Early intravenous unfractionated heparin and mortality in septic shock*

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Background: **Sepsis and septic shock represent a systemic inflammatory state with substantial pro-coagulant elements. Unfractionated heparin is a known anticoagulant, which also possesses anti-inflammatory properties. Unfractionated heparin has been shown to increase survival in experimental models of septic shock.**

Objective: **To evaluate the impact of intravenous therapeutic dose unfractionated heparin in a cohort of patients diagnosed with septic shock.**

Design: **Retrospective, propensity matched, multicenter, cohort study.**

Setting: **Regional intensive care units in Winnipeg, Canada between 1989 and 2005.**

Patients: **Two thousand three hundred fifty-six patients diagnosed with septic shock, of which 722 received intravenous therapeutic dose heparin.**

Measurements and Main Results: **The primary outcome of study was 28-day mortality, and mortality stratified by severity of illness (Acute Physiologic and Chronic Health Evaluation II quartile). Safety was assessed by comparing rates of gastrointestinal hemorrhage, intracranial hemorrhage, and the need for transfusion. By using a Cox proportional hazards model, systemic heparin therapy was associated with decreased 28-day mortality (307 of 695 [44.2%] vs. 279 of 695 [40.1%]; hazard ratio 0.85 [confidence interval (CI) 95% 0.73–1.00]; $p = 0.05$). In the highest quartile of severity of illness (Acute Physiologic and Chronic Health Evaluation II score 29–53), heparin administration was associated with a clinically and statistically significant reduction in 28-day mortality [127 of 184 (69.0%) vs. 94 of 168 (56.0%); hazard ratio 0.70 (CI 95% 0.54–0.92); $p = 0.01$]. The use of intravenous unfractionated heparin was associated with successful liberation from mechanical ventilation [odds ratio of 1.42 (CI 95% 1.13–1.80); $p = 0.003$], and successful discontinuation of vasopressor/inotropic support [odds ratio of 1.34 (CI 95% 1.06–1.71); $p = 0.01$]. No significant differences in the rates of major hemorrhage or need for transfusion were identified.**

Conclusion: **Early administration of intravenous therapeutic dose unfractionated heparin may be associated with decreased mortality when administered to patients diagnosed with septic shock, especially in patients with higher severity of illness. Prospective randomized trials are needed to further define the role of this agent in sepsis and septic shock. (Crit Care Med 2008; 36: 2973–2979)**

KEY WORDS: anticoagulants; heparin; mortality; sepsis; septic shock

Sepsis and septic shock account for approximately 5%–15% of all intensive care unit (ICU) admissions and constitute the second most frequent cause of death in the ICU after primary cardiovascular diseases (1–3). The incidence of sepsis in the United States has been estimated to be 660,000–750,000 cases per year (1, 2, 4, 5). Data from several large clinical trials in severe sepsis (i.e., sepsis with new onset organ failure) indicate that the incidence of septic shock approaches 435,000 cases annually (6). The mortality rate associated with severe sepsis is approximately 25%–50%, whereas mortality in septic shock ranges between 40% and 75% (1, 2, 4–6).

The pathogenesis of sepsis and septic shock involves a systemic inflammatory response to the presence of an uncontrolled infection (7). If excessive, this host response can develop into septic shock with severe cardiovascular instability, multiorgan dysfunction, coagulopathy, and death. Experimental models suggest that sepsis is not only associated with systemic inflammation, but also represents a pro-coagulant state with profound deficiencies in circulating endogenous anticoagulants including antithrombin, protein C, activated protein C, and tissue factor pathway inhibitor (5, 8, 9). Because of their anticoagulant and anti-inflammatory properties, these circulating glycoproteins have been investigated as potential therapies in sepsis (8). To date, only human recombinant activated protein C (drotrecogin alfa) has been shown to be of benefit in a single phase III trial (5). Long-term follow-up data and the results of two trials examining drotrecogin alfa

***See also p. 3098.**

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Supported, in part, by the Section of Critical Care Medicine at the University of Manitoba. Additional support was provided by the Health Sciences Centre Foundation. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Drs. Kumar and Zarychanski had full access to all the data in the study and take responsibility for the integrity of the database (Dr. Kumar) and the accuracy of the data analysis (Dr. Zarychanski).

