Heparin AND central AND venous AND (catheter OR catheters). Search was limited to English articles. The search retrieved 520 articles, full text assessed for 11 articles and 5 included. The Cochrane database of systematic reviews was searched and found no additional study.

### Summary

Table 1 Results of the relevant literature search:

Citation	Study group	Study type	Outcome	Key result	Comments
Pita Birch et al (2010)	Neonates (n=210) receiving TPN through a long line. Heparin group, n=102 received heparin mixed in TPN. Control group, n=108 had no heparin in TPN	Single centre RCT (Level1)	Primary outcome Episodes of catheter related sepsis (CRS)  Secondary outcomes Catheter occlusion Safety of heparin	There was statistically significant reduction in CRS in heparin group. RR=57; 95% CI (0.32-0.98), p=0.04  There were no statistically significant differences for catheter obstruction (RR=1.76; 95% CI 0.48-6.56, p0.42) or IVH progression in heparin group (RR=0.3; 95% CI 0.07-1.24; p.011)	Dose of heparin was 0.5 IU/ml of TPN. Peripherally inserted central venous catheters studied.

F Kamala et al. (2002)	Newborn babies were randomized to receive TPN containing either heparin (n= 35) or no heparin (n=31).	Single centre RCT (Level1)	Primary outcome Catheter occlusion  Secondary outcomes Safety of heparin	Heparin group had 14.3% blocked catheters and no heparin group had 22.6%. Difference is statistically not significant. RR= 0.6; 95% CI (0.2-1.08), p =0.4  There was no difference in platelet count, APTT, bilirubin or triglyceride level or worsening of IVH in heparin group.	Dose of heparin was 1 IU/ml of TPN. Due to confounding factors almost half of catheters were prematurely removed in each group limiting the firm conclusions to be drawn from the results. Also the study sample was too small as perceived by the author.
Bracho-Blanchet et al (2010)	Children <18 years of age including 12 newborn babies. One arm n=38 received heparin mixed in TPN/ IV fluids. Other arm n=38 had no heparin in IV fluids/ TPN	Single centre RCT (Level1)	Effect of heparin on thrombus formation and occlusion of catheters.  Safety of heparin	Heparin arm showed thrombus in 7.8%, control arm had 63%. RR=20; 95% CI (5.1-77.2), p<0.001 Heparin arm showed occlusion in 5.3%, control arm 47.8% RR= 2.3; 95% CI (1.6-3.38), p<0.001  There was no presence of bleeding or prolonged clotting times during the use of heparin.	Dose of heparin was 2 IU/ml of IV fluids/ TPN. Thrombosis was detected by visual inspection upon withdrawal of catheter. Most the double lumen catheters were inserted in subclavian or internal jugular veins.
PS Shah et al (2007)	Total of 201 neonates were enrolled. Experiment group (n=100) received heparin into the CVC through separate lumen and the controlled group (n=101) received placebo	Multicentre RCT (Level1)	Incidence of occlusion and thrombosis in heparin versus placebo group  Safety of heparin infusion.	The incidence of catheter occlusion was significantly lower in heparin group. RR =20, 95% CI (0.09-0.42), p=0.001 There was no statistically significant difference in thrombosis incidence in two groups. (20% in heparin versus 21% in placebo group)  No adverse effects attributable to heparin seen including IVH, significant thrombocytopenia or death	Dose of heparin was 0.5 IU/kg/hour. After contacting the author the concentration of heparin infusion was confirmed as 1 units/ml of heparin in 10% Dextrose. Author used Doppler USS within 72 hours of removal of catheter to diagnose the CVC related thrombosis.

