

Clinical Evaluation of the Hemotec Heparin Dose Response Cartridge

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Abstract

The intent of this study is to evaluate the ability of the Hemotec System Four to provide an accurate predictor of heparin requirements for patients undergoing cardiopulmonary bypass (CPB). The study group consisted of 27 consecutive patients undergoing CPB. Patient charts were reviewed for preoperative use of heparin or IV nitroglycerin therapy. Blood samples were drawn prior to induction of anesthesia and an Activated Clotting Time (ACT) obtained from a Hemochron 400 along with the heparin maintenance level (HML) in units/Kg and slope in sec/mg/kg obtained from the Hemotec System Four. Following heparinization of the patient at 300 units/kg an ACT was performed prior to initiation of CPB and additional heparin given if the value failed to reach at least 480 seconds. The amount of heparin (AHL) needed to reach an ACT of 480 seconds was calculated from a dose response curve utilizing the final heparin dose, the initial ACT, and the final ACT. The correlation of the HML and the AHL was .547. The correlation of the slope value to AHL was -.596. The level of false negative responses obtained from the HML or the slope value were not significantly different from the levels achieved from use of pre-operative heparin or IV nitroglycerin therapy as an indicator of heparin resistance. The heparin dose response system did not improve our ability to predict the individual patients heparin requirements.

Introduction

A significant portion of the patients presenting for cardiac surgical procedures involving the use of cardiopulmonary bypass (CPB) exhibit a heparin resistance manifested by a small increase in Activated Clotting Time (ACT) values with a standard loading dose of heparin. Heparin resistance can cause excessive time delays in initiating CPB in routine situations and can endanger the patient in emergent cases. Review of current literature brings forth pre-operative heparin therapy, pre-operative intravenous nitroglycerin therapy, thrombocytosis, and antithrombin III deficiencies as suggested indicators of heparin resistance (1, 2, 3). The Hemotec corporation produces the System Four (a) that in conjunction with the Heparin Dose

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Response (HDR) cartridge (a) provides a heparin level in units per kilogram (u/kg) and acts as a qualitative screen for patients with a heparin resistance. The HDR cartridge is a four chambered disposable cartridge with two chambers containing an equivalent, known concentration of heparin and an activator and two chambers containing the activator alone. An equivalent volume of the patients blood is introduced into each chamber of the cartridge and the cartridge placed in the System Four. Upon activation of the System Four, the blood, activator, and heparin are thoroughly mixed by air bubbling through the chamber. The occurrence of coagulation is detected by a photometric system. The System Four then calculates a heparin maintenance level (HML) in u/kg to reach an operator adjustable target time and a slope in seconds per milligram per kilogram (sec/mg/kg) based upon the difference in the ACT between the heparinized and the nonheparinized chambers. Hemotec suggests that the HML may be used to calculate the loading dose of heparin by multiplying the HML in u/kg by the patients body weight. Hemotec suggests administration of the institution's standard dose of heparin unless the maintenance level exceeds it, in which case, the dosage calculated from the maintenance level should be used. Hemotec also suggests that a slope of less than 132 sec/mg/Kg or an HML of more than 300 is indicative of heparin resistance. The intent of this study is to determine if the Hemotec HDR system is capable of predicting the heparin level needed for an adequate ACT value for CPB and the accuracy of the HDR as a qualitative predictor for patients with a heparin resistance as compared to pre-operative heparin or intravenous nitroglycerin therapy.

Materials and Methods

The study group consisted of 27 consecutive patients undergoing surgery involving the use of cardiopulmonary bypass. The patient chart was reviewed for pre-operative weight, use of intravenous nitroglycerin, or heparin within twenty four hours prior to surgery. Prior to induction of anesthesia, a seven milliliter (ml) blood sample was drawn from the arterial line after ten mls. of waste were removed. Two mls. of blood were introduced into a prewarmed (37°C) Hemochron tube (CA 510) (b) which was gently tipped upside down and

