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Evidence-Based Algorithm for Heparin Dosing Before Cardiopulmonary Bypass. Part 1: Development of the Algorithm

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Abstract: The incidence of heparin resistance during adult cardiac surgery with cardiopulmonary bypass has been reported at 15%–20%. The consistent use of a clinical decision-making algorithm may increase the consistency of patient care and likely reduce the total required heparin dose and other problems associated with heparin dosing. After a directed survey of practicing perfusionists regarding treatment of heparin resistance and a literature search for high-level evidence regarding the diagnosis and treatment of heparin resistance, an evidence-based decision-making algorithm was constructed. The face validity of the algorithm decisive steps and logic was confirmed by a second survey of practicing perfusionists. The algorithm begins with review of the patient history to identify predictors for heparin resistance. The definition for heparin resistance contained in the algorithm is an activated clotting time <450 seconds with >450 IU/kg heparin loading dose. Based on the literature, the treatment for heparin resistance used in the algorithm is anti-thrombin III supplement. The algorithm seems to be valid and is supported by high-level evidence and clinician opinion. The next step is a human randomized clinical trial to test the clinical procedure guideline algorithm vs. current standard clinical practice. **Keywords:** anti-thrombin III, evidence-based medicine, decision-making algorithm, clinical procedure guideline, heparin, heparin resistance. *JECT 2007;39:238–242*

The practice of evidence-based medicine has become a valuable and popular method to standardize care and reduce errors in the practice of medicine. The use of "evidence" in medicine has been around a long time (1). Sackett et al. (2) described evidence-based medicine as incorporating clinical expertise with evidence garnered from systematic research. The evidence provides clinicians with cutting edge knowledge and innovative technology so that changes to the standards of care can be made to best meet the needs of patients. To create a standard of care and share the pool of knowledge, communication among the research and practitioner community is vital. Professional meetings and seminars are important arenas for conveying and displaying new evidence to practitioners. Another medium to operationalize practice guidelines is the evidence-based decision-making algorithm.

According to *The American Heritage Science Dictionary*, an algorithm is "a finite set of unambiguous instructions performed in a prescribed sequence to achieve a goal." One well-known algorithm in the medical community is the American Heart Association's Advanced Cardiac Life Support algorithm. These types of evidence-based decision-making algorithms are important for establishing consistent standards of care within health care facilities and from hospital to hospital and region to region. The field of cardiovascular perfusion has embraced evidence-based guidelines, and AmSECT has formed the International Consortium for Evidence-Based Perfusion. As Likosky (3) states, "Evidence-based guidelines would help assist clinicians in knowing the state of the evidence concerning the practice of cardiopulmonary bypass." The first evidence-based guidelines for key management issues in the practice of cardiopulmonary bypass (CPB) were published in 2006, and more published guidelines are promised (4,5).

One aspect of perfusion management that lacks consistency is anticoagulant dosing for CPB. Heparin has been the most widely used anticoagulant for CPB over the past 50 years, yet there is still no standardized protocol for its administration (6). Two researchers have published decision trees for heparin use with CPB, and both examples focus on heparin resistance (HR). Avidan et al. (7) created an algorithm that randomized heparin-resistant patients to either a recombinant anti-thrombin III (AT-III) group or a placebo group. The second study by DeBois et al. (8) looked at the development of a heparin sensitivity test for patients requiring CPB.

Both of these studies, although very valuable, concentrate on a small percentage of our patients. The focus of

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this research is the creation of an evidence-based decision making algorithm for heparin dosing, to include HR, during CPB.

MATERIALS AND METHODS

AT-III Use Survey

After reviewing the results of a manufacturer-directed survey of 100 clinical perfusionists (The Kinetix Group, personal communication, November 2006) regarding the treatment of HR with the use of AT-III, the authors set out to construct an evidence-based heparin-dosing algorithm for incorporation in adult CPB clinical procedure guidelines.

The AT-III use survey explored the demographics of the respondents, the clinical definition of HR, and the existence of protocols for treating HR. The survey asked respondents to list and rank the treatments for HR at their institution. The survey explored the availability of AT-III, which professionals make the decision to use AT-III, and the prevalence of AT-III use compared with other HR treatments.

Literature Review

The literature search for high-level evidence for clinical treatments for HR before CPB was conducted at the National Library of Medicine and the National Institutes of Health PubMed website. Keywords "heparin resistance" and "cardiac surgery" yielded 15 articles published between 1990 and 2007. Searching "heparin resistance" only yielded 140 articles published between 1953 and 2007. Of these articles, one reached the level of IA evidence. The highest evidence articles are described in Table 1.

