

plexus blocks with bupivacaine with and without epinephrine, of which 742 (49%) were administered with 250–300 mg of bupivacaine. Of the 5,593 intercostal nerve blocks done with bupivacaine with and without epinephrine, 4,042 (72%) were done with 250–400 mg. While following such blocks with over 300 mg, five patients had systemic toxic reactions (four convulsions, one cardiac arrest), no sequelae resulted. Therefore, bupivacaine 250–400 mg for a regional block, as used in this report, has proven in our hands to be a reasonable dose.

To conclude, hyperkalemia appears not to contraindicate the use of bupivacaine, and succinylcholine can be used to terminate bupivacaine-induced convulsions without the fear that hyperkalemia may result, which could enhance the cardiotoxicity of bupivacaine.

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## Changes in Serial Platelet Counts Following Massive Blood Transfusion in Pediatric Patients

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Massive blood transfusion, defined as the transfusion of one or more blood volumes, commonly occurs in children undergoing major orthopedic, tumor, or burn wound surgery. One of the many problems associated with massive blood loss is dilutional thrombocytopenia.<sup>1–7</sup> Several studies have addressed this issue in the adult population, but none has examined this problem in children. We therefore undertook a prospective analysis of serial platelet counts during surgical procedures involving extensive blood loss and correlated the changes

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in serial platelet counts with blood volumes transfused and signs of clinical bleeding.

### METHODS

This study was approved by the Subcommittee on Human Studies at Massachusetts General Hospital (MGH). Pediatric patients at both MGH and Shriners Burns Institute (SBI) who were to undergo major surgical procedures were candidates for study. The anesthetic technique, anesthetic agents, monitoring, and blood product management were left to the discretion of the anesthetizing team. The estimated blood volume (EBV) was assumed to be 75 ml/kg for all children younger than 1 year of age and for all burned children; all others were assumed to have an EBV of 70 ml/kg.<sup>8,9</sup> Attempts were made to maintain a constant blood volume as judged by urine output, central venous pressure, and contour of the arterial wave form. Coagulation profiles, including a platelet count (laser beam ELT-800),§ prothrombin time (PT),¶ and partial thromboplastin time (PTT),¶ were obtained at the beginning of anesthesia and during the surgical procedure after transfusion of blood products equivalent to 1, 2, 3, 4, or 5 blood

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§ Ortho Diagnostics.

¶ Optical densitometry General Diagnostics X-2.

