Original Article

Heparin Dose Response in Pediatric Cardiopulmonary Bypass

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Recipient of the Fellowship Award as the outstanding scientific presentation at the 32nd Annual International Conference of the American Society of Extra-Corporeal Technology, Anaheim, California, April 8-11, 1994

Keywords: cardiopulmonary bypass, heparin, heparin dose response, pediatric

ABSTRACT

Heparin dosing for cardiopulmonary bypass is frequently based on empirical loading doses. Most cite this heparin loading dose as 3 mg/kg (300 units/kg) for both adults and pediatric patients. The purpose of this study was to retrospectively evaluate the heparin dose response (HDR) in a pediatric population.

The HDR of 268 pediatric patients presenting for repair of congenital heart defects at Children's Hospital, Columbus, Ohio, was gathered retrospectively from May 1992 to October 1993. The HDR was gathered for the entire population and divided into four groups based on patient weight: Group I ≤ 5.0 kg; Group II 5.1 to 10.0 kg; Group III 10.1 to 20.0 kg; Group IV > 20 kg.

The HDR is reported as mean (SD, range) in mg/kg. For the entire population (n = 268) the HDR was 3.5 mg/kg (1.20, 1.0 to 7.3). For patients > 20 kg (group IV, n = 58) the HDR was 3.0 mg/kg (0.8, 1.0 to 4.9); Group III (10.1 to 20.0 kg, n = 80) HDR was 3.5 mg/kg (1.1, 2.0 to 7.3). Group II (5.1 to 10.0 kg, n = 66) HDR was 3.8 mg/kg (1.2, 1.8 to 7.3). Group I (≤ 5.0 kg, n = 64) HDR was 3.9 mg/kg (1.3, 1.5 to 7.3). Twenty-seven percent of the total population had a HDR > 4.0 mg/kg. When compared by weight, 10% of the patients > 20.0 kg had a HDR > 4.0 mg/kg compared to 45% of the patients < 5.1 kg.

The heparin dose required by children becomes greater as the patient weight (size) decreases with more patients requiring > 400 units/kg. The use of a fixed dose protocol of heparin in the pediatric patient becomes increasingly inadequate as the patient size decreases. Heparin administration in the pediatric patient should be specific to the individual patient with a heparin dose response calculated for each patient.

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INTRODUCTION

Heparin administration for cardiopulmonary bypass (CPB) is frequently based on empirical loading doses. Most cite this heparin loading dose as 3 mg/kg (300 units/kg) for both adults and pediatric patients (1-4). Many of the protocols used in pediatrics have been extrapolated from adults without assessing the optimal heparin dose in pediatric patients of different ages and sizes (5). Bull, et al, noted that the majority of protocols used for heparin administration were empirically based (6,7). Bull further noted that patients have varied responses to heparin and developed the heparin dose response curve to individualize administration specific to each individual patient. Bull's original technique required a baseline activated clotting time (ACT). Heparin was then administered at 2 mg/kg. After 5 minutes of circulating, another ACT was drawn. These two ACT values were then graphed with time along the abscissa and heparin dose on the ordinate. The purpose of this study was to retrospectively evaluate the heparin dose response (HDR) in a pediatric population.

MATERIALS AND METHODS

The HDR of 268 pediatric patients presenting for CPB and repair of congenital heart defects at Children's Hospital, Columbus, Ohio, was studied. The HDR was gathered retrospectively from May 1992 to October 1993. The HDR was gathered for the entire population and divided into four groups based on patient weight. Group I ≤ 5.0 kg (n = 64); Group II 5.1 - 10.0 kg (n = 66); Group III 10.1 - 20.0 kg (n = 80); Group IV > 20.0 kg (n = 58).

The HDR was determined for all patients with Hepcon HMS[a] using the heparin dose response cartridge. The heparin dose response cartridge is a 6 channel (chamber) cartridge with kaolin as the activating agent. The test requires 2.1 ml of whole blood which is dispensed in 0.35 ml increments. Channel 1 and 2 contain bovine heparin at a sample concentration of 2.5 units/ml. Channels 3 and 4 have enough heparin to reach a concentration of 1.5 units/ml. Channels 5 and 6 contain no heparin and are used for determining the baseline ACT. Prior to performing the test the HDR cartridge is placed in the unit to prewarm to 37°C for ≥ 5 minutes. Within 5 minutes of arterial line insertion, an arterial blood sample was drawn for baseline analysis. After withdrawing 10 ml of blood from the arterial line, a 3 ml sample is drawn and the syringe is immediately placed in the syringe holder of the HMS and the test started with the reference (target) time set at 480 seconds.