Constructing the Algorithm

An algorithm based on clinical practice recommendations from the literature review was constructed using software (Micrografx ABC FlowCharter version 6.0a; Micrografx, Allen, TX) designed to create decision-making flowcharts of the quality to include in clinical procedure guidelines. Generally accepted flowcharting symbols were used to represent decisions and actions.

Algorithm Decision-Point Survey

The results of an on-line, 21-question survey were used to support or refute the main decision points in the evidence-based algorithm. Thirty-two hundred members of PerfList were solicited (April 17, 2007) to respond to a survey posted at SurveyMonkey.com. The survey instrument items used to support or refute the face validity of the algorithm decision points are listed in the appendix.

RESULTS

AT-III Use Survey

One hundred perfusionists performing >80 CPB procedures annually responded to a private, industry-solicited on-line survey regarding the use of AT-III to treat HR. The respondents rated themselves as key stakeholders in the use of AT-III and believed that AT-III has significant advantages over fresh frozen plasma. The surveyed perfusionists reported that they (even the ones that had never used AT-III before) were likely to use AT-III if it was on their hospital formulary and available.

Literature Review

Table 1 lists the best evidence published in the last 10 years regarding the clinical management of heparin-resistant adult CPB patients. Only one article (7) reached level IA evidence (3).

Constructing the Algorithm

Figure 1 presents the first page of the algorithm. Figure 2 presents the second page of the algorithm. The optimal path through the algorithm is on the left side of the diagram. Decision paths to the right are deviations or variances from the expected clinical course.

The evidence to support the order and logic of each decision point is referenced in brackets in the algorithm flowchart symbols. Based on the survey results and literature review, we defined HR as an activated clotting time (ACT) < 450 seconds after a loading dose ≥450 IU heparin/kg or an ACT < 600 seconds with the same heparin dose if using aprotinin injection (Trasylol; Bayer Pharmaceuticals Corp., Pittsburgh, PA) (6).

Table 1. Heparin resistance evidence.

Authors	Evidence*	HR Patients	Country	Heparin Resistance	Percent HR Incidence
Avidan et al. 2005 (7)	IA	54	United States, Europe	ACT < 480 s after 400 U/kg	18
Chan et al. 2006 (16)	IB	32	China, India, Malaysa	ACT < 400 s after 5 mg/kg	8
Conley and Plunkett 1998 (17)	IIA	311	United States	ACT < 400 s after >5 mg/kg	18
Debois et al. 2007 (8)	IIB	61	United States	ACT < 480 after >400 U/kg	20
Lemmer and Depostis 2002 (9)	IB	53	United States	ACT < 600 s after >600 U/kg	—
Ranucci et al. 2002 (10)	IB	104	Italy	ACT < 480 s after >300 U/kg	20
Staples et al. 1994 (18)	IIA	949	United States	ACT < 480 s after >500 U/kg	22
Williams et al. 2000 (6)	IB	85	United States	ACT < 480 s after >450 U/kg	4

*Evidence levels defined by American College of Cardiology and the American Heart Association (3).
HR Patients, heparin-resistant patients; % Incidence, percent of operative patients presenting with heparin resistance; —, not reported.

