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Utilization and Efficacy of Activated Drotrecogin Alpha in a University Surgical Intensive Care Unit

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Abstract

Severe sepsis is a major cause of mortality in hospitalized surgical patients. Drotrecogin alpha has been approved for the treatment of high-risk patients in severe sepsis following the publication of a large randomized controlled trial. However, concerns over serious bleeding stand against its widespread use in surgical patients. The aim of this study is to compare the incidence of bleeding and 28-day mortality with the PROWESS trial under similar administration criteria. We performed a retrospective chart review of 35 patients admitted to tertiary care university hospital surgical intensive care unit. On evaluation, we found compared with PROWESS, our study demonstrated a comparable incidence of bleeding (3.3% vs. 3.1%) and a slightly higher, but not significant 28-day mortality (30% vs. 24.8%). We concluded that Drotrecogin alpha use in exclusively high-risk surgical cases is associated with comparable bleeding complications and mortality rates. Prospective studies in this homogenous patient population would be very beneficial.

Introduction

Severe sepsis is a major cause of morbidity and mortality among the surgical patients. According to recent epidemiologic data, it is estimated that approximately 750,000 patients develop severe sepsis in the United States annually, of whom 167,000 (21.4%) are surgical patients [1]. Despite adequate antibiotics, source control and supportive care, the mortality rate from severe sepsis ranges from 30% to 50% resulting in a high cost of care for affected patients (17 billion dollars annually) [1,2]. In addition, outcome from nosocomial infections are greater in patients who have recently undergone major operations as opposed to those who have not [3]. And in many patients, the "second hit" phenomenon is widely described as the etiology [4]. However, severe sepsis is alsoa consequence of a perioperative nosocomial infection of a non-surgical variety [5].

Drotrecogin alfa [activated] (DrotAA; Xigis; Eli Lilly, Indianapolis, Ind) was first approved by Food and Drug Administration (FDA) for adult patients with severe sepsis in 2001. As widely published, DrotAA possesses multiple effects including the promotion of fibrinolysis, and inhibition of thrombosis and inflammation. Due to the pathophysiology of severe sepsis these actions have been deemed desirable in patients suffering fromsevere sepsis [6]. The clinical indication supporting the administration of DrotAA with severe sepsisis based on the results of the phase III PROWESS trial [7]. This study demonstrated a reduction in 28-day mortality in patients with severe sepsis (24.8% mortality compared to 30.8% in placebo group). However, serious bleeding events occurred in 3.5 % of DrotAA treated patients and 2.0% of placebo patients in this heterogeneous patient population. Lingering questions remained regarding the safety and efficacy of DrotAA in surgical patients. As a result, the PROWESS Surgical Evaluation Committee conducted a retrospective analysis of prospectively collected data to assess the safety and efficacy of DrotAA, with focus exclusively on the surgical cohort from PROWESS. The results demonstrated that 28% of PROWESS cases were confirmed as surgical. The absolute risk reduction for mortality in all surgical patients was 3.2% and 9.1% for patients undergoing intra abdominal procedures. Serious bleeding during the infusion and 28-day period was similar between surgical and non-surgical patients [7]. In a larger cohort of surgical patients from 5 integrated clinical studies suffering from severe sepsis patients (1659/4459; 37 %), investigators examined drug safety and efficacy of Drot AA [8]. A 10.7% absolute all-cause mortality risk reduction (adjusted odds ratio, 0.66; 95% CI, 0.45-0.97) was observed for DrotAA-treated, high-risk (APACHEII ≥ 25) surgical patients. Although surgical patients who were treated with DrotAA demonstrated a greater proportion of serious bleeding events during the infusion period, the majority of patients were successfully treated.

Due to relative paucity of data and continued reluctance of many clinicians to use DrotAA in surgical patients with severe sepsis in our institution, we conducted a retrospective review of the medical records of all of the patients who were prescribed DrotAA in our surgical intensive care unit (SICU) following our own protocol. The objectives of this analysis were to describe the patient population, to review adherence to the SICU protocol for the use of DrotAA, to determine incidence of bleeding complications and 28-day mortality in comparison to the PROWESS trial, and attempt to explain any difference that were observed.