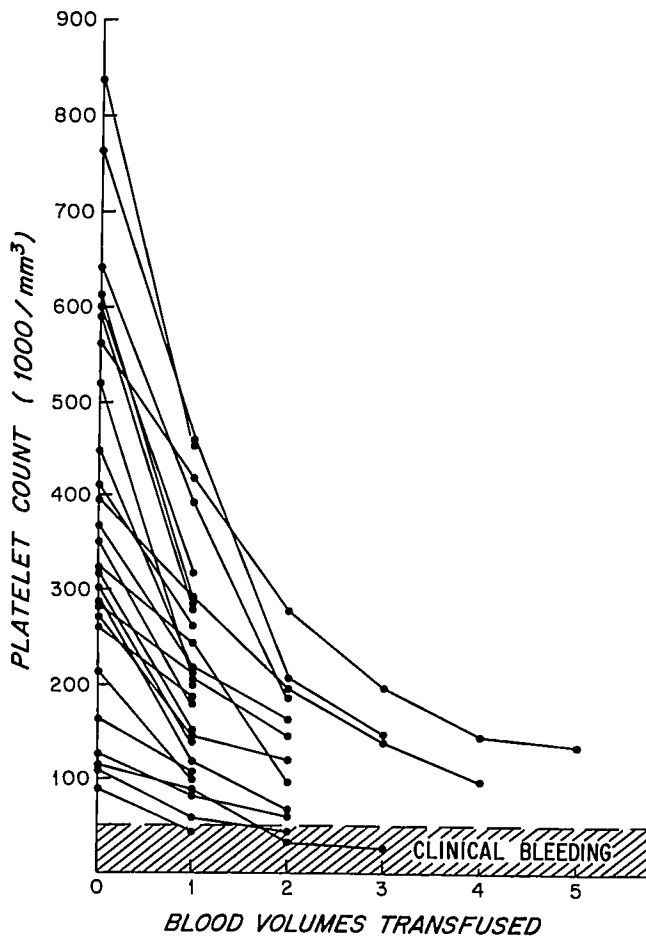


FIG. 1. Serial changes in platelet count *versus* blood volumes transfused in 26 pediatric patients. Note how two patients with a high initial platelet count still had adequate circulating platelets despite blood losses of four or five blood volumes. Three patients who started out with low platelet counts developed thrombocytopenia and clinical bleeding after one or two blood volume losses.

volumes. Transfusions consisted of citrated packed red blood cells (PRBC), frozen PRBC, fresh frozen plasma, 5% albumin, and lactated Ringer's solution as indicated. Fresh frozen plasma was administered in sufficient quantity so as to maintain normal PT and PTT. When lactated Ringer's was used for volume replacement, a volume of 3 ml was assumed to be equivalent to 1 ml whole blood.<sup>10,11</sup> Although it is impossible to be unbiased, patients were observed for clinical signs of coagulopathy such as abnormal bleeding or oozing; when *both* the attending anesthesiologist and surgeon agreed that there was abnormal bleeding, notation was made of this fact and repeat coagulation profiles obtained. Abnormal bleeding is defined as generalized oozing from multiple areas that did not respond to packing, pressure, or electrocoagulation. At no time did any of the patients studied demonstrate hypoxia, acidosis, or hypovolemic hypotension. Data for serial platelet counts were com-

pared with several formulas for exchange transfusion.<sup>2,12</sup> The method to calculate theoretic platelet counts uses an exponential decay curve given by the formula

$$(\text{platelet})_{\text{BV}} = (\text{platelet})_0 e^{-\text{BV}},$$

where BV denotes blood volumes lost, 0 denotes baseline, and  $e = 2.719 \dots$ , the base of the natural logarithms. Data are expressed as the mean  $\pm$  SEM.

## RESULTS

Twenty-six pediatric patients were studied; the mean age was  $5.9 \pm 1.1$  yr (range 1.0–17.0 yr) and the mean weight was  $25.3 \pm 3.8$  kg (range 10–70 kg). Seventeen underwent burn wound excision and grafting, six Harrington rod instrumentation, one Wilm's tumor excision, one neuroblastoma resection, and one radical pancreatoduodenectomy (Whipple procedure) for congenital pancreatic duct obstruction. All patients lost at least one blood volume, 12 lost two, four lost three, two lost four, and one lost five blood volumes.

Figure 1 plots the observed changes in platelet counts, which have an inverse relationship with blood volumes transfused. Calculations of standard washout curves for changes in serial platelet counts would result in much lower counts than those observed. Seven children received platelet transfusions of 0.3 ( $n = 6$ ) to 0.8 ( $n = 1$ ) units/kg. Three received platelets because their platelet count had fallen to a nadir of 64,000, 142,000, and 100,000/ $\text{mm}^3$ , and, by nature of the surgery, considerably more blood loss was anticipated; none of these patients developed signs of abnormal bleeding. Two of these were burn patients and one was not. Four patients did develop signs of abnormal bleeding; these children had platelet counts of 92,000, 46,000, 46,000, and 34,000/ $\text{mm}^3$ . Each had a normal PT and PTT. The child with the platelet count of 92,000/ $\text{mm}^3$  had a rolled blanket compressing the abdominal cavity; when this blanket roll was removed, the "abnormal" bleeding stopped, although platelets subsequently were administered. Each of the remaining patients with signs of abnormal bleeding also received platelets; all three were burn victims. One of these received 0.8 units of platelets/kg, while the other two received 0.3 units/kg. The platelet counts increased by 82,000, 14,000, and 5,000/ $\text{mm}^3$ ; the latter patient still had a total platelet count of 39,000/ $\text{mm}^3$  2 hs later but no evidence of abnormal bleeding. The abnormal bleeding in these patients stopped immediately after they received platelets.