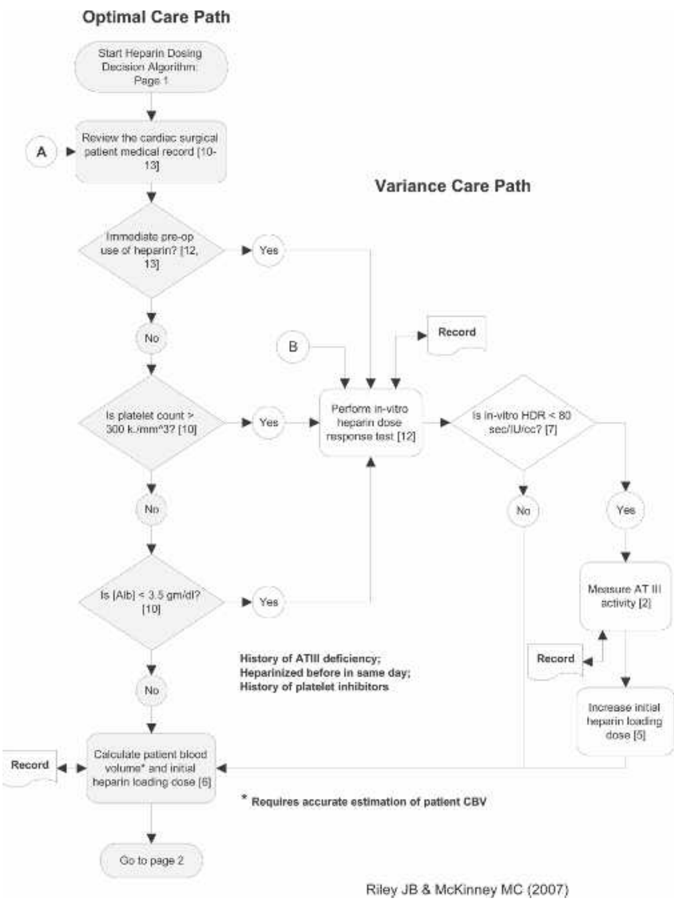

Figure 1. Page one of evidence-based algorithm for adult CPB patient heparin dosing.

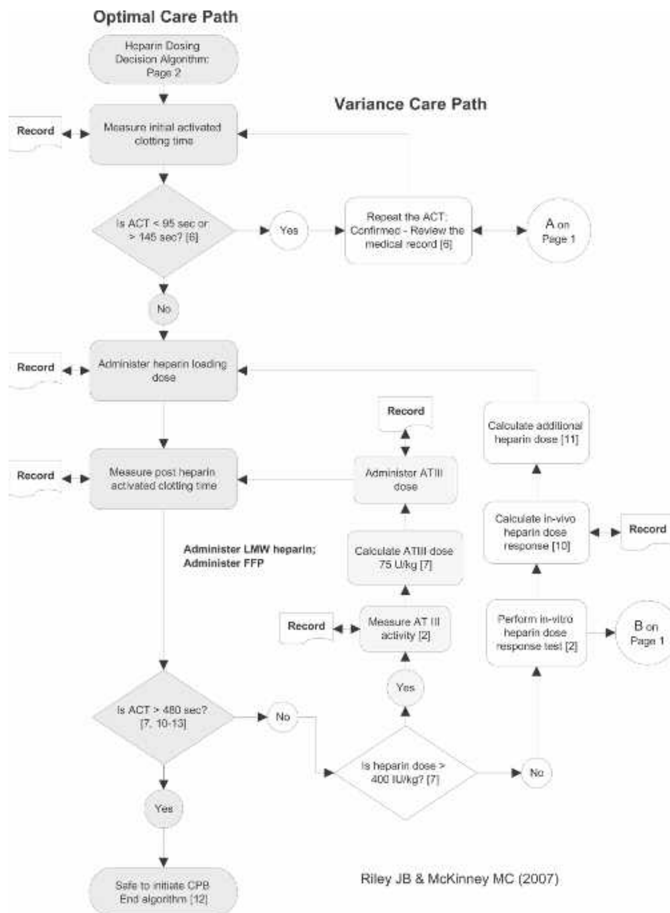

Figure 2. Page two of evidence-based algorithm for adult CPB patient heparin dosing.

Algorithm Decision-Point Survey

More than 200 perfusionists, 40% having >20 years of experience, responded to the survey solicited at PerfList. Approximately 53% of those responding to the survey currently use a written evidence-based clinical procedure guideline for heparin dosing. Less than 60% of the respondents interview their patients or review their medical records before surgery >80% of the time.

Preoperative intravenous heparin therapy was the most frequently reported (90%) predictor of HR, followed by preoperative subcutaneous heparin therapy (53%), an AT-III activity of <60% (43%), and a platelet count >300,000/mm^3 (30%). Only 10% of the respondents prophylactically increase the heparin loading dose based only on discovering patient characteristics in the medical history.

Having access to a patient-side analyzer to perform in vitro heparin dose response was reported by ~48% of the respondents; however, only ~34% routinely performed heparin sensitivity tests before heparin dosing. About 10% measured blood AT-III activity levels if they suspect HR, whereas 30% stated the AT-III assay is not available to them.

The most popular initial loading dose of heparin routinely used for adult CPB patients was 300 IU/kg (54%), whereas the next highest was 350 IU/kg (17%). To safely initiate CPB, the acceptable low limit of the ACT after heparin administration was expressed to be 400 seconds by 47% of the respondents. Four hundred fifty and 480 seconds were the next most frequent choices at 13% and 12%, respectively. Thirty-eight percent of the respondents acknowledged that, when using aprotinin, they increase the safe acceptable minimal ACT to initiate CPB, whereas 17% stated they do not use aprotinin. The maximum heparin dose administered before taking additional measures to reach the minimal safe ACT for CPB was reported to be 600 IU/kg by 31% of the respondents. Twenty percent affirmed 500 IU/kg to be their maximum dose.

