An Open-Labelled, Randomized Cross-Over Study of the Effect of Electromechanical Pumps versus Conventional Gravity Flow on Platelet Transfusion in Adult Haematology Patients

Alhossain A. Khalafallah^{a,b,c} Abdul Majeed Al-Barzan^{a,b} Annette Camino^a Iain K. Robertson^b
Gerald Bates^{a,b} Dawn Richardson^a Catherine Austen^c David Seaton^a Wolfgang Heller^c
Terry Brain^a

^a Department of Haematology and Pathology, Launceston General Hospital,

^b School of Human Life Sciences, University of Tasmania,

^c Department of Medicine, Launceston General Hospital, Launceston, Tasmania, Australia

Keywords

Platelet transfusion · Electromechanical pump · Gravity method · Platelet-increment

Summary

Background: Only few data are available regarding the effect of the method of platelet transfusion on the platelet increment. Although administering platelets via either a free-flowing gravity or an electromechanical pump is common practice, there are no randomized trials addressing differences between these techniques. **Objectives:** Our study aimed to determine whether infusion methods influence the platelet increment. **Methods:** We studied the effect of 3 different electromechanical pumps that are used routinely for transfusion at our hospital; the Graseby 3000, Imed Gemini PC-1, and the Baxter Colleague in comparison to the free-flow gravity method. Between January 2007 and January 2011, we prospectively randomized the platelet transfusion method for 35 patients, in total 171 transfusion episodes. Most of the patients received platelets by each of the 4 different techniques. Patients with factors that may have influenced platelet recovery, such as infection, coagulopathy, platelet or HLA antibodies, were excluded. **Results:** The Baxter Colleague pump method was associated with the highest platelet increment at 1 h after transfusion ($p = 0.03$). This effect vanished after 24 h. The Gemini and Graseby pumps gave results similar to those of the gravity flow method. **Conclusion:** None of the different infusion pumps were inferior to the gravity flow method. Further studies to confirm these findings are warranted.

Introduction

Platelet transfusion is a common practice at the Launceston General Hospital (LGH) and in many centres in Australia and around the world. Platelets are administered either via a free-flowing gravity line or an electromechanical pump [1, 2]. There are few centres that employ an electromechanical pump for platelet transfusion as a routine practice [2, 3]. Although administration of platelets via a pump offers a well-controlled infusion rate, accurate volume measurements and an alarm system for monitoring the infusion, there are theoretical concerns regarding potential damage to the transfused platelets [4–7].

Three types of pumps are available on the haematology ward at the LGH that are used for both red cell and platelet transfusion: the Graseby 3000 (Watford, Herts, UK), the Imed Gemini PC-1 (San Diego, CA, USA), and the Baxter Colleague (Oklahoma City, OK, USA) pump.

In the paediatric population, it is important to reduce erratic infusion rates and inaccurate volume measurements to improve the quality of transfusion [4]. Medical staff recognize that the alarm systems associated with electromechanical infusion pumps provide quality of care in a timely fashion compared to the gravity infusion method. In addition, the alarm system decreases the number of times a member of the medical staff is required to monitor the infusion rate [8, 9]. In theory, platelets may be mechanically damaged or functionally altered, i.e. a quantitative and qualitative defect, through the use of electromechanical pumps due to the peristaltic movement resulting in possible injury or activation of the platelets.

However, up to now no data regarding the assessment of the effect on platelets through the different methods of transfusion have been available. In our trial we compared the effects of conventional gravity flow transfusion with those of these 3 commonly used electromechanical pumps on platelet recovery in an adult population, examining the platelet increment at 1 and 24 h after infusion. This study will help in assessing different techniques for administration of platelets in adult populations.

Material and Methods

Design Overview

We describe an open-labelled randomized study conducted between January 2007 and January 2011 at the LGH, a tertiary referral centre for Northern Tasmania, Australia. The study was approved by the Tasmania Health and Medical Human Research Ethics Committee (EC00337). The study was registered in the Australia and New Zealand clinical trial registry under ACTRN #12609000597291 (www.ANZCTR.org.au/ACTRN12609000597291.aspx), as well as in the World Health Organization (WHO) website under <http://apps.who.int/trialsearch/trial.aspx?trialid=ACTRN12609000597291>. Informed consent was obtained from all participating patients in accordance with the Code of Ethics.