Methods

From January 2002 to February 2005, after obtaining an approval from Institutional Review Board, we retrospectively reviewed the medical records of patients who were treated with DrotAA as per SICU protocol of our institution. Patients were enrolled in the protocol if they meet the criteria for starting DrotAA. Patients were eligible for the DrotAA if they had a known or suspected infection on the basis of clinical data and had at least three of the following Systemic

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Inflammatory Response Syndrome (SIRS) criteria: temperature ≥ 38°C or ≤ 36°C, heart rate ≥ 90/min, respiratory rate ≥ 20/min or PaCO2 ≤ 32 or have been on mechanical ventilator and white blood cell ≤ 4000 or ≥ 12,000 or immature neutrophils ≥ 10%. In addition, patients must have had one or more sepsis-induced organ failure occurring within 48 hours that included mean arterial pressure (MAP) < 70 mmHg or systolic blood pressure (SBP) < 90 mmHg or have been on vasopressor, urine output < 0.5 ml/kg/hr, PaO2/FiO2 ratio < 250, platelets < 80,000 or had a 50% decline in 3 days and had an unexplained metabolic acidosis pH ≤ 7.3 or base excess (BE) ≤ -5 with lactate level > 1.5 times normal. According to the protocol, DrotAA was contraindicated in patients who had active bleeding at any site, had a recent blunt trauma with uncertain hemostasis, had a recent gastrointestinal bleeding, had closed head injury, intracranial or spinal injury or stoke within 2 months, had intracranial mass lesion, arterio-venous malformation or aneurysm and had a recent or planned for epidural catheter insertion. Additionally, the relative contraindication included platelets level < 30,000, INR > 3, had a recent use of unfractionated or low-molecular weight heparin at the dose other than DVT prophylaxis, using thrombolytic, hepatic failure, known bleeding disorder and pregnancy. After obtaining an approval from the critical care medicine attending of record, DrotAA was commenced at a dose of 24 mcg/kg/hr intravenous infusion for 96 hours in conjuction to routine care. The infusion was held 2 hours prior to any percutaneous procedure and resumed 2 hours after if there was no bleeding. In addition, DrotAA infusion was also held 2 hours prior to any non-emergent surgical procedure and resumed 12 hours later if no significant bleeding occurred.

Results

Patient Population

A total of 35 patients met the initial selection criteria for DrotAA SICU protocol. Medical records of 5 of the 35 patients were deemed incomplete, thus unable to be utilized for the study, leaving 30 patient records to be reviewed (Table 1). With regards to demographic characteristics, 50 % of the patients were female, the average age and weight were 60 ± 18 years and 82 ± 26 kg respectively. Thirty three percent of these patients were transferred from outside hospital. The majority of patients underwent intra abdominal surgical procedures (43%) (Table 2) Not surprisingly, the abdomen was the major site of infection (33%) followed by pulmonary and blood (17%) (Table 3) Regarding severity of patients, 90% of patients had septic shock and 93% were on mechanical ventilation at the time of DrotAA prescription. The need of vasopressors throughout infusion was 2.1 ± 1.1, 0.7 ± 0.5 and 0.5 ± 0.9 agents at 0, 48 and 96 hours respectively. The average APACHE II score in this population was 19 ± 6 with a 32% predicted mortality rate.

	SICU	PROWESS
Study design	Retrospective review	Prospective randomized controlled trial
No. of patients	30	1690 (28% surgical cases)
APACHE II	19.3	24.6
Bleeding complication	3.30%	3.10%
28-day Mortality in DrotAA treated group	30%	24.80%
28-day Mortality in controlled group		31.30%
Exclusion criteria		Stricter

Table 1: Comparison of our SICU experience versus Prowess.

Type of Surgical Procedure	# of Procedures
Abdominal	13
Thoracic	3
Vascular	3
Urologic	2
Obstetric	2
Incision and Drainage	2
Otolaryngologic	1
None	4
	30

Table 2: Types and Number of Surgical Procedures Performed.

Source	# of cases
Intraabdominal	10
Pulmonary	5
Hematologic	4
Genitourinary	3
Unknown	3
Soft Tissue	1
Pulmonary/ Blood	1
GenitoUrinary blood	1
Intraabdominal/ blood	1
Soft Tissue/ Blood	1
	30

Table 3: Sources of Sepsis.

Protocol adherence

Three of 30 patients had absolute contraindications for prescribing DrotAA. One of them suffered from gastrointestinal bleeding 13 days prior to DrotAA administration. The other 2 patients had perforated duodenal ulcer and surgery for bladder abscess 10 hours before starting DrotAA, respectively. With regard to relative contraindication, 4 patients were on heparin and 1 patient had platelets ≤ 30,000. All 30 patients were strongly suspected to harboring infection based on clinical examination. Moreover, they all met SIRS and sepsis-induced organ failure criteria for an enrollment into SICU protocol. There were 15 procedures or surgeries performed during DrotAA infusion period. Among these, the infusion was held appropriately according to the protocol in 8 circumstances. (central venous catheter insertion, gastrojejunostomy, bilateral thoracostomy, inferior venacava filter and undergone operations). The infusion was not held appropriately in 6 procedures and surgeries including central venous catheter insertion, arterial line insertion, and pulmonary artery catheter insertion, surgery for revision of colostomy and surgery for necrotic bowel. For the last two operations, DrotAA was restarted after 6 and 8 hours respectively. The infusion was held in another case for an unknown reason.