S Uslu et al (2010)	239 Newborn babies were randomized to receive heparin (n=118) through a separate lumen into the CVC or no heparin (n= 121)	Single centre RCT (Level1)	Catheter related thrombosis and occlusion.  Safety of heparin	The incidence of catheter occlusion in heparin group is significantly low. R=3.44; 95% CI (1.92- 6.44), p=0.0001 The incidence of thrombosis is low in heparin group but is not significant. (1.7% versus 4.1%)  No heparin related adverse effects seen including thrombocytopenia, prolonged aPTT, IVH, arrhythmia and death.	Dose of heparin was 0.5 IU/kg/hour along with TPN. Author used visual inspection to detect the thrombus along the length of CVC after its removal.
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RCT, randomized controlled trial; IV, intravenous; TPN, total parenteral nutrition; IU, international units; IVH, intraventricular haemorrhage; USS, ultrasound scan

## Discussion

Neonates treated in neonatal intensive care units (NICUs) usually needs a protracted venous access for the administration of parenteral nutrition, fluids and medications. Peripherally inserted percutaneous central venous catheters (PICVCs) and umbilical venous catheters (UVCs) are the two commonly used methods to gain a dedicated venous access in neonates. Although PICVC is considered the preferred route of venous access in many NICU settings it has complications including mechanical problems (like kinking of tube, dislodgement and extravasation), occlusion, catheter related sepsis and thrombosis [1, 2]. There has been a strong concordance between intravenous catheter occlusion and thrombus formation. Found that occlusion of CVCs has greater than 80% of concordance for detecting thrombosis [5]. Studies have revealed that CVC also correlates with the intravascular fibrin sleeve formation around the catheter which may be considered a step towards thrombus formation [6]. Attempts have been made to prevent thrombus formation in indwelling CVCs by using heparin infusion into the catheters. The anticoagulative properties of heparin and its postulated anti-fibrin sleeve formation effects are thought to prevent CVC related thrombus and the catheter occlusion [7]. Evaluated the prophylactic use of heparin to prevent the catheter related thrombus formation in adults. In the meta-analysis of 7 randomized controlled trials it concluded that prophylactic heparin significantly decreases CVC related thrombosis by 57% (RR, 0.43; 95% CI; 0.23, 0.78) [8]. Results remained significant after exclusion of 1 trial that assessed heparin bonded catheters (RR; 0.44; 95% CI; 0.22, 0.87), and concluded heparin dosed at 3 U/ml of TPN was effective in reducing CVC related thrombosis in adults however lower doses may not be.

Trialled safety and efficacy of heparin to prevent thrombosis and occlusion of neonatal CVCs [9, 10, 11]. The dose used was 0.5-2.0 IU/ml of heparin mixed in TPN or intravenous (IV) fluids. Bracho-Blanchet used the highest dose of 2.0 IU/ml of heparin mixed in TPN/IV fluids. There was no significant difference in the incidence of thrombosis or catheter occlusion in any of these 3 studies even with the highest dose of heparin. Used low equivalent dose of 0.5 IU/kg/hour of heparin infused in the CVC through a separate lumen [12, 13]. The incidence of catheter occlusion, patency and

catheter related thrombosis was found to be significantly reduced in these studies. Shah used Doppler ultrasound scan to detect CVC related thrombosis and found only 1% less incidence of thrombosis in heparin group and Uslu used visual detection of thrombosis at the tip of catheter after its removal and found more than twice the number of catheters with thrombosis in no heparin group. For an average weight of 2.5 kg neonate who is on 150ml/kg/day of total PN/IV fluids the babies who received 2 IU of heparin mixed with PN/IV fluids were given 25 times higher dose as compared to the study groups who had heparin infusion given through a separate lumen into the CVC. Effects of heparin to prevent CVC related occlusion or thrombosis was significantly higher in latter group though none of the groups showed heparin related adverse effects. These results warrant conducting larger studies with higher doses of heparin infused through a separate lumen into the CVC confirm if these effects are real.

## Clinical Bottomline

Heparin infused through a separate lumen into the central venous catheter may reduce the incidence of thrombosis and catheter occlusion in neonates with central venous catheter as compared to the babies with no heparin or the heparin mixed with the PN/IV fluids. (Grade A)

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