The study was designed to evaluate the influence of electromechanical pumps compared to gravity flow on post-transfusion platelet increment. The 4 methods for platelet transfusion (free-flowing gravity line, and Graseby 3000, Gemini PC-1, and Baxter Colleague pumps) were assigned using a 4-pack randomization key chart. For patients who needed further platelet transfusions, a randomization for the remaining 3 methods took place each time a transfusion was required.

Objectives

The primary objective of this study was to evaluate the influence of the 3 different electromechanical pumps compared with gravity flow infusion on post-transfusion platelet increments at 1 and 24 h after the transfusion. The secondary objectives were to determine the most efficient procedure for the administration of platelets and to assess whether the method of transfusion plays a role in maintaining the quantity of the platelet increment.

Participants

At the LGH Haematology and Oncology ward, the treating team identified potential candidates with thrombocytopenia most likely secondary to the underlying haematological disorder or secondary to the treatment received. All candidates were ≥ 18 years of age. Informed consent was obtained prior to enrolment. Exclusion criteria included: infection or sepsis with a temperature $> 38.5^{\circ}\text{C}$, coagulopathy or disseminated intravascular coagulopathy (DIC), hypersplenism and platelet refractoriness, e.g. platelet antibody, human leucocyte antigen (HLA) antibody or immune thrombocytopenia. Furthermore, patients with any condition that might increase the consumption of platelets, such as infections, sepsis or DIC, were excluded from the trial. None of the oncology patients included in this trial required surgery or had bleeding. Patients with any condition that can cause platelet refractoriness such as immune-mediated thrombocytopenia (ITP), thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS) were also excluded from this trial.

In all, 35 patients were included in the study, and 171 episodes of platelet transfusion were examined. Most of the patients received multiple platelet transfusions. Platelet transfusion was indicated primarily for patients with a platelet count of less than 20/nl as a baseline.

Randomization

Following recruitment, a random allocation sequence was generated by the researcher using 4 cards each representing a different transfusion method as follows: 1, Baxter Colleague pump; 2, Gemini PC-1 pump; 3, Graseby 3000 pump; and 4, gravity flow. Based on this, a randomization key chart was prepared. Randomization was carried out by the nurse who was transfusing the platelets at the time. Participants were asked to select 1 card from the 4 offered to them and were thus assigned the transfusion method according to the randomization key chart. The patient was unable to see the randomization symbol. Once a card had been selected it was set aside, so subsequent transfusions for the same patient involved a selection of 1 of the remaining 3, and so on, to ensure an equal frequency of each of the different transfusion methods and minimize the effect of random selection of platelet transfusion method on the overall outcome.

Procedure and Platelet Increment Measurement

Patients enrolled into the study were assigned a unique identification (ID) number. Patients' registration forms were filed accordingly and saved in a password-protected folder. Clinical trial patient stickers were attached to the medical history by the researcher and the medical officer notified the Pathology Laboratory of the patient's enrolment in the study. To assure maximum safety and control, a laminated PLATTRANS Patient Participation Notification Chart was fixed above the patients' beds and Data Collection Forms were added to the patients' end-of-bed charts.

Platelets for transfusion were ordered by the Haematology/Oncology team from the Blood Bank, Pathology Laboratory, LGH. The platelet-increment counts at 1 and 24 h post transfusions were collected for all participants. The volume per unit, Rh type and platelets' age were documented on the PLATTRANS Data Collection Form for each patient.

All platelet units involved in the study were collected and transfused according to the policy and standard procedure of the LGH, using blood transfusion sets with a 170- to 200- μm filter. Platelet units were collected by nurses and transfused using the randomly assigned transfusion method, determined by the randomization method described above. The electromechanical pumps were set to deliver platelets over 20 min, while gravity flow lines were set with the roller clamp in the fully open position. The time required for platelets transfusion using gravity flow varies according to the intravenous (IV) line resistance. For instance, patients who have a central venous catheter tend to have the least resistance and fastest transfusion time compared to that for patients with a peripherally inserted central catheter (PICC); the longest transfusion time is observed when a peripheral cannula is used, especially if it is a small gauge cannula ($> 21\text{ G}$). The transfusion flow rate through a cannula may also vary according to the site of insertion (i.e. if the IV cannula is located over a joint, possible resistance may occur during binding the joint or moving the elbow or wrist joints).