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- a. Hemotec Inc., Englewood, CO 80112
 - b. International Technidyne, Edison, NJ 08820

back 10 times. The timer of the Hemochron Four Hundred (b) was started as the blood was introduced into the tube and the tube placed in the Hemochron after thorough mixing. The baseline ACT value was recorded. The remaining sample was introduced into a room temperature Hemotec HDR cartridge (302-20) (a). A 0.8 ml sample was injected into each of the four chambers beginning with the far right chamber and moving to the left. A Tridack pipettor was used to assure the accuracy of the volume introduced into the chambers. The test cartridge was then inserted into the test block of a Hemotec System Four and the system actuated by pulling the cover down. The target time of the Hemotec System Four was set at 480 seconds and the values of the baseline clotting time, the slope, clotting times for each of the individual channels, and the heparin maintenance level were recorded. The patients were anesthetized and prepared for surgery in the usual manner. Prior to cannulation the patients were heparinized with 300 units of porcine heparin, or the dose recommended by the maintenance level from the System Four which ever was larger. An ACT was drawn from the arterial line five minutes after the heparin administration with a 10 ml waste being drawn previous to the sample. Two mls. of blood from the sample were introduced into a prewarmed Hemochron ACT tube (CA510) and the timer of the Hemochron 400 started. The sample was turned upside down and back 10 times to mix the activator with the blood and the tube placed in the test well and turned until the magnet was detected. The value of the ACT was recorded and additional heparin given if the ACT fell below the 480 second target time. In those patients requiring additional heparin, a second ACT was performed to document the effect of the additional heparin.

The final pre-bypass dose of heparin in units was divided by the extension of the ACT in seconds to calculate a value for the number of units per second increase in the ACT. This value was then divided by the kilogram body weight of the patient to yield a value for units per second of ACT elevation per kilogram of patient body weight. Following the concepts of Bull (4) a value for the dosage of heparin (units/kg) needed to reach an ACT of 480 seconds was calculated. The correlation for the relationship between the units per kilogram body weight needed to reach 480 seconds and the maintenance level and the slope provided by the Hemotec System Four was calculated. The chi-squared test was used to evaluate the significance of differences in the true positive and false negative responses of each of the indicators.

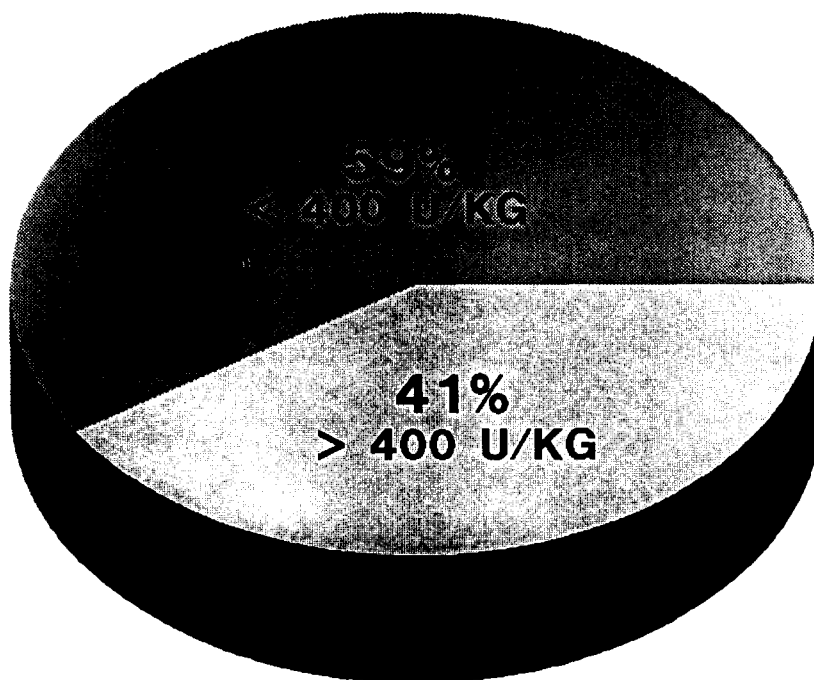
Results

Forty one percent (11/27) of the patients failed to reach an ACT of 480 seconds at a 400 units/kg dose (Graph 1). Thirty three percent (9/27) of the patients received heparin therapy and 37% (10/27) received intravenous nitroglycerin therapy within 24 hours prior to surgery. The maintenance level indicated by the Hepcon System Four was below 300 u/kg for 81% (22/27), 300 u/kg for four percent (1/27), and above 300 u/kg for 15% (4/27). The slope provided by the Hepcon System showed 82% (22/27) of the patients to have a slope above 132 sec/mg/kg body weight and 19% (5/27) of the patients to have a slope below 132 sec/mg/kg (Graph 2). Sixty percent (6/10) of the patients on intravenous nitroglycerin therapy prior to surgery required more than 400 u/kg. to reach 480 seconds. Forty four percent (4/9) of the patients on heparin therapy prior to surgery