This specific research concept and the septic shock database were developed by Dr. Kumar. Dr. Zarychanski, Mr. Doucette, Dr. Fergusson, and Dr. Kumar were responsible for the methodological design issues and data analysis. The manuscript was prepared by Dr. Zarychanski. All authors assisted with data interpretation and manuscript revisions.

None of the authors have financial or personal relationships or affiliations that could influence (or bias) the decision regarding the analysis or manuscript in any regard.

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DOI: 10.1097/CCM.0b013e31818b8c6b

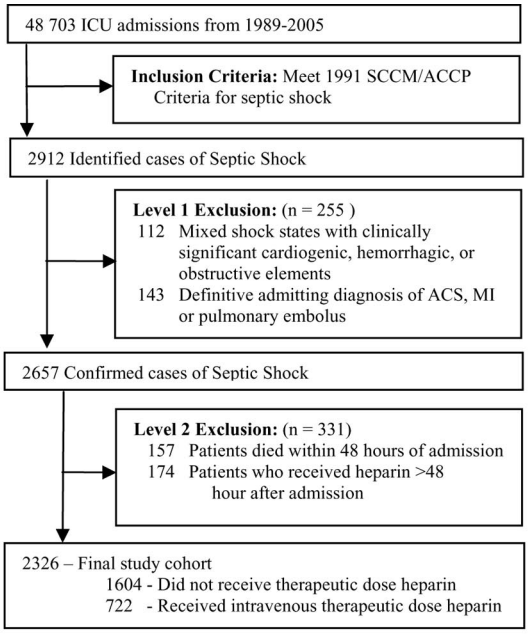
in low-risk patients with sepsis and in children have been negative (10–12). These negative outcomes may be partially due to the inclusion of significant numbers of relatively low-risk patients within these trials (13).

Unfractionated heparin (UFH) is a negatively charged glycosaminoglycan macromolecule composed of alternating residues of D-glucosamine and iduronic acid. UFH is an effective anticoagulant, but also has well-established anti-inflammatory properties (14–19). Some experimental animal models of sepsis, both endoxtoxin-induced and live pathogen infusion, have demonstrated the potential benefit of UFH in sepsis, in terms of reducing activation of coagulation, and improving survival (20–23). Other animal studies have failed to demonstrate such a benefit (24, 25). Although controversial, secondary analyses of prospectively collected data from several large phase III trials in sepsis are consistent with a potential survival advantage in placebo-group patients who received subcutaneous heparin (26, 27).

We have determined that a significant subset of patients admitted to the ICU with septic shock receive intravenous heparin therapy for 1 or more days. This occurs most commonly in the context of undifferentiated shock where the etiology of hemodynamic instability is initially uncertain and multiple therapies are being started simultaneously. Typically, the potential etiological concerns are septic vs. cardiogenic (i.e., acute coronary syndrome)/obstructive (i.e., pulmonary embolus-related) shock. Given heparin's anticoagulant and anti-inflammatory properties, the hypothesis of this study was that early, systemically administered therapeutic dose heparin would be associated with reduced mortality among patients diagnosed with septic shock.

METHODS

Data Source. This study was approved by the University of Manitoba Research Ethics Board under a waived consent protocol. Patients aged 18 yrs or greater who were diagnosed with septic shock and admitted to ICUs in Winnipeg, Manitoba, Canada, between May 1989 and July 2005 were retrospectively identified using a clinical ICU database. Primary and multiple secondary/comorbid diagnoses were encoded by the attending physician at the time of admission. Specially trained data quality assurance nurses prospectively collected and entered clinical and laboratory data including APACHE II (Acute Physiologic and Chronic Health Evaluation) score elements (28). Supplemental data for this study were collected retrospectively by trained research nurses/medical students using a standardized and piloted data extraction template.



SCCM – Society of Critical Care Medicine; ACCP – American College of Chest Physicians; ACS – Acute coronary syndrome; MI – Myocardial Infarction

Figure 1. Patient flow through study.

