

# Effect of heparin in arterial line flushing solutions on platelet count: a randomised double-blind study

Kelly FM Hall, Trish M Bennetts,  
Rob K S Whitta, Lorraine Welman and Peter Rawlins

Arterial catheters are widely used in intensive care units for continuous blood pressure monitoring and blood sampling. The patency of these lines is maintained by continuous flushing, usually with the addition of the anticoagulant heparin to the flushing solution. Although various studies have compared the effects of heparinised and normal saline solutions on patency of arterial catheters,<sup>1-3</sup> few studies have considered the effect of these heparinised solutions on platelet count.

We undertook a prospective, randomised double-blind study comparing the effects of normal saline and heparinised saline, administered via a continuous flush device to an arterial catheter, on functioning of arterial lines in patients in our intensive care unit.<sup>4</sup> As part of this study, we monitored patients' platelet counts daily to assess the effect of low-dose heparin on these counts.

## Methods

All patients (elective and emergency) presenting to the mixed medical and surgical, six-bed Level 2 ICU of our regional hospital between April and December 2003 were eligible for inclusion in the study, as previously described.<sup>4</sup> Exclusion criteria were pre-existing coagulopathy that would preclude heparin use, history of heparin-induced thrombocytopenia, known heparin sensitivity, requirement for therapeutic heparin, and age under 16 years. All patients were given subcutaneous low molecular weight heparin when appropriate.

Arterial lines were 20 cm 20-gauge lines inserted in radial, brachial or femoral arteries (AKS-2020, Smiths Medical Deutschland GmbH, Kirchseeon, Germany). The flushing solution and giving set (TranStar 213 cm, Medex, Dublin, Ohio, USA) were prepared using a 500 mL normal saline bag pressurised to 300 mmHg.

Syringes containing 5 mL of either normal saline or normal saline plus heparin (500 IU) were specially prepared by the manufacturer (Baxter Healthcare, Auckland, New Zealand). The hospital pharmacy blanked out the manufacturer's labelling, assigned each syringe a random number, and retained the code.

On admission of a patient requiring invasive blood pressure monitoring, a numbered syringe was taken from the ICU refrigerator in numerical order. The contents were

## ABSTRACT

**Introduction:** Arterial catheters are widely used in intensive care units for continuous blood pressure monitoring and blood sampling. Studies have examined the effect of heparin on patency of arterial catheters but not on platelet counts. Heparin is a naturally occurring anticoagulant that helps prevent clotting and is given to prevent and treat thrombosis. It has many other effects, including reducing platelet counts.

**Methods:** A prospective, randomised, double-blind study compared the effects of heparinised and normal saline (both administered via a continuous flush device to an arterial catheter) on patients' platelet counts. All patients admitted to a mixed medical-surgical ICU between April and December 2003 were eligible for entry. Exclusion criteria were age under 16 years, known sensitivity to heparin, pre-existing coagulopathy that precluded heparin, or requirement for therapeutic heparin. Lines were inserted into radial, brachial or femoral arteries. A 500 mL bag of saline for the flush was injected with numbered syringes, containing either normal saline (NS, 35 patients) or 500 IU heparin (HS, 30 patients), and pressurised. Platelet count was assessed daily.

**Results:** Mean platelet counts were  $234.6 \times 10^9/L$  (NS) versus  $256.6 \times 10^9/L$  (HS). Comparison using the central limit theorem showed means were not different at the 95% confidence interval (-77.6 to  $37 \times 10^9/L$ ).

**Conclusion:** Use of heparin in normal saline as a continuous flush for an arterial catheter does not reduce platelet counts in critically ill patients.

Crit Care Resusc 2006; 8: 294-296

injected into the 500 mL bag of saline for the flushing solution, which was hung and pressurised as usual, and delivered as a continuous flush at a rate of 3 mL/h. If the patient required an arterial line for longer than 72 hours, when the giving set would usually be changed, then the pharmacy was asked to provide a further syringe of the same constituents.

Blood samples were taken daily for platelet count. Patients remained in the study while the arterial line