Of the 74 respondents to answer the question about what method they use to estimate the AT-III dose used to treat HR, 52% prophylactically give one vial, 23% calculate the dose based on the patients body weight, 19% prophylactically give two vials, and ~5% calculate the dose based on the patient's AT-III level and body weight.

DISCUSSION

We present a method to use evidence to create a heparin-dosing algorithm for CPB that may be incorporated into clinical procedure guidelines. The literature review for high-level evidence was lacking. The algorithm decision points were confirmed by a survey of perfusionists. In our methods, perfusion experts were solicited from a frequently used e-mail list service to review the decision points in the algorithm. Although this method may be criticized, these are the steps necessary to create a clinical algorithm and may be improved on in a specific health care facility.

The algorithm proposed here centers on finding the minimum heparin dose to reach a safe minimum ACT. The algorithm uses the evidence that AT-III deficiency secondary to preoperative heparin use is the most likely cause for HR in adult cardiac surgical patients (6,7,9,10).

Based on the response to the decision-point survey, there is a gap in clinical practice and the ability to discover HR before administering the loading dose. Current perfusion practice standard does not seem to include in vitro heparin sensitivity testing such as described by DeBois et al. (8). In contrast, others have not found HR after preoperative heparin use with liberal use of heparin (11,12). Elevated preoperative platelet count did not consistently predict HR in one retrospective study (13).

It seems from the higher-evidence literature (Table 1) that HR may be defined as an ACT $<$ 450 seconds after a heparin dose $\geq$450 U heparin/kg. The most frequent maximum heparin dose before use of AT-III or fresh frozen plasma reported in the decision-point survey was 600 U/kg (37%), with the most frequent minimum safe ACT to initiate CPB reported at 400 seconds (47%). From the survey, it seems that clinical practice is liberal compared with the published evidence.

The research regarding the safe low ACT for CPB is incomplete with values $<$400–480 seconds associated with microscopic fibrin formation (14). With the concern for possible fibrinolysis and disseminated intravascular coagulopathy, the algorithm should help to avoid an inadequate ACT.

The heparin-dosing algorithm presented here is evidence based, and the logic is fairly consistent with current clinical practice as evaluated by an open solicited survey from the professional e-mail list server. Results of the decision-point survey strongly suggest that there is a need for a written guideline for heparin dosing when about one half of the decision-point respondents report not having a written procedure guideline.

Sixty-two percent of the decision-point survey respondents report the use of FFP first to treat patients with their team's definition of HR. The randomized clinical trial of Avidan et al. (7) revealed that treating prospectively identified HR with fresh frozen plasma was not successful in raising the ACT above the target minimal CPB value. Considering that there are major possible complications with the use of fresh frozen plasma (15), it should not be transfused with the expectation that the ACT will increase (7).

It is apparent that more high-level evidence and more expert review might improve the use and success of the algorithm. The next step for the algorithm is clinical trial. Perfusionists and cardiac teams should consider adopting the algorithm if they are in the 47% of the survey respondents that do not have a written clinical procedure guideline for heparin dosing for adult CPB.

APPENDIX

1. Do you currently use a written evidence-based clinical procedure guideline for heparin dosing for your adult CPB patients?
2. How often do you interview patients or review their medical records for signs or predictors of heparin resistance prior to administering heparin?
3. Which of the following patient signs do you consider a predictor of heparin resistance?
4. Do you prophylactically increase the heparin loading dose based ONLY on patient characteristics in the medical history?
5. Do you have access to a patient-side analyzer (Medtronic HMS, ITC HDR, etc.) to perform in-vitro heparin dose response tests prior to patient heparin dosing?
6. Do you routinely perform in-vitro heparin dose-response tests on your adult CPB patients before heparin dosing?
7. Do you measure blood AT-III activity (assay) levels if you suspect that a patient is heparin resistant?
8. What initial loading dose of heparin do you routinely use for adult CPB patients?
9. To safely initiate CPB, what is your team's acceptable LOW limit for the ACT after heparin administration?
10. When using aprotinin (Trasylol), does your team INCREASE the safe acceptable minimal ACT to initiate CPB?
11. What is the maximum heparin dose your team will administer BEFORE taking additional measures to reach the minimal safe ACT for CPB?
12. If you have used AT-III injections to treat heparin resistance, what method do you use to estimate the AT-III dose?

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