Study Population. All patients admitted to the ICUs of one of six Winnipeg hospitals between May 1989 and July 2005 were eligible for study inclusion (n = 48,703). The algorithm used to identify the final study population is outlined in Figure 1. After initial identification through a database query, each potential case was reviewed to determine whether it met specific criteria for septic shock as described by the 1991 Society of Critical Care Medicine/American College of Chest Physicians Consensus Statement on Sepsis Definitions (7). Septic shock was defined by the presence of suspected or documented infection plus two of the following four systemic inflammatory response elements: 1) temperature >38°C or <36°C; 2) heart rate >90 beats/min; 3) respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg; 4) white blood cell count >12,000 cells/mm^3, <4000 cells/mm^3, or >10% immature (band) forms; and postfluid resuscitation hypotension (mean arterial pressure <65 mm Hg for >2 hrs). Mixed shock states with a clinically significant primary cardiogenic, hemorrhagic, or obstructive (e.g., cardiac tamponade) element were excluded (n = 112). Likewise, a definitive admitting diagnosis of acute coronary syndrome, myocardial infarction, or pulmonary embolus (concomitant with evidence of septic shock), also resulted in exclusion (n = 143). A primary admission diagnosis of septic shock was confirmed in 2657 patients. Another 157 cases were eliminated from analysis based on *a priori* criteria to exclude patients who died within the first 48 hrs of ICU admission. Intravenous and subcutaneous heparin utilization was obtained from the ICU pharmacy database. To capture the effect of early heparin therapy, patients who received intravenous heparin >48 hrs after admission to the ICU (n = 174) were excluded. The final cohort included 2326 patients who were admitted with septic shock and could have received intravenous heparin within 48 hrs of ICU admission (Fig. 1).

Study Variables. Variables collected included patient demographics, baseline comorbidities, APACHE II score, physiologic/laboratory parameters, and the need for hemodynamic or ventilatory support. The presumed or documented site of sepsis, microbiological culture results, and the time to effective antimicrobial therapy from the onset of hypotension were also recorded. Effective antimicrobial therapy was defined as an antibiotic with *in vitro* activity appropriate to isolated pathogenic organisms or, if an organism was not isolated, appropriate for the underlying clinical syndrome (29).

Outcome Measures. The primary outcome variable was mortality over 28 days. Mortality stratified by severity of illness (APACHE II quartile) was identified as an *a priori* outcome measure. Secondary end points included successful liberation from ventilatory support and vasopressor/inotropic support, and hospital length of stay. The secondary outcomes were not truncated at 28 days. The safety of heparin administration was assessed by comparing rates of gastrointestinal hemorrhage, intracranial hemorrhage, and the need for allogeneic transfusion.

Statistical Analysis. Baseline characteristics between patients receiving and not receiving intravenous heparin were compared using Student's *t* test or the Wilcoxon's rank sum test for continuous variables, or the chi-square test for categorical variables. All reported *p* values were two-tailed. Because heparin therapy was not randomly assigned, a propensity analysis was undertaken to account for potential confounding factors and selection biases. The propensity matching and analytic methods used in this study incorporated aspects from several reference sources (30, 31). A propensity score for intravenous heparin use was developed using multivariable logistic regression. This score represents the probability that a patient would receive intravenous heparin based on variables, which were known or suspected to be relevant to hospital mortality. These variables included age, sex, APACHE II score, time to effective antimicrobial therapy, preexisting medical conditions (including liver failure, chronic obstructive pulmonary disease, diabetes, chronic renal insufficiency, malignancy, human immunodeficiency virus/autoimmune deficiency syndrome, New York Heart Association class IV heart failure, infecting organism group (Gram-positive, Gram-negative, fungal, or unknown pathogen), the need for mechanical ventilation, and a variety of laboratory data including mean arterial pressure, white blood cell count, platelet count, the international normalized ratio, and serum creatinine. To account for changes in practice patterns over time, the date of ICU admission was also incorporated as a matching variable.

