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Has the New USP Assay for Heparin Affected Dosage for Patients Undergoing Cardiopulmonary Bypass?

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Abstract: In October 2009, the U.S. Pharmacopoeia (USP) changed the monograph for heparin to bring USP units in line with international units for heparin. The result was a 10% decrease in potency as measured by in vitro laboratory tests. This decrease led to questions regarding dosing guidelines. There existed a need for an in vivo study to determine the practical changes that may need to be implemented in regard to heparin administration for cardiopulmonary bypass in the clinical setting. A retrospective study was conducted to determine the heparin dose administered and the corresponding effect on patients undergoing coronary artery bypass grafting surgery using cardiopulmonary bypass. The study compared the heparin dose requirements and activated clotting time (ACT) results using the heparin before and after the USP changes. An analysis of the data was performed to determine the increased heparin dose required to achieve the same effect as before the USP change. This new heparin dosing protocol was instituted at Concord Hospital, Concord, NH. A prospective study was then preformed to verify the effects of the dosing change. In the new heparin group, the postheparin ACT fell by 9.1% ($p = .028$) and the patients achieving an ACT > 479 seconds fell by 12.8% as compared with the old heparin group. After adjustment of the loading dose calculation for heparin, the prospective study demonstrated the postheparin ACT ($p = .684$) and the percentage of patients achieving an ACT > 479 seconds ($p = 1.000$) to be similar to the values obtained before the USP change. An increase of the loading dose of approximately 12% is needed to achieve the patient effects seen before the UPS change. **Keywords:** blood, anticoagulation, CPB, anticoagulation, pharmacology, cardiovascular; heparin; N heparin, USP monograph. *JECT. 2013;45:112–115*

Unfractionated heparin is commonly used for anticoagulation during procedures requiring extracorporeal circulation. Between November 19, 2007, and January 31, 2008, over 150 adverse reactions were reported to the Centers for Disease Control and Prevention. Most of these reactions were associated with heparin manufactured by Baxter Healthcare (1). The U.S. Food and Drug Administration (FDA) conducted an investigation. They found that the active pharmaceutical ingredient (API) originated in China. The API had been contaminated with oversulfated chondroitin sulfate (OSCS) (2). OSCS has anticoagulation properties and is less costly to produce than porcine intestine heparin (3). As a result of the OSCS contamination, changes were made to the U.S. Pharmacopoeia (USP) monograph for heparin. These became effective October 1, 2009 (4).

The USP monograph change consisted of two parts. The first dealt with the detection of contaminants. The second addressed revising the assay for potency. Historically, USP units have been approximately 10% more potent than the World Health Organization international units for heparin (5,6).

As a result of the change in the USP monograph, the assay standard for heparin was decreased. This was done to bring the potency of heparin in the United States in line with international standards. The result was an approximate 10% decrease in potency. The FDA requested that laboratory testing be done to assess the impact of the new heparin monograph. These laboratory tests have confirmed a 6–10% decrease in potency. All these tests were conducted on animal and human plasma in vitro (6).

The FDA funded one study to test the in vivo impact of these changes. The study tested the effect on monkeys and minipigs. The conclusion was that there was a modest reduction in the anticoagulant response with the new heparin. The author noted that the variability of the animal's

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response to heparin demonstrates the importance of monitoring the heparin effect (7).

Many institutions in the United States use an empiric formula to calculate the loading dose of heparin for cardiopulmonary bypass (CPB), generally 300–400 units/kg weight (Anderson D., unpublished survey of Northern New England cardiovascular surgery programs, 2010). It was not known if an increase in heparin dose of 10% would translate to an in vivo patient response equal to the response of the old heparin.

Concord Hospital protocol sets an activated clotting time (ACT) of >479 seconds to initiate CPB. This level of ACT was established by the manufacturer of the oxygenator (SORIN GROUP USA, Inc. Cardiopulmonary and Heart Valve Business Units, Arvada, CO), in use at Concord Hospital, based on the work by Bull (8). Underdose of heparin has led to delays during surgery while additional heparin was given.

To date, there have been no studies done that address the in vivo consequences of the decreased potency (9). The purpose of this study was to determine to what extent the change in the USP heparin assay has affected the dosing requirements of heparin for (CPB) patients and, based on these results, make a recommendation for dosing using the new heparin monograph.

MATERIALS AND METHODS

This project consists of four parts.