required more than 400 u/kg to reach a 480 ACT value. Eighty percent (4/5) of the patients with a slope of less than 132 sec/mg/kg required more than 400 u/kg to reach a 480 second ACT value. Seventy five percent (3/4) of the patients with a HML above 300 u/kg required more than 400 u/kg to reach a 480 second ACT value (Graph 3). Twenty nine percent (5/12) of the patients not receiving intravenous nitroglycerin therapy required more than 400 u/kg to reach an ACT value of 480

GRAPH 1

HEPARIN LEVEL TO REACH ACT > 480 SECONDS



seconds. Thirty eight percent (7/18) of the patients not receiving heparin therapy prior to surgery required greater than 400 units per kilogram to obtain an ACT value of 480 seconds. Thirty two percent (7/15) of the patients with a slope above 132 sec/mg/kg required greater than 400 units per kilogram to reach a 480 second ACT value. Thirty two percent (7/15) of the patients with a maintenance level of less than 300 units/kg required more than 400 units/kg (Graph 4). The correlation of the slope value in seconds/mg/kg to the value of the units/kg to attain an ACT value of 480 seconds was a $-.596$ (Graph 5). The correlation of the maintenance level in units/kg to the value of the units/kg to attain an ACT value of 480 seconds was $+.547$ (Graph 6).

Discussion

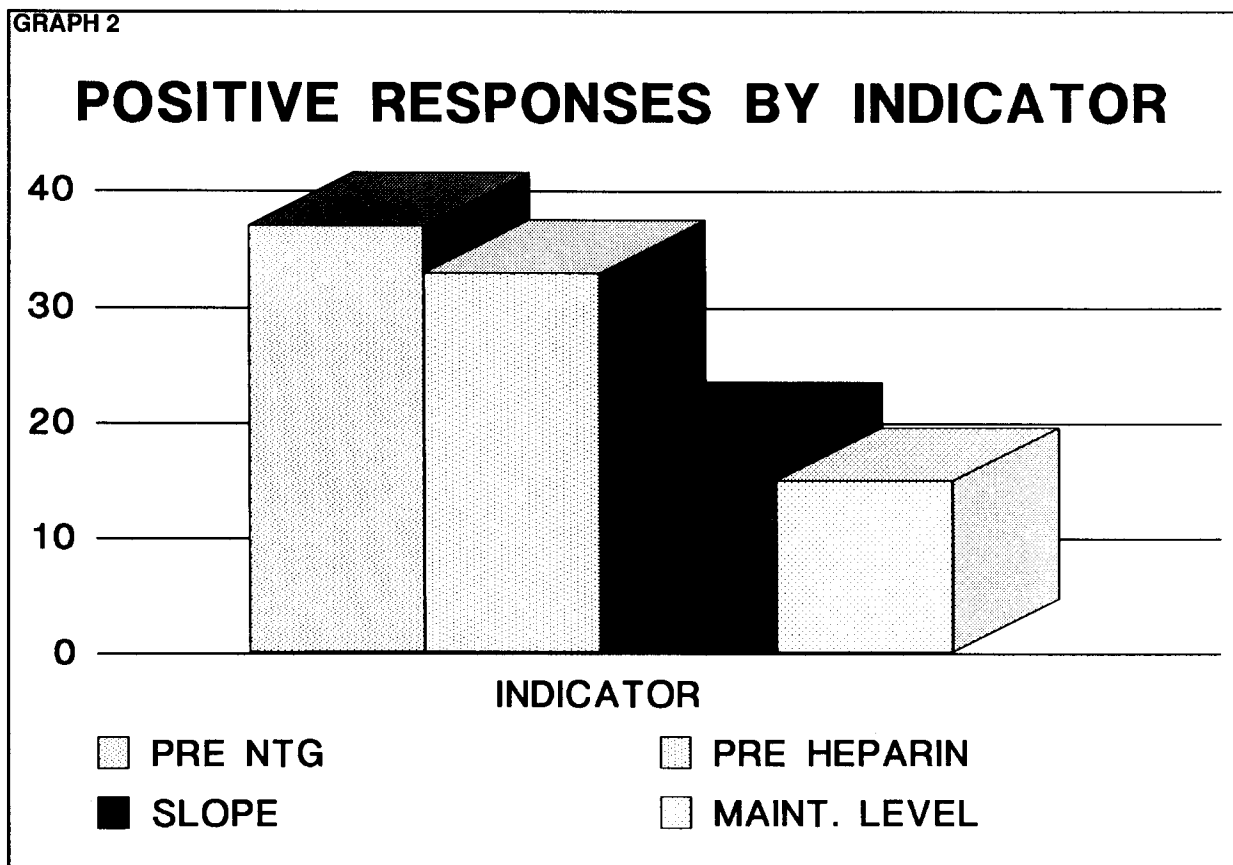
Forty one percent of the 27 patients included in this study failed to reach 480 second ACT level with a 400 unit/kg dose. To predict which patients would require an increased heparin dose, prior to the point of full heparinization, would be a true asset increasing patient safety and eliminating time delays at a critical point in surgeries requiring the use of cardiopulmonary bypass systems. The Hepcon System Four, utilizing the Heparin Dose Response cartridge provides a calculated heparin dose in units/kg and a slope value for use in predicting a proper dosage and as screen for heparin resistance. Neither the slope value ($r = -.596$) nor the maintenance value ($r = .547$) exhibited a strong correlation to the units/kg dose required to reach an ACT value of 480 seconds. Hence, these values are of little use for quantifying the level of heparin required to achieve adequate