Propensity scores were used to match patients who received intravenous heparin to a control patient using a software macro. A greedy matching procedure selected match pairs initially identical to five decimal places of probability (32). If no match existed at five decimal places, matching would occur at four decimal places and so on. If no match existed at one decimal place then that patient receiving intravenous heparin was excluded from the study. By using this strategy, 695 of 722 (96%) of patients who received intravenous heparin were able to be matched using propensity scores. The high matching success reduces the possibility of introducing systematic biases.

Mortality over 28 days was assessed using a Cox proportional hazard model. Hazard models incorporated survival data over the complete duration of the study period (28 days) or until the time of censoring (i.e., death). Mortality estimates stratified by severity of illness (APACHE II quartiles) were assessed by the addition of an interaction term to the hazard model (33). A hazard <1 signifies decreased mortality in the heparin group compared with the control group. Statistical analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). The confidence limits and *p* values reported reflect an α level of 0.05.

RESULTS

Baseline Characteristics. Our study population consisted of 2376 patients who were potentially eligible to receive intravenous heparin therapy. Intravenous therapeutic dose heparin was administered to 722 (31%) patients.

Baseline demographics, preexisting medical conditions and relevant clinical, physiologic, and laboratory parameters in the unmatched study population are summarized in Table 1. Men comprised 56% and 55% of the heparin and control groups. The mean admission APACHE II score in the study population was 25.4 (±8.3). APACHE II scores were significantly lower in the heparin group compared with the control group. Those receiving heparin were also older. The median time to appropriate antimicrobial therapy was similar in each group (5.8 hrs vs. 6.3 hrs).

Several clinical differences between the heparin and control groups existed in the unmatched cohort. The baseline prevalences of liver failure and neutropenia were higher in the control group, whereas the prevalences of chronic obstructive pulmonary disease, diabetes, and New York Heart Association class IV heart failure were significantly higher in

Table 1. Baseline characteristics in the unmatched septic shock cohort

	Heparin (n = 722)	Control (n = 1604)	*p*
Male, n (%)	404 (56.0)	877 (54.7)	0.57
Age, mean ± SD	63.2 ± 15.8	62.4 ± 16.6	<0.01
Mean date of admission	09 August 2000	05 June 2000	0.32
APACHE II score,[a] mean ± SD	23.4 ± 7.6	25.6 ± 8.6	<0.001
Time to 1st antibiotic (hrs) (median, IQR)	5.8 (2.0, 15.0)	6.3 (2.2, 16.1)	0.34
Preexisting medical conditions, n (%)			
Liver failure	32 (4.4)	154 (9.6)	<0.001
Chronic obstructive pulmonary disease	88 (12.2)	86 (5.4)	<0.001
Diabetes	198 (27.4)	367 (22.9)	0.02
Chronic renal insufficiency	104 (14.4)	207 (12.9)	0.33
Malignancy	158 (21.9)	418 (26.1)	0.03
Neutropenia	20 (2.8)	140 (8.7)	<0.001
HIV positive	6 (0.8)	13 (0.8)	0.96
NYHA class IV	40 (5.6)	40 (2.5)	<0.001
Recent surgical history, n (%)			
Elective surgery	129 (17.9)	238 (14.8)	0.06
Emergency surgery	60 (8.3)	109 (6.8)	0.19
No surgical history	542 (75.1)	1269 (79.1)	0.03
Physiologic and laboratory parameters at admission, median (IQR)			
Mean arterial pressure (mm Hg)	56.0 (50–63)	55.0 (48–62)	0.03
Admission WBC ($\times 10^6$ cells/L)	15.5 (9.3–23.9)	14.8 (6.0–23.2)	<0.01
Platelet count ($\times 10^9$ cells/L)	216.0 (143–304)	165 (89–261)	<0.001
Serum creatinine (mg/dL)	1.5 (1.0–2.5)	1.7 (1.1–2.6)	0.29
INR	1.3 (1.2, 1.6)	1.4 (1.2, 1.8)	<0.001
Infection types, n (%)			
Fungal	38 (5.3)	125 (7.8)	0.02
Gram positive	227 (31.4)	425 (26.5)	
Gram negative	255 (35.3)	560 (34.9)	
Culture negative	202 (28.0)	494 (30.8)	
Life support measures, n (%)			
Respiratory failure	553 (76.6)	1126 (70.2)	<0.01
Cardiovascular failure	722 (100.0)	1604 (100.0)	1.00
Cointerventions, n (%)			
Activated protein C	32 (4.4)	50 (3.1)	0.11
Stress-dose steroids	145 (20.1)	371 (23.1)	0.10
Surgical source control	247 (34.2)	546 (34.0)	0.96

HIV, human immunodeficiency virus; NYHA, New York Heart Association; WBC, white blood cell; INR, international normalized ratio; IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Evaluation.