First, a retrospective study was conducted to determine the heparin dose administered and the corresponding effect on patients undergoing coronary artery bypass grafting (CABG) surgery using CPB. The study compared the heparin dose requirements and ACT (ACT Plus® System Medtronic World Headquarters, Minneapolis, MN) results using the heparin manufactured under the old USP monograph (old heparin) and heparin manufactured under the revised USP monograph (new heparin). HR-ACT cartridges were used for all ACTs. An analysis of the data was performed to determine the percent of patients who received a loading dose of heparin, which achieved an ACT of >479 seconds. These data were retrieved from a chart review of patients undergoing CABG at Concord Hospital. The study time periods were January 1, 2007, through December 31, 2008, for the old heparin and April 1, 2010, through November 21, 2011, for the new heparin. The loading dose of heparin for both periods was 300 units/kg.

Second, based on the analysis of the information collected, a recommendation was made for a new patient-loading dose using the new heparin.

Third, after approval of the Institutional Review Board on November 16, 2011, the new loading dose protocol using the retrospective study recommended 336 units/kg dose was implemented at Concord Hospital.

Fourth, a prospective new heparin loading dose (NHLD) study was conducted at Concord Hospital. Data were collected on patients undergoing CABG to determine the percentage of patients who achieve an ACT > 479 using the new heparin loading dose protocol. These results were compared with the percentage of patients who achieved an ACT > 479 using the old loading dose calculation. The study period was December 1, 2011, through October 20, 2012.

Enrollment

The retrospective and prospective study enrollment consisted of all patients at Concord Hospital who met the following inclusion criteria:

1. Elective surgery (same-day admission);
2. CABG only;
3. First-time cardiac surgery (no reoperations); and
4. Use CPB.

Data Collection

The following data points were collected consecutively for both the retrospective and prospective studies:

1. Date of surgery;
2. Patient weight (kg);
3. Height (cm);
4. Priority (urgency) of surgery;
5. Type of surgery;
6. Procedure;
7. Prior cardiac surgery (reoperation);
8. CPB time (minutes);
9. Total heparin given (loading dose, prime heparin, supplemental heparin);
10. Loading dose of heparin; and
11. Postloading dose of heparin ACT.

Statistics

An analysis of variance was used to analyze the total heparin/kg and postheparin ACT of the old heparin, new heparin, and the NHLD study patients with post hoc comparisons adjusted for multiple comparisons using Scheffe's method. A Pearson χ^2 test was used to compare the percentage of patients achieving an ACT > 479 seconds. Statistical significance was accepted at $p \leq .05$. All statistical analyses were conducted using STATA Version 12 (STATA Corp., College Station, TX).

Results

Results for the retrospective portion of the project are summarized in Table 1. The total heparin given increased 15.6% after changing to the new heparin (unadjusted $p = .0128$; adjusted $p = .049$). It was noted that the average patient weight also increased by 3.9 kg. This represents an increase of 4.49%. The total heparin given per kilogram patient weight increased 61 units ($p = .038$) with the new

Table 1. Retrospective study data: comparison old heparin vs. new heparin.

Comparison	Old Mean (SD) OR no. (%) [95% CI]	New Mean (SD) OR no. (%) [95% CI]	*p* Value
Patient weight (kg)	86.9 (19.0) [81.7–92.2]	90.8 (20.2) [84.2–97.3]	.644†
Total heparin (U)*	43.6 (10.8) [40.6–46.6]	50.4 (15.0) [45.6–55.3]	.049† .0128§
Total heparin (U/kg)	504 (81) [482–527]	565 (150) [516–613]	.038†
Postheparin ACT value	535 (114) [503–566]	486 (87) [458–241]	.0278§
Percent patients with ACT > 479 seconds postheparin loading dose	32 (61.5%) [47.9–75.2%]	19 (48.7%) [32.3–65.1%]	.255‡
Extra heparin U/kg/min of CPB	1.55 (.71) [1.35–1.75]	1.87 (.97) [1.56–2.19]	.153†
No.	52	39	

*In thousand U.
†Analysis of variance (ANOVA) post hoc comparison adjusted for multiple comparisons using Scheffe's method.
‡Pearson χ^2 test.
§ANOVA not adjusted for multiple comparisons.
SD, standard deviation; OR, odds ratio; CI, confidence interval; ACT, activated clotting time; CPB, cardiopulmonary bypass.

heparin. This represents an increase of just over 12%. The postheparin ACT in the new heparin group fell by 9.1% ($p = .028$). The percentage of patients achieving an ACT > 479 fell 12.8% in the new heparin group.