anticoagulation. The large variation in heparin potency previously reported may contribute to the inability of this test to predict the proper loading dose for a particular patient (5). The slope and maintenance level provided significantly better ($p < .001$) results in the true positive category as compared to either the pre-heparin or pre-nitroglycerin indicators. However, the HDR (slope and maintenance level) did not provide a statistically significant ($p < .05$) difference in the number of false negative responses. Since the patients in the false negative category (predicted as normal, but requiring a greater than normal heparin dose) are at greatest risk for injury, that category tends to discount the worth of the HDR in identifying heparin resistant patients.

The Hemotec System Four, in conjunction with the HDR cartridge, was unable to accurately calculate heparin loading doses or significantly improve our ability to predict heparin resistance in patients anticoagulated with porcine heparin and monitored with the Hemochron ACT system.

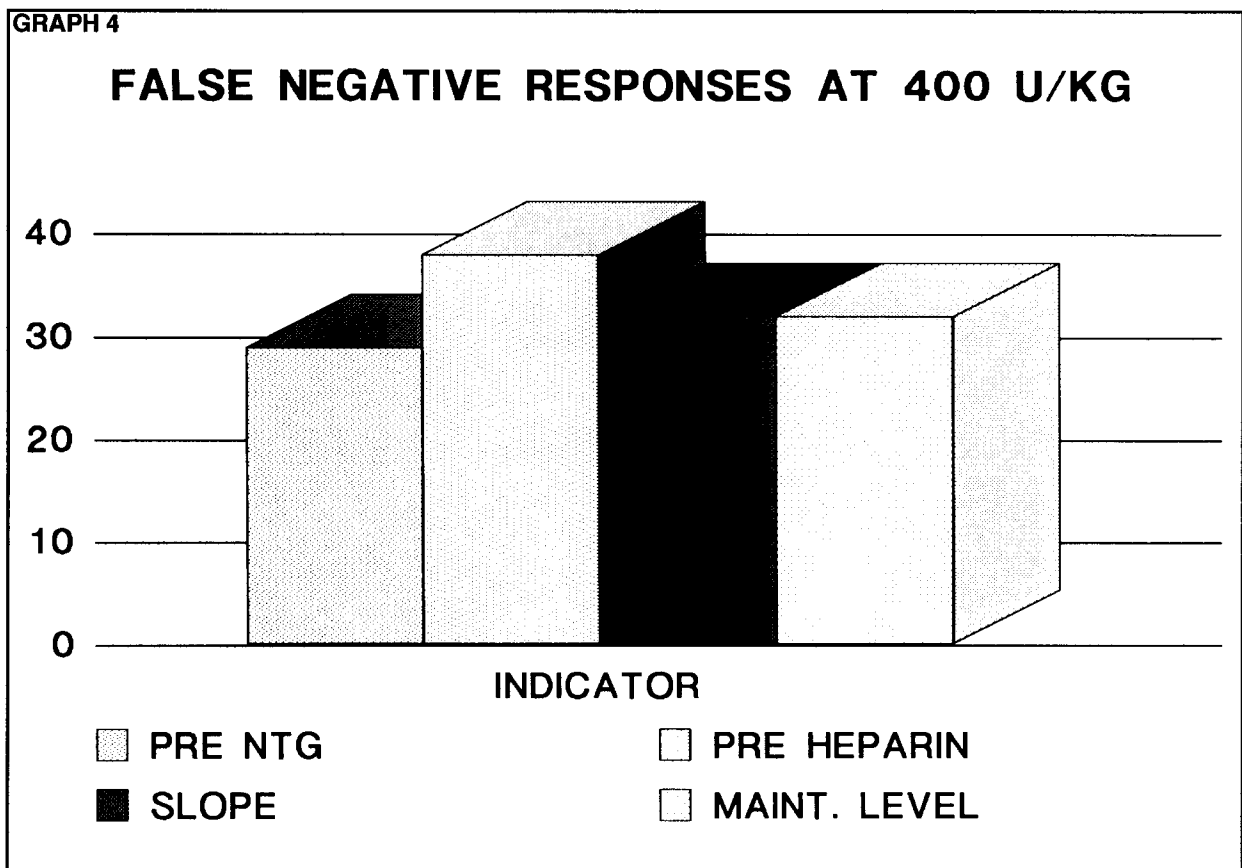
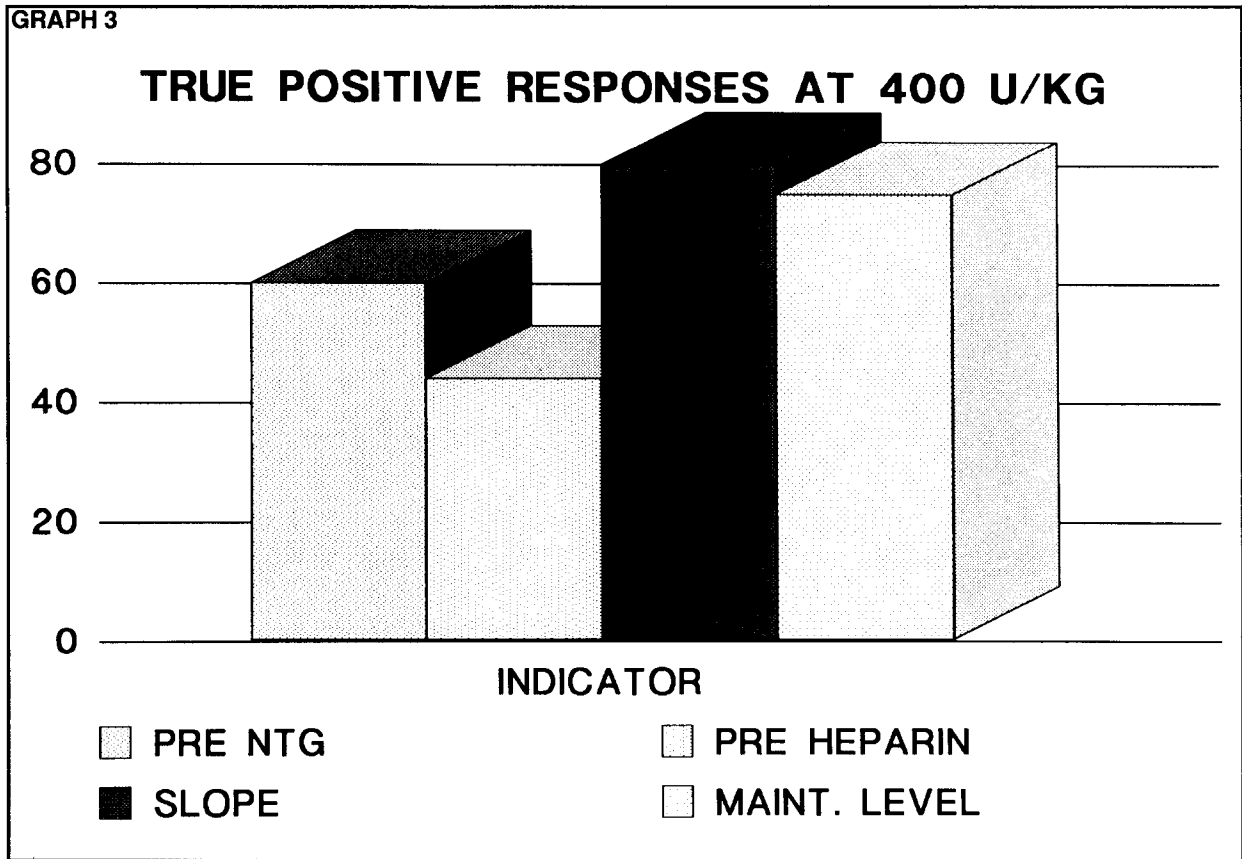
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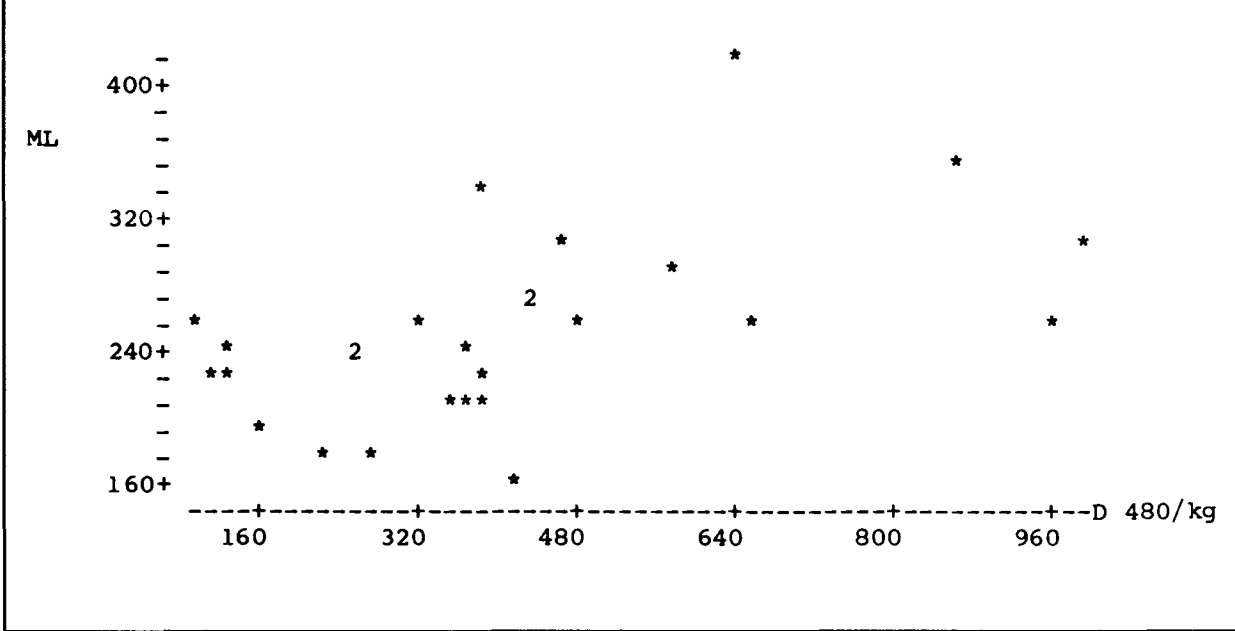


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GRAPH 5



GRAPH 6