Platelet increment measurements were performed twice on each blood sample, at 1 and 24 h after platelet transfusion, using a standard technique. Blood collection and sample handling were carried out according to the policy and procedure of the LGH using 4-ml EDTA vacutainers. Each blood sample was labelled with the patient's name and sent immediately to the National Association Testing Authority (NATA) accredited Pathology laboratory of the LGH. All blood samples were processed in 1 machine (Beckman Coulter 500, Brea, CA, USA). All blood samples were processed within 2 h of collection. If a patient in the trial required more than 1 platelet transfusion, for the second (and any subsequent) transfusion they were blindly randomized to a different method until all 4 methods were exhausted. If more platelet transfusion was required, the whole randomization procedure was restarted.

Sample Size Calculation

Since no data were available regarding the differences between the various blood transfusion methods studied, sample size calculations were made using the data from the first 100 platelet transfusion episodes.

These indicated the need for at least 168 platelet transfusion episodes to detect a minimum mean of 20% improvement in platelet count using 1 of the transfusion pumps compared to gravity transfusion (assuming a mean improvement in the gravity transfusion of 20/nl platelets, a standard deviation (SD) of change of 16.8, power 90% and alpha 0.05).

Statistical Methods

The 1- and 24-hour post-transfusion mean platelet counts of the patients at each separate visit were compared with the pre-transfusion counts. The differences between the changes using the different transfusion methods were estimated using a random-effects mixed methods linear regression with unstructured covariance corrected for repeated measures. As the assumptions of linear regression were found to have been violated (significant heteroskedasticity, skewness and kurtosis of residuals when using the Cameron and Trivedi's decomposition of IM test, and significant deviation from linearity of response using the Ramsey's rest test), p values were estimated using ordered logistic regression (a non-parametric equivalent of repeated measures ANOVA). All analyses were performed using Stata SE 11.1 (StataCorp, College Station, TX, USA).

Table 1. Description of demographic variables in patients receiving platelet transfusion

Gender ratio (male:female)	18:17
Mean age (range), years	59 (20–84)
Mean weight (range), kg	75.9 (55–104)
Diagnosis, number of patients	
Acute myeloid leukaemia	20
Acute lymphocytic leukaemia	2
Multiple myeloma	4
Aplastic anaemia	2
Malignant lymphoma	7

Results

Participants

For this trial, 35 patients were enrolled between January 2007 and January 2011 at the LGH (table 1). The male to female ratio was 18:17, the mean age was 59 years and the mean weight was 75.9 kg. For transfusion, the average platelet content per adult unit was 2.2×10^{11} . All units were quality controlled by the Red Cross, Australia. The age of platelets was 1–5 days after donation, with a median of 3 days.

The recruited patients received a total of 171 platelet transfusions. 45 transfusions were performed by gravity flow, 34 using a Gemini pump, 31 using a Graseby pump and 61 using a Baxter pump. Single-donor platelets as well as pooled platelets were used randomly, as determined by the availability of these blood products in the blood bank, without influence on the trial outcome. The average age of the platelets was 4 days and platelet unit volumes ranged from 180 to 300 ml. To explore the theoretical influence of the pumping action of the different mechanical pumps on the transfused platelets, we conducted an ex vivo platelet infusion testing all 4 methods used in the trial. A constant number of platelets were infused with each method in a closed bag system using the same infusion line set as used for patients. We measured platelet counts prior to and after each transfusion method using the same platelet unit 4 times (for each method) to ensure that any possible quantitative damaging effect on the platelets was recognised. The difference between pre- and post-infusion platelet readings for each infusion technique did not reveal any

Table 2. Improvement of platelet counts at 1 and 24 h after platelet transfusion using different infusion pumps or gravity flow