The seven patients who received platelets had changes in platelet count at 1 h after transfusion, ranging from +82,000/ $\text{mm}^3$  to -20,000/ $\text{mm}^3$  in a patient with ongoing blood loss. There were no intraoperative or postoperative complications due to blood product transfusions. The PT and PTT were measured 38 times at

intervals coinciding with one or more blood volumes transfused. Six of 38 PTs were prolonged by  $>2.0$  s, while seven of 38 PTTs were  $>38$  s. There was no evidence of abnormal bleeding at any point where these abnormalities existed. The liberal use of FFP accounts in part for the majority of these clotting studies being normal.

### DISCUSSION

Dilutional thrombocytopenia commonly causes abnormal coagulation during massive blood transfusion.<sup>1-6</sup> Studies of adults have attempted to correlate the change in platelet count with units of blood transfused; these studies fail to account for the patient's blood volume.<sup>1,3</sup> In an infant, one unit of blood may represent the entire blood volume or a large fraction of it. Patient *blood volumes transfused* seems more pertinent than units of blood transfused.<sup>12</sup> We examined the changes in serial platelet counts' relation to blood volumes transfused. Coagulopathy due to dilution of platelets reportedly occurs when the platelet count decreases to less than  $60-100,000/\text{mm}^3$ .<sup>1-7,13-15</sup> In our study of 26 pediatric patients, we found three children with platelet counts less than  $50,000$ ; each demonstrated signs of abnormal bleeding. Three other children with platelet counts of  $64,000$ ,  $62,000$ , and  $100,000/\text{mm}^3$  did not show signs of abnormal bleeding. It would thus appear that an acute decrease in platelet count to less than  $100,000/\text{mm}^3$  should alert the patient care team to anticipate possible coagulopathy and a decrease to less than  $50,000/\text{mm}^3$  often requires exogenous platelet replacement. Although it is difficult to remove the biases of the surgeons and anesthesiologists from our study, the formation of blood clots in the surgical field usually settled any discussion.

The decrease in platelet counts that we observed closely parallels that found by Miller *et al.*<sup>2</sup> in Vietnam War combat casualties (fig. 2). Both studies found the decrease in platelet counts to be less than predicted by standard washout formulae, therefore suggesting that mobilization of platelets is occurring simultaneously with dilutional losses. We used percent decrease in platelet count as a means of comparison rather than actual decrease in platelet count because our patient population had such a large range in baseline values ( $89-838,000/\text{mm}^3$ ), whereas Miller's population was more homogeneous. In that study there was a poor correlation between abnormal PT and PTT *versus* abnormal bleeding. Counts *et al.* more recently examined their experience with 27 adult trauma patients who received large volumes of modified whole blood (cryoprecipitate and platelets removed).<sup>3</sup> They found a high correlation between abnormal bleeding and a platelet count less than  $100,000/$