[a]The patients were assessed on the day of onset of shock. The range of scores for this test is 0–71.

the heparin group. The platelet count was notably higher in the heparin group. All patients required vasoactive medications because of hypotension. The need for mechanical ventilation at admission was higher in the heparin group. There were no statistically significant differences in the use of stress-dose steroids or activated protein C or in the provision of surgical source control between the heparin and control groups.

A manual review of 25% of charts of patients receiving intravenous heparin was performed to determine potential reasons for heparin administration. A concern regarding the possibility of acute coronary syndrome (primarily on the basis of modest elevations of troponins consistent with sepsis) was present and concomitant with septic shock in 71.3% of cases. In addition, 9.6% received systemic heparin for possible pulmonary embolus or deep venous thrombosis; 5.2% for chronic atrial fibrillation; 5.2% for possible ischemic bowel; and 3.6% for other reasons. The doses of heparin used were consistent with these intended indications. The use of heparin increased substantially after the introduction of cardiac troponins to clinical practice, presumably intended as treatment for acute coronary syndrome. The mean duration of heparin therapy was 4.7 days (±2.9). Low-dose prophylactic heparin was administered to 73.7% patients in the control group within 48 hrs of shock.

Baseline Characteristics After Propensity Matching. Suitable propensity matches were found for 695 (96%) of 722 patients receiving intravenous heparin. The *C* statistic for the propensity derivation model was 0.67. The range of propensity scores was similar in both the heparin and the control groups (heparin, 0.05–0.80; control, 0.00–0.75). The matching process eliminated all significant differences that existed between the heparin and control group regarding patient demographics, preexisting medical conditions, or relevant clinical, physiologic, and laboratory parameters (Table 2).

Heparin Use and Mortality. In the propensity adjusted Cox model, mortality over 28 days was significantly reduced in the heparin group [307 of 695 (44.2%) vs. 279 of 695 (40.1%); hazard ratio 0.85 (confidence interval [CI] 95% 0.73–1.00); $p = 0.05$] (Fig. 2). Stratified analyses revealed a trend toward reduced mortality over 28 days with increased severity of illness (test for interaction $p = 0.09$). The absolute reduction in mortality in patients with the highest APACHE II quartile scores was 13% (CI 95% 3%–23%), with a corresponding hazard ratio of 0.70 (CI 95% 0.54–0.92; $p = 0.01$) (Table 3).

Secondary Support Measures. In the propensity matched cohort, the proportion of ventilated patients successfully liberated from mechanical ventilation was higher in the heparin-treated group compared with the control group (62.5% vs. 54%; odds ratio 1.42; CI 95% 1.12–1.79; $p = 0.003$). Successful discontinuation of vasopressor/inotrope support was also higher in the heparin group (74.7% vs. 68.8%; odds ratio of 1.34; CI 95% 1.06–1.70; $p = 0.01$). The median hospital length of stay was significantly longer in heparin group [19 days (interquartile range 8–36) vs. 14 days (interquartile range 5–31); $p < 0.001$].

Safety. There was no difference in the propensity adjusted incidence of gastrointestinal hemorrhage or central nervous system hemorrhage among the heparin and the control group (Table 4). The number of patients who required transfusion of red blood cell units was also similar between the two groups (52.4% vs. 55.3%). Likewise, the rate of transfu-