Results of the prospective portion of the project are summarized in Table 2. The postheparin ACT in the old heparin and NHLD study groups was separated by 19 seconds ($p = .684$). The percentage of patients achieving an ACT > 479 for both groups was 61.5% ($p = 1.000$).

DISCUSSION

Inclusion Criteria

The inclusion criteria were used in an attempt to minimize the varied effects of heparin on patients. Elective patients, defined as same-day admission, had not recently been exposed to heparin. Only first-time (nonreoperation) CABG patients were included. This was done in an effort to reduce variability in surgical time, tissue exposure, pump suction use, etc. which might alter the patient response to heparin.

Retrospective Study

Comparing the patients using the old heparin with those using the new heparin showed that the change in the USP heparin standard resulted in the need to increase the dose of heparin to achieve an adequate ACT. The average ACT decreased by 50 seconds. This is a 9.3% decrease. Total heparin given increased by 15.6%. This change needs to be considered in light of the patient population increasing in weight by an average of 3.9 kg (4.5%) during the same period. Correcting for this increase in patient weight results in a total heparin increase of 11.1%. The average postheparin, pre-CPB ACT has decreased by 9.3% since changing to the new heparin. Because heparin dosing is based on patient weight, the better representation of heparin needs would be the total heparin U/kg given to the patient, which increased by 12.1%. The postheparin ACT reflects the in vivo effect of heparin on the patient. The number of patients who obtained a postheparin ACT of >479 seconds fell by 12.8% (Table 1). Considering the results of total heparin U/kg and postheparin ACT of >479 seconds, both demonstrating a change of approximately 12%, it was determined that the loading dose of

Table 2. Study data: comparison of old heparin vs. NHLD study.

Comparison	Old Mean (SD) OR no. (%) [95% CI]	Study Mean (SD) OR no. (%) [95% CI]	*p* Value
Patient weight (kg)	86.9 (19.0) [81.7–92.2]	86.7 (18.6) [80.6–92.7]	.998†
Total heparin (U)*	43.6 (10.8) [40.6–46.6]	53.9 (13.3) [49.6–58.3]	.001†
Total heparin (U/kg)	504 (81) [482–527]	624 (97) [593–656]	<.001†
Postheparin ACT value	537 (115) [505–569]	518 (107) [483–552]	.684†
Percent patients with ACT > 479 seconds postheparin loading dose	32 (61.5%) [47.9–75.2%]	24 (61.5%) [45.6–77.5%]	1.000‡
Extra heparin U/kg/min of CPB	1.55 (.71) [1.35–1.75]	2.10 (.66) [1.88–2.31]	.005†
No.	52	39	

*In thousand U.
†Analysis of variance post hoc comparison adjusted for multiple comparisons using Scheffe's method.
‡Pearson χ^2 test.
SD, standard deviation; OR, odds ratio; CI, confidence interval; ACT, activated clotting time; CPB, cardiopulmonary bypass.

heparin should be increased from 300 units/kg to 336 units/kg (a 12% increase) to achieve the desired postheparin ACT.

Prospective Study (NHLD study)

A new heparin dosing protocol was implemented at Concord Hospital on December 1, 2011. This consisted of a loading dose of heparin calculated as 336-units/kg patient weight (rounded to the nearest thousand units). Thirty-nine consecutive patients, who met the inclusion criteria, were enrolled. Analysis of the data showed the increase of the initial heparin dose to 336 units/kg resulted in an average postheparin ACT of 518 seconds compared with 537 seconds with the old heparin and protocol (p = .684). The data also showed 61.5% of the patients archived a postheparin ACT of >479. This equaled the results achieved using the old heparin at a loading dose of 300 units/kg, which was also 61.5% (p = 1.000).

Statistical analysis shows the old heparin/protocol and the NHLD study new heparin/protocol are not different (p > .05).

CONCLUSION

An increased loading dose of approximately 12% is needed to achieve the results seen before the UPS change. The null hypothesis can be rejected based on the data from this study. Therefore, the new USP assay for heparin has affected heparin dosage for patients undergoing CPB.

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