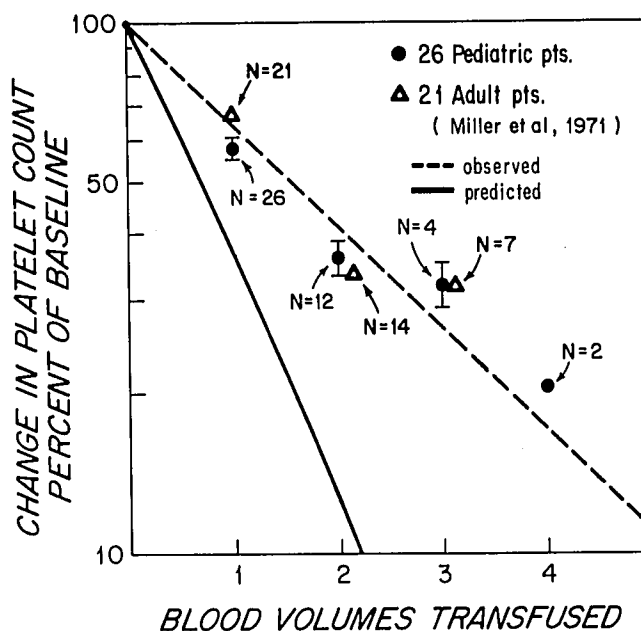


FIG. 2. This figure compares the data from our study of pediatric patients with a study of adult Vietnam War trauma victims.<sup>2</sup> The broken line represents the observed changes; the solid line represents the expected changes. If we assume in the adult study that 10 units (5 l) of whole blood is equivalent to one blood volume and plot the percent change from baseline, the adult values closely agree with those we found in pediatric patients. The changes in platelet concentration during massive blood transfusion are similar in pediatric and adult patients when all data are correlated with estimated *blood volumes transfused* (see text).

$\text{mm}^3$  (7/8) but a poor correlation between abnormal bleeding and a prolonged bleeding time or abnormal PT and PTT. Our findings are consistent with both of these studies, since the children with low platelet counts and signs of abnormal bleeding had both a normal PT and PTT.

All of the patients we studied had apparently "normal" coagulation prior to operation, as demonstrated by normal PT and PTT, as well as the absence of clinical signs of platelet dysfunction, such as bruising or oozing from venipuncture sites. The bleeding time was normal in the seven patients in whom it was tested. The burned children represent a unique population of patients because, unlike the orthopedic and tumor excision cases, these patients had severe systemic disease related to their burn injury. Many burned patients (9/17) started with a high platelet count (greater than  $350,000/\text{mm}^3$ ), which is common for patients 7-10 days after burn injury.<sup>16</sup> None of the burned or other patients who started with a platelet count over  $150,000/\text{mm}^3$  developed signs of clinical bleeding, despite blood losses of one or more blood volumes. The three patients who did develop signs of abnormal bleeding were burn victims with low baseline platelet counts ( $107,000$ ,

105,000, 89,000/mm<sup>3</sup>). Two of these patients developed coagulopathy after a two blood volume loss and the third after one blood volume had been lost. Thus, it appears that despite severe systemic disease and low initial platelet counts, these children did have normally functioning platelets until the blood replacement became so extensive that the platelet counts decreased to 33,000, 46,000, and 46,000/mm<sup>3</sup>, respectively, and abnormal bleeding developed. We did not observe any patients with signs of abnormal bleeding who had platelet counts greater than 100,000/mm<sup>3</sup>, despite extensive blood transfusions; this is in contrast to some studies of adult patients that suggest that thrombocytopenia, *i.e.*, intrinsic platelet dysfunction, will develop in all patients sustaining massive transfusion.<sup>3,5</sup> The transfusion of 0.8 units/kg in one patient was excessive; however, the observed increments in platelet counts following platelet transfusions of 0.3 units/kg in five of six patients were far below those calculated according to the formula from the American Association of Blood Banks.<sup>17</sup> This suggests rapid utilization at a time of maximal platelet need, since further blood loss could not have resulted in the changes observed. Abnormal bleeding stopped in two patients after platelet transfusions, despite a platelet count of 50,000/mm<sup>3</sup> or less. Thus, careful observation of the patient and surgical field are also important guides to the adequacy of platelet transfusion therapy. The dose of 0.3 units/kg is three times higher than those generally recommended for the treatment of adults (1 unit/10 kg); however, higher doses are recommended for the first transfusion during a bleeding episode.<sup>18</sup> This dose was appropriate for these patients.

A plan regarding platelet use must be formulated prior to an elective surgical procedure that may involve massive blood loss. The most obvious and perhaps the most important observation of our study is that most patients who start with a high platelet count may not require exogenous platelet transfusion until many blood volumes have been lost, whereas the patient who starts with a low platelet count may require exogenous platelets after just one blood volume loss. We think that a preoperative platelet count provides a reliable prediction of the patient's probable platelet requirements that cannot be achieved with a blood smear that merely describes a crude estimate of platelet concentration.