Table 2. Baseline characteristics in the matched septic shock cohort

	Heparin (n = 695)	Control (n = 695)	*p*
Male, n (%)	385 (55.4)	394 (56.7)	0.63
Age, mean ± SD	64.4 ± 15.9	64.7 ± 15.2	0.91
Mean date of admission	11 August 2000	08 August 2000	0.96
APACHE II score,[a] mean ± SD	24.1 ± 7.6	24.2 ± 7.9	0.81
Time to 1st antibiotic (hrs) (median, IQR)	6.0 (2.0, 15.3)	5.7 (1.8, 16.0)	0.74
Preexisting medical conditions, n (%)			
Liver failure	32 (4.6)	28 (4.0)	0.60
Chronic obstructive pulmonary disease	74 (10.7)	66 (9.5)	0.48
Diabetes	188 (27.1)	203 (29.2)	0.37
Chronic renal insufficiency	102 (14.7)	103 (14.8)	0.94
Malignancy	154 (22.2)	156 (22.5)	0.90
Neutropenia	20 (2.9)	22 (3.2)	0.75
HIV positive	6 (0.9)	7 (1.0)	0.78
NYHA class IV	29 (4.2)	32 (4.6)	0.69
Recent surgical history, n (%)			
Elective surgery	123 (17.7)	114 (16.4)	0.52
Emergency surgery	58 (8.4)	51 (7.3)	0.48
No surgical history	522 (75.1)	537 (77.3)	0.34
Physiologic and laboratory parameters at admission, median (IQR)			
Mean arterial pressure (mm Hg)	56.0 (50.0–63.0)	56.0 (49.0–63.0)	0.37
Admission WBC ($\times 10^6$ cells/L)	15.4 (9.0–23.6)	15.5 (8.7–23.5)	0.87
Platelet count ($\times 10^9$ cells/L)	214 (142–302)	212 (129–304)	0.37
Serum creatinine (mg/dL)	1.5 (1.0–2.5)	1.5 (1.0–2.7)	0.88
INR	1.3 (1.2, 1.6)	1.3 (1.2, 1.7)	0.61
Infection types, n (%)			
Fungal	38 (5.5)	45 (6.5)	0.74
Gram positive	213 (30.7)	204 (29.4)	
Gram negative	248 (35.7)	239 (34.4)	
Culture negative	196 (28.2)	207 (29.8)	
Life support measures, n (%)			
Respiratory failure	528 (76.0)	534 (76.8)	0.70
Cardiovascular failure	695 (100.0)	695 (100.0)	1.00
Cointerventions, n (%)			
Activated protein C	30 (4.3)	24 (3.4)	0.40
Stress-dose steroids	137 (19.7)	162 (23.3)	0.10
Surgical source control	222 (31.9)	218 (31.4)	0.82

HIV, human immunodeficiency virus; NYHA, New York Heart Association; WBC, white blood cell; INR, international normalized ratio; IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Evaluation.

[a]The patients were assessed on the day of onset of shock. The range of scores for this test is 0–71.