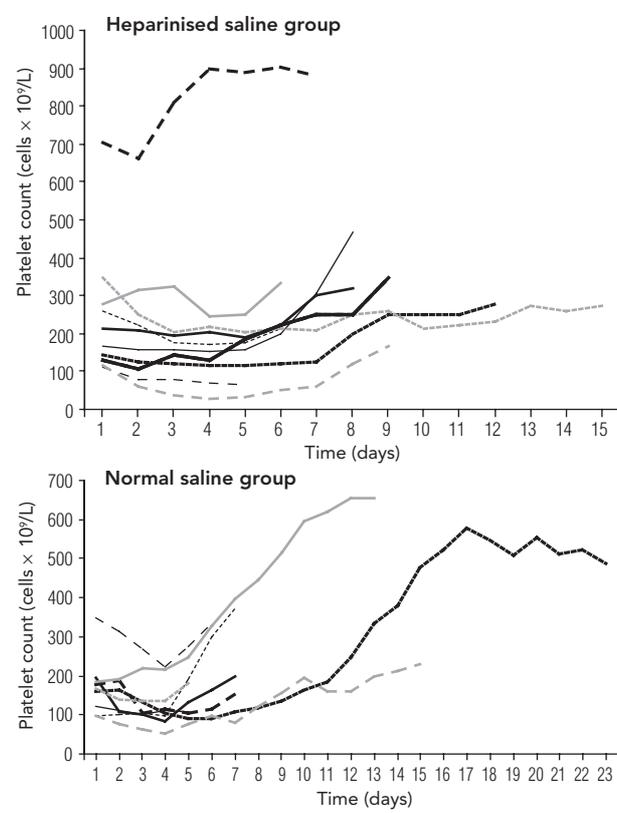
**Table 1. Characteristics of patients enrolled in the trial**

Patient characteristics	Normal saline (n = 35)	Heparinised saline (n = 30)
Male	18	14
Female	17	16
Mean age (years)	58	50

**Table 2. Outcomes of trial of normal versus heparinised saline**

Outcome	Normal saline (n = 35)	Heparinised saline (n = 30)
Mean duration of study (no. of 8-h nursing shifts)	12.0	12.1
Mean duration of ICU stay (days)	5.8	6.6
Mean platelet count ( $\times 10^9/L$ )		
Baseline	232.0	270.5
Daily	234.6	256.6
Mean daily APTT (s)	40.4	37.2

APTT = activated partial thromboplastin time.

**Figure 1. Daily platelet counts in patients who had an arterial line for longer than 4 days**

remained in situ and functioning. Each patient's daily platelet counts were summed, and means were compared using the central limit theorem.

Parallel studies included daily measurement of activated partial thromboplastin time (APTT) and scoring of line function as previously described (3 = functioning well for monitoring and sample-taking; 2 = functioning well most of the time, requires some attention; 1 = functioning poorly; 0 = required changing).

## Results

Sixty-five patients were recruited over 8 months: 35 in the normal saline group and 30 in the heparinised saline group. Their characteristics are shown in Table 1.

The mean platelet count was  $256.6 \times 10^9/L$  for the heparinised saline group, compared with  $234.6 \times 10^9/L$  for the normal saline group (Table 2). Comparison of means with the central limit theorem showed there was no significant difference at the 95% confidence interval ( $-77$  to  $37 \times 10^9/L$ ).

Platelet counts over time for individual patients who had arterial lines for 4 days or longer are shown in Figure 1. Counts showed an early decline and then recovery to normal levels in both the heparinised and normal saline groups.

The parallel study comparing arterial catheter life in the two groups showed no difference at the 95% confidence interval using the central limit theorem.

## Discussion

Heparin is a naturally occurring anticoagulant that helps prevent intravascular clotting. It is produced by mast cells and basophils, which are found in large numbers in the connective tissue surrounding capillaries. It is also given as a drug to prevent intravascular clotting and extension of existing clots.<sup>5</sup>

Heparin has many effects, including both inhibiting and inducing platelet aggregation. Thrombocytopenia is an abnormal reduction in the number of platelets. It has a variety of causes, including an immune response to a drug<sup>6</sup> such as heparin. When heparin is administered as treatment, it can bind with platelet factor 4 (PF4) (stored within the alpha granules of platelets as a small peptide). The resulting complex is released into the bloodstream, where it initiates the production of immunoglobulin G (IgG). The IgG-PF4-heparin complex activates platelets, increasing the thrombolytic effects of heparin-induced thrombocytopenia (HIT).<sup>5,7</sup> Platelets are then consumed in a thromboembolic process, with HIT at the extreme end. Clinical HIT is defined

as a decrease in platelet count by 50% or more, the development of new thromboembolic conditions, or both.<sup>8</sup>

Patients with HIT frequently develop thrombotic complications, especially deep venous thrombosis and pulmonary embolism. Other clinical associations include arterial thrombosis, skin lesions, and uncommon thrombotic events, such as adrenal gland thrombosis and haemorrhage.<sup>6,7</sup> Thrombosis results from IgG-induced platelet activation, which leads to the generation of procoagulants and platelet-derived microparticles, tissue factor expression by endothelium, and inactivation of heparin by PF4 released from platelets.

Increased levels of thrombin-antithrombin complex indicate disseminated intravascular coagulopathy in almost all patients with HIT, although an increased international normalised ratio (INR) or low fibrinogen level occur in fewer than 10% of cases. Unfractionated heparin is more immunogenic than low-molecular weight heparin.