Bleeding complications

Bleeding complications occurred in one patient (3.3%). This patient had a diagnosis of ischemic bowel and subsequently developed mental status changes after two days of receiving DrotAA. A computed tomography of the head revealed massive cerebral hemorrhage, however, it was discovered that this patient had a history of fall before being admitted to hospital that had been undisclosed. In addition, this patient did not have any known absolute or relative contraindications. In addition, 23 of 30 patients completed 96 hours of the DrotAA infusion, whereas 7 cases were unable due to the following reasons; 3 patients died before the completion (unrelated to DrotAA), one infusion inadvertently stopped early, one patient was transferred to a different ICU and therapy was not continued, one patient had an

intracranial hemorrhage discovered and one patient had low platelets, anemia and was scheduled for an urgent surgical procedure.

28- day Mortality

Of the 30 patients studied, 9 patients died within 28 days. Regarding mortality by surgical system, 4 died from intra abdominal pathology, 2 from a thoracic source, and 2 from soft tissue sources. The cause of death was not found in one patient. On the other hand, 21 patients survived more than 28 days, however, 3 patients died after 28 days. In all, 18 patients were discharged alive. In summary, our 28-day mortality was 30 %.

Discussion

This retrospective study describes our experience with DroctAA (activated) in a cohort of surgical patients with severe sepsis and septic shock. As per our protocol DroctAA at a dose of 20 mcg/kg/hr was associated with an incidence of bleeding of 3.3% and a 28-day mortality of 30%.

The abdomen was the major site of infection, accounted for the majority of surgical procedures and was associated with the highest mortality. This is consistent with data from the PROWESS [8] surgical cohort and the International integrated database for the evaluation of severe sepsis and DroctAA (activated) therapy (INDEPTH) [9].This might be due to the fact that surgical patients with severe sepsismay often present with a perforated viscous, peritonitis and/or an abscess [10].Generalized peritonitis was associated with an increase in organ-related dysfunction and mortality among critically ill surgical patients [11].

The 28-day mortality was slighter higher but not significant in our study compared to the study group in PROWESS (30% versus 24.8%) despite having a lower APACHE II score (19.6 versus 24.6). This can be explained by several reasons. First, our study contained no control group. Second, there were fewer adherences to the protocol for using DrotAA in our study compared with PROWESS in terms of patients with contraindications receiving DrotAA, and the inappropriate timing for which DrotAA was initiated or restarted relative to surgical procedures. A mortality benefit might have been shown had DrotAA been started in the first 24 hours instead of 48 hours as shown by Hodder et al in a retrospective analysis of a Canadian cohort of severely septic patients [12]. Third, our study contained a smaller number of patients compared with PROWESS. Fourth, our study population is different from PROWESS. Unlike PROWESS, we included patients with acute pancreatitis who died during the course of the study. Fifth, the APACHE II suffers from some limitations in assessing disease severity in surgical patients [13]. Therefore, the lower APACHE II scores might not reflect the disease severity in our surgical patients. Our higher 28-day mortality in relation to PROWESS is consistent with several retrospective observational studies. In a multicenter observational Canadian study, Kanji et al observed a 28 day mortality of 45 %. Authors found that age > 65 years, more than 3 organ failures and nosocomial source of sepsis to be independent predictors of mortality. They also found that early administration of DrotAA (within 12 hours) to be associated with less mortality [14].

Our study showed comparable bleeding events to PROWESS (3.3% versus 3.1%). Bleeding occurred in only one patient in our study with a recent head trauma who was inadvertently placed on DrotAA. None of the bleeding events were fatal. Similar findings were seen in the surgical cohort of PROWESS where serious bleeding during the infusion and 28-day period were similar between surgical and non surgical patients treated with DrotAA [9]. Our findings are consistent with INDEPTH where surgical patients treated with DrotAA experienced less fatal bleeding events (3/1230 patients 0.2%) compared with the nonsurgical group (10/1995 patients 0.5%). (10). In a chart review of 100 patients with severe sepsis treated with DrotAA, Taylor et al found no significant difference in the rate of bleeding complications (transfusion of greater than 3 units of blood, an intracranial hemorrhage or other serious bleeding event) between surgical and non surgical patients [15].

The limitations of our study are; first its retrospective nature. Second, the limited number of patients involved that precluded more rigorous statistical analyses. Third, in a chart review data are dependent on the accuracy and timing of charting. Fourth, there was no control group to make comparisons in adverse events.

Our experience demonstrates that the use of DrotAA in high-risk surgical patients suffering from severe sepsis can be conducted and does not necessarily increase the risk of adverse outcomes as one may anticipate. However, we believe that further studies are needed to evaluate the relationship between sepsis severity, bleeding management, surgical intervention and the postoperative timing of DrotAA administration.

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