In summary, this clinical study observed the changes in serial platelet counts in children undergoing extensive surgical procedures. We found that the decrease in platelet count when related to blood volumes transfused was nearly identical to similar studies in adults. A baseline platelet count proved to be a reliable predictor of possible platelet transfusion needs; a patient with a low initial platelet count (less than 150,000/mm<sup>3</sup>) may require exogenous platelets after only one blood volume

loss; however, patients with normal or above-normal counts and normal platelet function may not require exogenous platelet therapy until more than two blood volumes have been lost. We observed no difference in platelet concentration changes between burned and unburned children. Prophylactic platelet transfusions should be considered only when the platelet count has decreased to less than 100,000/mm<sup>3</sup> and considerably more bleeding is anticipated. If abnormal bleeding occurs with a platelet count of more than 50,000/mm<sup>3</sup>, other causes of bleeding, such as mechanical factors, disseminated intravascular coagulopathy, or dilution of the clotting factors, must be sought; 0.3 units of platelets/kg appears to be adequate initial therapy.

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## Hypothermic Cardiopulmonary Bypass and Neuromuscular Blockade by Pancuronium and Vecuronium

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In patients undergoing coronary artery bypass grafting, vecuronium has fewer cardiovascular effects than pancuronium.<sup>1</sup> Yet, the impact of hypothermic cardiopulmonary bypass on the neuromuscular blocking effect of vecuronium has not been investigated. We therefore compared the response of pancuronium- and vecuronium-induced neuromuscular blockades during hypothermic cardiopulmonary bypass.

### MATERIALS AND METHODS

Twenty patients, ASA classes III and IV, undergoing open heart surgery under nitrous oxide-narcotic anesthesia gave informed consent to participate in this study. They were assigned randomly to receive either pancuronium or vecuronium. Patients with evidence of neuromuscular, kidney, or liver disease or under medication known to affect neuromuscular transmission were excluded from the study. All patients received triflupromazine 0.15 mg·kg<sup>-1</sup>, meperidine 0.7 mg·kg<sup>-1</sup>, and atropine 0.007 mg·kg<sup>-1</sup> im 45 min before induction of anesthesia, which was with triflunitrazepam 1-2 mg and fentanyl 0.5-1.0 mg iv. After topical application of local

anesthesia, the trachea was intubated without the aid of a muscle relaxant. Anesthesia was maintained with 50% nitrous oxide in oxygen, fentanyl 0.01-0.02 mg·kg<sup>-1</sup>·h<sup>-1</sup> and controlled ventilation. Monitoring included continuous intraarterial and central venous blood pressure, arterial blood gas analysis every 15 min, and serum electrolytes before induction of anesthesia, after cessation of bypass, and at the end of surgery. Temperature was monitored by a nasopharyngeal, rectal, and skin probe at the right thenar. The pump was primed with lactated Ringer's solution 500 ml, oxypolygelatin 500 ml, and heparinized blood 500 ml. The pump rate was 55 ml·kg<sup>-1</sup>·h<sup>-1</sup> (table 1). Neuromuscular transmission was monitored with the evoked compound electromyogram (EMG) of the right thenar in response to supramaximal trains of four stimuli every 15 s (pulse width 0.1 ms) delivered to the ulnar nerve at the wrist. The EMG action potentials were measured from peak to peak, and their changes were related to nasopharyngeal temperature. The electromyograph used in this study was a modification of a device described by Lee *et al.*<sup>2</sup>

After obtaining a stable baseline and after at least 30 min following induction of anesthesia, Group 1 received 0.075 mg·kg<sup>-1</sup> of pancuronium and Group 2 received the same dose of vecuronium. Maintenance doses of 0.015 mg·kg<sup>-1</sup> of either drug were injected into an internal jugular catheter, whenever the size of the EMG action potentials had recovered 25% of control. No antagonists to neuromuscular blockade were administered. The time from end of injection of the loading and the maintenance doses to recovery of 25% of control neuromuscular transmission are referred to as DUR<sub>L</sub>25 and DUR<sub>M</sub>25, respectively. All numbers are expressed as means and standard deviations. Student's *t* test was used to assess statistical significance.

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