A previous study described two types of thrombocytopenia caused by heparin administration.<sup>5</sup> In type 1 non-immune-mediated or heparin-associated thrombocytopenia, there are no heparin-dependent antibodies.<sup>5</sup> It is usually associated with high-dose heparin and usually occurs within 4 days of heparin administration. Type 2 immune-mediated or heparin-induced thrombocytopenia is associated with variable doses of heparin,<sup>5</sup> and would be more likely in our patient population. The authors suggested that patients whose thrombocytopenia develops early after heparin exposure may already have heparin-dependent antibodies caused by a previous exposure less than 100 days before the current treatment.

In 1991, Clifton conducted a double-blind, randomised study comparing the effects of heparin solutions (4 IU/mL) and normal saline solutions on patency of arterial catheters. They concluded that heparinised solutions were preferable for reducing the rate of catheter occlusions and other malfunctions and that they did not significantly alter platelet count. However, their study included only 30 patients, and patients were excluded from the study if baseline platelet counts were below  $50 \times 10^9/L$ .<sup>1</sup>

Another study of 35 ICU patients compared use of either heparin (4 IU/mL) or 1.4% sodium citrate, both in 0.9% sodium chloride solution, as a continuous flush solution. Again, platelet counts were similar in the two groups.<sup>9</sup>

While our sample did not include children, HIT was reported in 2.3% of paediatric ICU patients exposed to heparin for 5 days or longer by arterial line via a continuous flushing device.<sup>10</sup> HIT was confirmed by measurement of antibody levels. However, as a diagnosis of HIT relied on patients developing a thrombosis and serological confirmation, the incidence may be higher than reported.

In our study, measurement of platelet counts over time in patients admitted to the ICU for 4 days or longer suggested an early decline and then recovery, which one would expect as patients recover from critical illness.

## Conclusion

Heparin at the dose used (3 IU/h) had no effect on platelet count. The use of heparin in normal saline (1 IU/mL) in continuous flushing devices for an arterial catheter does not significantly reduce platelet counts in critically ill patients in comparison to normal saline.

## Acknowledgements

We thank Baxter Healthcare for providing the syringes of heparinised and normal saline used in this study.

## Author details

Kelly F M Hall, Intensive Care Nurse<sup>1</sup>

Trish M Bennetts, Intensive Care Nurse<sup>1</sup>

Rob K S Whitta, Anaesthetist<sup>1</sup>

Lorraine Welman, Pharmacist<sup>1</sup>

Peter Rawlins, Statistician<sup>2</sup>

1 Midcentral Health, Palmerston North, New Zealand.

2 Massey University, Palmerston North, New Zealand.

Correspondence: kelly.hall@midcentral.co.nz

## References

- 1 Clifton GD, Kelly HJ, Record KE, Thompson JR. Comparison of normal saline and heparin solutions for maintenance of arterial catheter patency. *Heart Lung* 1991; 20: 115-8.
- 2 Hook ML, Reuling J, Luettgen ML, et al. Comparison of the patency of arterial lines maintained with heparinized and nonheparinized infusions. *Heart Lung* 1987; 16: 693-9.
- 3 Kulkarni M, Elsner C, Ouellet D, Zeldin R. Heparinized saline versus normal saline in maintaining patency of radial artery catheter. *Can J Surg* 1994; 37: 37-42.
- 4 Whitta RKS, Hall KFM, Bennetts TM, et al. Comparison of normal and heparinised saline flushing on function of arterial lines. *Crit Care Resusc* 2006; 8: 205-8.
- 5 Pravinkuma E, Webster NR. HIT/HITT and alternative coagulation: current concepts. *BJA* 2003; 90: 676-85.
- 6 Warrell DA, Cox TM, Firth JD, Benz Jr EJ, editors. Oxford textbook of medicine. 4th ed. New York: Oxford University Press, 2003.
- 7 Warkentin TE, Kelton JG. Temporal aspects of heparin induced thrombocytopenia. *N Engl J Med* 2001; 344: 1286-92.
- 8 Klenner AF, Fush C, Rakov A, et al. Benefit and risk of heparin for maintaining arterial catheters. *J Pediatr* 2003; 143: 741-5.
- 9 Branson PK, McCoy RA, Phillips BA, Clifton GD. Efficacy of 1.4 percent sodium citrate in maintaining arterial catheter patency in patients in a medical ICU. *Chest* 1993; 103: 882-5.
- 10 Schmutz M, Risch L, Huber AR, et al. Heparin-induced thrombocytopenia-associated thrombosis in pediatric intensive care patients. *Pediatrics* 2002; 109: E10. □