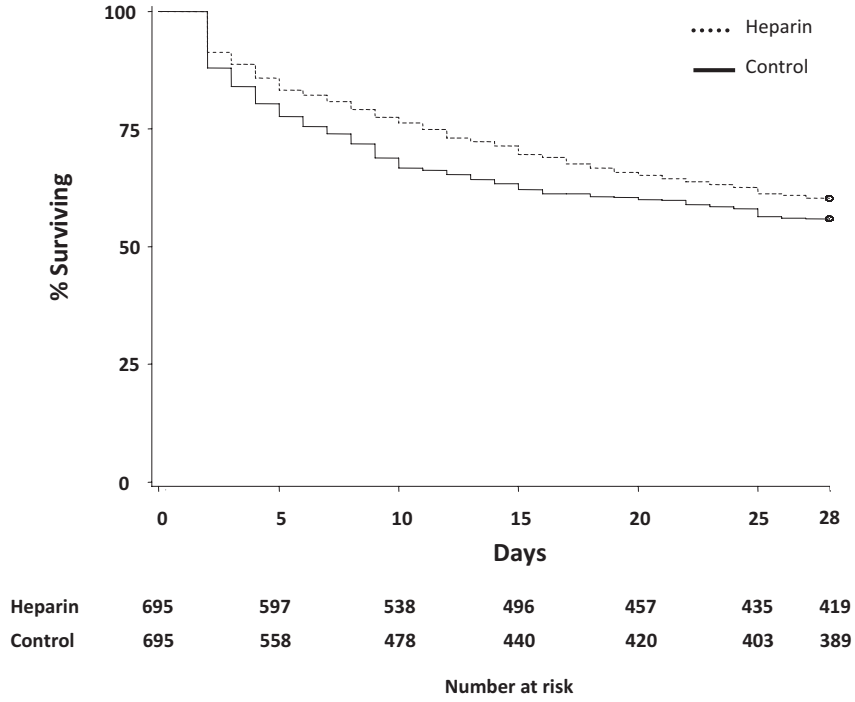


Figure 2. Adjusted Cox proportional hazards of mortality associated with therapeutic dose intravenous heparin.

Table 3. Mortality over 28 days

Septic Shock Cohort	Sample Size, n	Mortality Rate by Heparin Status, No. Deaths/Total No. Patients (%)		Hazard Ratio (95% Confidence Interval)	*p*
		Heparin	Control		
28-day mortality					
Adjusted for propensity score	1390	279/695 (40.1)	307/695 (44.2)	0.85 (0.73–1.00)	0.05
Stratified 28-day mortality analysis in matched cohort (APACHE II quartile)					
5–18	333	41/166 (24.7)	36/167 (21.6)	1.11 (0.70–1.73)	0.65
19–23	381	63/186 (33.9)	68/195 (34.9)	0.93 (0.66–1.342	0.70
24–28	324	81/175 (46.3)	76/149 (51.0)	0.86 (0.63–1.18)	0.34
29–53	352	94/168 (56.0)	127/184 (69.0)	0.70 (0.54–0.92)	0.01

APACHE, Acute Physiology and Chronic Health Evaluation.

Table 4. Acquired[a] rates of clinically significant bleeding complications and need for transfusion

	Heparin (n = 695)	Control (n = 695)	*p*
GI hemorrhage, n (%)	36 (5.2)	26 (3.7)	0.19
CNS hemorrhage, n (%)	7 (1.0)	7 (1.0)	1.00
Number of patients transfused PRBC units, n (%)	364 (52.4)	384 (55.3)	0.28
PRBC (units/patient) mean (SD)	5.0 (5.8)	4.7 (5.2)	0.52
Platelets (units/patient) mean (SD)	5.7 (5.5)	6.6 (6.8)	0.19
FFP (units/patient) mean (SD)	16.9 (17.8)	18.4 (19.5)	0.58

GI, gastrointestinal; CNS, central nervous system; PRBC, packed red blood cell; FFP, fresh frozen plasma (approximately 250 mL per donor unit).

[a]Diagnoses and interventions recorded >24 hrs after intensive care unit admission.

sion (units/patient) was comparable in the heparin and control group regarding packed red cells, platelets, and fresh frozen plasma (Table 4).

DISCUSSION

In this retrospective, propensity matched cohort study, the use of therapeutic dose, intravenous UFH was associated with reduced mortality over 28 days. The reduction in mortality was more pronounced with increasing severity of illness and was statistically significant in the highest APACHE II quartile. Intravenous heparin was associated with an increase in successful liberation of ventilatory support and discontinuation of vasoactive medications. The use of heparin was not associated with a measured increase in the incidence of major hemorrhage or transfusion of allogeneic of blood products.

Sepsis is known to be associated with systemic activation of coagulation with a concomitant decrease in circulating natural anticoagulants. Several of these natural anticoagulants, including antithrombin, recombinant activated protein C, and tissue factor pathway inhibitor, have been studied in phase III trials (4, 5, 34). Only recombinant activated protein C, has been shown to reduce mortality in sepsis; however, this drug is costly (approximately $6800 US dollars per patient), and seems to be most effective in adult patients with APACHE II scores ≥25 (10). In our study, heparin similarly seemed most effective in patients with the highest severity of illness scores.