Transfusion technology	Time	N	Mean (SD) ¹	Mean Δ (SD) ²	Comparison of change			
					time	difference	95% CI	p value ³
Gravity	pre-Tx	45	14.6 (6.9)					
	post-Tx	45	36.4 (15.6)	21.8 (7.1)				
	24 h	43	24.4 (13.9)	9.8 (7.3)				
Gemini	pre-Tx	34	16.0 (5.8)					
	post-Tx	34	37.7 (12.1)	21.7 (6.8)	post-Tx vs. pre-Tx	–0.09	–6.09 to 5.90	>0.90, NS
	24 h	34	23.4 (10.3)	7.4 (6.9)	24 h vs. pre-	–2.44	–8.34 to 3.46	0.16, NS
Graseby	pre-Tx	31	15.4 (5.4)					
	post-Tx	31	35.8 (11.1)	20.4 (6.4)	post-Tx vs. pre-Tx	–1.38	–7.54 to 4.78	0.77, NS
	24 h	30	23.0 (11.9)	7.7 (6.4)	24 h vs. pre-Tx	–2.12	–8.24 to 3.99	0.50, NS
Baxter	pre-Tx	61	12.2 (7.6)					
	post-Tx	61	37.2 (13.1)	25.0 (6.5)	post-Tx vs. pre-Tx	3.22	–1.97 to 8.40	0.03
	24 h	61	22.3 (12.5)	10.1 (6.7)	24 h vs. pre-Tx	0.36	–4.76 to 5.48	0.25, NS

SD = standard deviation, Tx = platelet transfusion, NS = no significant difference between different methods and gravity method, CI = confidence interval.

¹Mean platelet count (SD).

²Mean change (Δ) (at each treatment) between pre- and post-treatment, between platelet counts before and 24 h after infusion, and differences between these mean changes between the different platelet transfusion technologies; estimates using repeated measures random effects mixed methods linear regression, adjusted for age, gender and initial platelet count. These values are shown for illustration only.

³The post-estimation checking of the assumptions of linear regression in the above mixed methods linear regression analysis demonstrated significant deviations, so p values were estimated using ordered logistic regression.

Fig. 1. Differences between mean baseline platelet counts and mean platelet counts after transfusion for different platelet transfusion methods.

significant alteration in the platelet counts for the different methods.

There were no statistically significant differences based on Rh or ABO group compatibility, age of platelets or patient weight among all the studied methods of transfusion.

Primary Outcome

For the patients, the mean platelet count before platelet transfusion was 14.0 (SD 6.8), which rose to 36.8 (SD 13.5; difference 22.8; 95% confidence interval (CI) 20.8–24.9; $p < 0.001$) 60 min after transfusion, and fell back to 22.6 (SD 11.6; difference 8.6; 95% CI 6.5–10.6; $p < 0.001$) 24 h after transfusion. At 60 min, the differences in counts using the Gemini and Graseby pumps were similar to those using gravity flow transfusion, but were about 15% higher when using the Baxter pump (table 2). At 24 h, the differences in counts were similar in all 4 methods (fig. 1). No severe adverse events occurred.

Discussion

While administration of platelets via a pump offers a well-controlled infusion rate, accurate volume measurement and an alarm system for monitoring the infusion, the effect of different pumping devices on the transfused platelets has not been investigated. In addition, no research has been conducted in adult populations comparing effects on platelet increments after transfusion using either conventional gravity flow or different pumps.

This study, for which strict exclusion and inclusion criterion were applied, investigated 171 episodes of platelet transfusion. The pumping action of the 3 devices used is very similar; each produces peristaltic movements by multiple mechanical compressions at a constant rate and speed on the plastic tube via which platelets are being transfused into the body. Using a simple comparison of the changes in platelet counts from that before the transfusion to that 24 h after transfusion confirmed that all studied methods demonstrate a similar platelet increment count after 24 h. However, there was a higher platelet increment at 1 h post platelet transfusion using the Baxter colleague electromechanical pump compared to the other methods ($p = 0.03$). The Gemini PC-1 and Graseby 3000 pumps showed similar results, which were not significantly different from those gained using the gravity method in terms of platelet increments at 1 h after transfusion. It is possible that the high variability of the absolute increments in our cohort of patients may have influenced the statistical significance associated with the Baxter pump for the 1-hour platelet increment findings. The difference favouring the Baxter method after 1 h of transfusion was not confirmed either in the ex vivo study that used a constant amount of platelets, or in the 24-hour platelet increment.

This study compared the outcome using the 3 electromechanical pumps to that using conventional gravity flow. While in theory the gravity flow method for platelet transfusion should be the least damaging for platelets, the electromechanical pumps showed very similar results. The outcome using the Baxter colleague electromechanical pump was almost identical to that of the free-flow method, with a superior re-

sult in the 1-hour platelet increment. Although the aim of this study was certainly not to promote any commercial product, since platelet transfusion via electromechanical pumps showed similar increments of the transfused platelets to those found using the conventional free-flow method with its high speed rate of transfusion in this adult population, their use is considered to be justifiable.