RESULTS

Table 1 shows that the mean HDR was inversely related to weight group. As the weight decreased from Group IV to Group I the mean HDR increased from 3.0 mg/kg to 3.9 mg/kg. As the weight of the patient decreases the percentage of patients requiring > 4.0 mg/kg increases from 10% in Group IV (>20 kg) to 45% in Group I (weight ≤ 5.0 kg). Figure 1 shows the number of patients in each HDR range by weight. It is important to note that the distribution of the HDR in Group I (weight ≤ 5.0 kg) is much wider and flatter than the other groups. The HDR in Group I has fewer patients in each HDR category and is spread out over a wider range of HDR. As the weight class increases, the HDR becomes narrower with a greater number of patients falling within a smaller range of HDR.

Table 1
Heparin Dose Response Results.

Group	Wt. (kg) Mean (SD)	n	HDR (mg/kg) Mean (SD, range)	n < 3.0 mg/kg n (%)	n > 4.0 mg/kg n (%)
I	3.7 (0.7)	64	3.9 (1.3, 1-5-7.3)	17 (26)	29 (45)
II	7.3 (1.4)	66	3.8 (1.2, 1.8-7.3)	19 (29)	20 (30)
III	14.6 (2.8)	80	3.5 (1.1, 2.0-7.3)	28 (35)	20 (25)
IV	47.9 (23.5)	58	3.0 (0.8, 1.0-4.9)	28 (48)	6 (10)
Total	17.9 (19.8)	268	3.5 (1.2, 1.5-7.3)	92 (34)	72 (27)

DISCUSSION

Heparin administration and appropriate anticoagulation prior to the initiation of CPB is critical in both children and adults. The coagulation system of the child and infant have been shown to be substantially different than that of the adult and thus requires special attention (8,9). The patients > 20 kg most closely resemble an adult population and are comparable to the results of Horkay, et al, with a range of HDRs from 2.1 to 4.5 mg/kg (mean 3.0 mg/kg) in 20 adults (1). It is in the progressively smaller infant

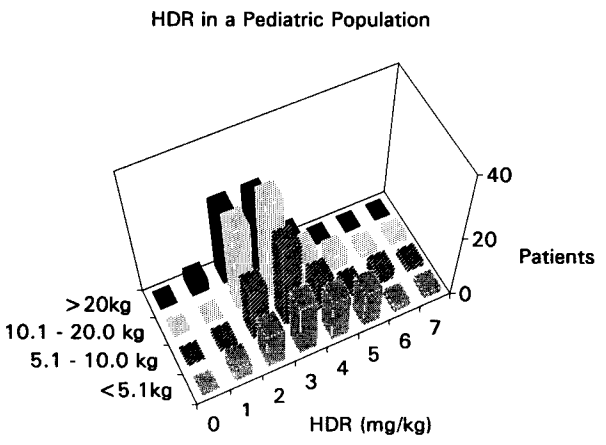

Figure 1
Heparin dose response by weight.

a Medtronic HemoTec, Englewood, CO 80112

that both a greater resistance and sensitivity to heparin is seen. Horkay showed a range of HDRs from 2.2 to 4.9 (mean 3.3 mg/kg) in a population of 22 pediatric patients, with an average weight of 17.3 kg. While this approximates the mean of the population of this study, it may be necessary in future research to further classify pediatric patients by weight in reference to anticoagulation response.

While some centers may establish a HDR as described by Bull, et al, the vast majority of centers administer heparin empirically. Groom, et al, found in a survey of North American pediatric cardiac surgical centers that only 5.7% of the programs constructed a dose response curve (10). Even if an empirical dose of heparin as high as 4 mg/kg (400 units/kg) is administered, a large number of infants would potentially be inadequately anticoagulated (up to 45% in this study). Alternatively, a substantial number may be excessively anticoagulated. Young, et al, have previously identified an ACT threshold of 400 seconds as necessary for coagulation-free CPB (11). Based on this, it may be more efficacious to give a greater heparin dose in an emergency situation when time may not allow for additional administration of heparin. Other factors, however, also affect the role of anticoagulation in the pediatric patient after CPB is initiated (12). These include hemodilution with subsequent dilution of all clotting factors, hypothermia, and the amount of heparin in the prime. These factors require further investigation.

CONCLUSION

The heparin dose required by children increases as the patient weight decreases with substantially more patients requiring > 400 units/kg to achieve an ACT of 480 seconds. The use of a fixed dose protocol of heparin in the pediatric patient becomes increasingly inadequate as patient weight decreases. Heparin administration in the pediatric patient should be specific to the individual patient with a heparin dose response calculated for each patient. Children, in general, and neonates specifically, have a wide variability in response to heparin administration as evidenced by heparin dose response. It is vital for the perfusionist to establish a heparin dose response for every patient to avoid inadequate heparinization and the possibility of subclinical coagulation or clot formation. This would also identify those patients sensitive to heparin and avoid the unnecessary administration of excess heparin.

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