UFH is primarily used as an anticoagulant and its anticoagulant effect is due to its ability to enhance antithrombin-mediated inactivation of factors Xa and thrombin (factor IIa), but also factors IXa, XIa, and XIIa. By inactivating factors Xa and thrombin, heparin effectively limits its thrombin generation. Because thrombin generation is intimately linked with inflammation, heparin also acts as an anti-inflammatory agent. The anticoagulant effects of heparin are mediated through a specific pentasaccharide sequence with high affinity to antithrombin; however, UFH binds nonspecifically to endothelium and to many plasma constituents, which contributes to the many anticoagulant-independent effects of heparin. *In vitro* experiments demonstrate that many of these anticoagulant-independent effects of heparin serve to mitigate inflammation (16, 17, 35). For example, heparin has been shown to neutralize endotoxin and increase serum tumor necrosis factor binding protein-1, which directly limits both activation of coagulation and inflammation (16, 36).

As with any retrospective analysis, this study has limitations which merit attention. There are at least two potential time-dependent biases associated with

this study. Immortal time bias is, in essence, a mathematical problem in which survival duration may be linked to an inappropriate reference point yielding an inaccurate time-dependent survival probability (37). A retrospective study of critically ill patients with a very high early mortality risk may also demonstrate a survival duration-related selection bias. In this case, the group of patients who are known to have lived long enough to receive heparin during septic shock (even within 48 hrs) may be more likely to live to a given temporal end point than the group who cannot be predicted to have lived long enough to receive the therapy. Several statistical approaches can be used to control for immortal time bias. One conservative approach to control for both types of potential biases is to ensure that subjects in both groups live long enough to potentially receive intravenous heparin. For that reason, death within 48 hrs of the diagnosis of septic shock was an *a priori* exclusion. The limitation with this exclusion criterion is the loss of clinical information and event data within the first 48 hrs.

Despite sophisticated methods to account for individual patient differences, retrospective studies may also be confounded by indication. There are certain comorbid conditions that might indicate or contraindicate heparin use that may also be associated with clinical outcomes. We attempted to control for potential confounders both by excluding certain conditions (acute coronary syndrome, myocardial infarction, and pulmonary embolus/significant potential obstructive, cardiogenic or hemorrhagic elements to shock) and through propensity matching of other variables (antecedent surgery or trauma, chronic severe liver disease, thrombocytopenia, coagulopathy, and malignancy). Other potential confounders were specifically tested in the matched cohorts to ensure an absence of significant differences in distribution (atrial fibrillation, ischemic bowel, and the provision of surgical source control). Nonetheless, it is possible that residual confounders not recorded in the dataset could exist (e.g., congenital bleeding diathesis, stroke within 3 mos). Propensity methods are unable to account for these unknown factors.

Because of the retrospective design of the study the allocation of patients and the use of heparin were not randomized, nor could the heparin treatment regimen be standardized. Indications for the use of heparin could not be clearly defined in the entire cohort and the dose varied depending on the indication (e.g., potential acute coronary syndrome vs. suspected thromboembolism). Although intravenous heparin was not associated with increased major bleeding, this could reflect the insensitivity of the study design to adequately capture major bleeding events. Lastly, increased hospital length of stay associated with heparin use was likely secondary to decreased mortality within this group, but this assumption cannot be formally proven given the study design.

This study also has important strengths. A comprehensive clinical database allowed for the identification of a large number of patients eligible for analyses in this study. Baseline differences between the heparin and control group existed which could have the potential to bias mortality estimates; however, the large sample size allowed for a rigorously conducted propensity matched analyses whereby patients were successfully matched for over 20 clinically relevant variables. Although no retrospective method can replace the advantage of prospective randomization, propensity analyses have been demonstrated to be an effective means of reducing bias in baseline characteristics when assessing treatment effects (31, 38). In our study, all significant baseline differences between study groups were adequately reconciled using this method. The inclusion of patients from multiple hospitals adds further to the generalizability of the findings.

CONCLUSIONS

Early administration of therapeutic dose UFH seems to be associated with improved survival in patients diagnosed with septic shock. Although this study cannot justify the use of full-dose intravenous heparin therapy for septic shock at this time, these results highlight the need to conduct a prospective randomized control trial studying this drug in such patients.

ACKNOWLEDGMENTS

The authors acknowledge the intellectual contribution of Mr. Geoff MacDonell who assisted with the initial interpretation and evaluation of the data.

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