All the devices examined in our cohort of patients were volumetric peristaltic infusion pumps. The necessity for an accurate and rapid transfusion rate in some medical situations, particularly in the paediatric setting, dictates the need for highly efficient infusion pump devices. Although the electromechanical infusion pumps were designed originally for delivery of crystalloid solutions, and despite the fact that randomized trials exploring their possible effect(s) on viable blood cells are lacking, nowadays they are routinely used for different blood product transfusions [4, 8, 9]. There are no robust data in the literature on the effect of infusion pumps on different blood products; in addition, newer devices are constantly being developed and are entering the medical market. For most of these infusion pumps, it is not clear whether the use of these devices is associated with detrimental effects on platelets [8]. Therefore, our randomized trial also documents the effects of the different currently available infusion pumps on the platelets.

In summary, our study shows that the gravity flow method is efficient and easy to use. It requires no special training and no regular maintenance. Although a high speed rate of platelet transfusion was essential in our adult study group, the gravity flow method cannot be used in paediatric wards where a precise volume and an accurate rate are required. Therefore, electromechanical pumps, which can provide accurate

volume delivery, slower delivery speed and an automatic alarming system, are crucial in such departments. Moreover, there was wide variability in the time required for transfusion in the gravity method with an average transfusion rate of 60 min versus 20–30 min with the electromechanical pump methods.

In conclusion, none of the infusion pumps investigated was inferior to the gravity flow method, indicating that there is very little effect on the transfused platelets caused by the different electromechanical pumps. The Baxter colleague showed superior results in the first 60 min post transfusion for platelet counts compared to the gravity flow method ($p = 0.03$). However, this effect was not significant for platelet counts after 24 h. Furthermore, the free-flow gravity method seems to be an efficient method for platelet transfusion albeit it cannot provide an accurate control for perfusion rate when required.

Acknowledgements

The authors wish to thank the Head of Medicine Department, Dr. Alasdair MacDonald, and the CEO, Mr. John Kirwan, of the Launceston General Hospital for their support in enabling this trial to be conducted. Statistical support was funded by the Clifford Craig Medical Research Trust, Launceston, Tasmania, Australia. The authors acknowledge the enormous help of all nursing staff of the Oncology Ward (Ward 5D), the Launceston General Hospital, Tasmania, Australia.

Disclosure Statement

The authors declare no conflict of interest in relation to this research.

References

- 1 National Health and Medical Research Council and Australasian Society of Blood Transfusion: Clinical Practice Guidelines on the Use of Blood Components. Commonwealth of Australia 2002; 2.2, 11–12.
- 2 Blumberg N, Heal JM, Phillips GL: Platelet transfusions: Trigger, dose, benefits, and risks. *F1000 Med Rep* 2010;2:5.
- 3 Slichter SJ: Platelet transfusion therapy. *Hematol Oncol Clin North Am* 2007;21:697–729.
- 4 Norville R, Hinds P, Wilimas J, Fairclough D, Fischl S, Kunkel K: The effect of transfusion methods on platelet count, morphology and corrected count increment in children with cancer: in vitro and in vivo studies. *Oncol Nurs Forum* 1994;21:1669–1673.
- 5 Norville R, Hinds P, Wilimas J, Fischl S, Kunkel K, Fairclough D: The effects of infusion rate on platelet outcomes and patient responses in children with cancer: An in vitro and in vivo study. *Oncol Nurs Forum* 1997;24:1789–1793.
- 6 Snyder EL, Rinder HM, Napychank P: In vitro and in vivo evaluation of platelet transfusions administered through an electromechanical infusion pump. *Am J Clin Pathol* 1990;94:77–80.
- 7 Snyder EL, Ferri PM, Smith EO, Ezeowicz MD: Use of an electromechanical infusion pump for platelet concentrates. *Transfusion* 1984;24:524–527.
- 8 Lieshout-Krikke RW, van der Meer PF, Koopman MM, de Korte D: Effect on the quality of blood components after simulated blood transfusions using volumetric infusion pumps. *Transfusion* 2011;51:1835–1839.
- 9 Frey B, Eber S, Weiss M: Changes in red blood cell integrity related to infusion pumps: A comparison of 3 different pump mechanisms. *Pediatr Crit Care Med* 2003;4:465–470.