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Decisions in Trauma Care: Managing Coagulopathy to Facilitate Organ Donation

September 25, 2009

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Introduction

On a clear windy day in December 1954, [Dr. Joseph Murray](#) performed the first successful human organ transplant at Brigham and Women's University in Boston, Massachusetts, thereby opening the door for future organ recipients. Fifty-five years later, organ transplants are performed regularly due, in part, to the advent of immunosuppressant agents and improved alternative care for patients with organ disease or organ failure.¹ According to data from the Institute of Medicine (IOM), in 2005, more than 28,000 solid organ transplants were performed in the United States, up from approximately 13,000 in 1988.² However, while the number of transplants has increased, so, too, has the demand, which now exceeds the supply ([Figure 1](#)).²

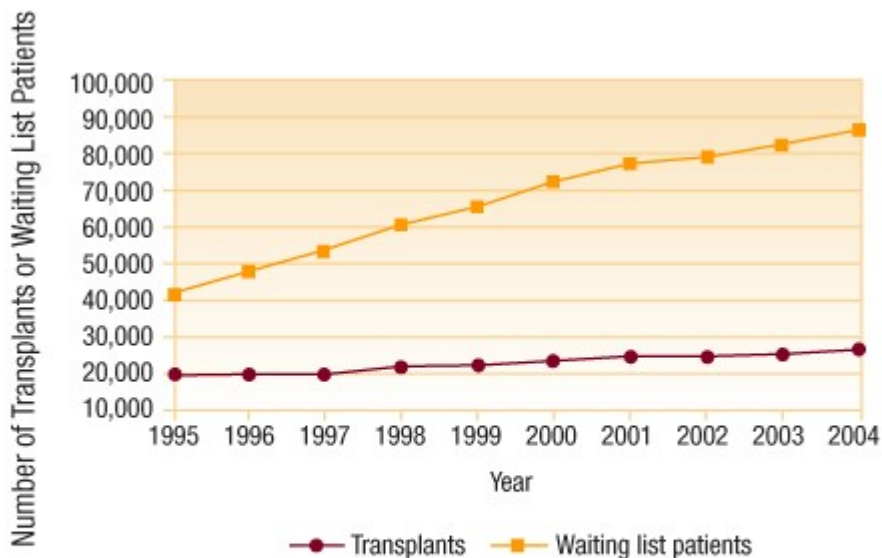


Figure 1

Growth in the number of transplants and in the number of candidates on the transplant waiting list. Posted with permission from the Institute of Medicine.²

Currently, there are more than 100,000 candidates on a waiting list for organs,³ and every 12 minutes, the list grows by one name.⁴ An average of 18 people die daily while waiting for an organ, and the list grows

exponentially; the average wait time for a kidney, for example, is more than 3 years.⁵ With an increasing prevalence of obesity, hypertension, and diabetes, as well as infectious diseases such as hepatitis C, the demand for organs is expected to increase further.⁶

In attempts to narrow the [organ donation](#) gap, local and federal initiatives have been created, including the [United Network for Organ Sharing](#) (UNOS), which operates the Organ Procurement and Transplantation Network (OPTN),⁷ and the Department of Health and Human Services Organ Donation Breakthrough Collaborative.⁶ The Breakthrough Collaborative encourages hospitals and organ procurement organizations (OPOs) to develop and implement best practices to facilitate organ procurement and transplantation and, equally importantly, calls for research targeting new ways to increase donation rates while maintaining quality end-of-life care for patients.² The goal of these initiatives is to increase the number of potential donors.^{6,7}

Strategies for Increasing Organ Donors

Recent investigations have explored strategies to increase the pool of deceased organ donors. Approximately 3 of every 4 organs that are transplanted come from deceased donors (**Figure 2**),⁷ and the number of deceased donors from all hospitals in the United States ranges from 10,500 to 13,800 annually.⁶ Perhaps clinicians in the trauma care setting are most affected by these statistics, as 40% of organ donors have sustained traumatic injury and devastating neurologic injury.⁸ Trauma care specialists often have very little time to make decisions that will ultimately impact a patient's mortality. Recent theories concerning the acute coagulopathy of trauma postulate that it occurs early in the postinjury period,^{9,10} and many trauma patients die within hours of admission to the hospital emergency department.¹¹ Typically in this setting, intervention strategies include judicious use of resuscitation fluids, replacement of coagulation factors, and administration of agents such as [recombinant factor VIIa](#) (rVIIa) to reverse coagulopathy.¹² In the traditional scenario, if patients did not survive their injuries, they often died as a result of multiple organ failure. The climate has changed, however. In an era with a limited organ supply and evolving resuscitation strategies, clinicians are presented with another option for their patients with nonsurvivable injuries: survival for organ donation.

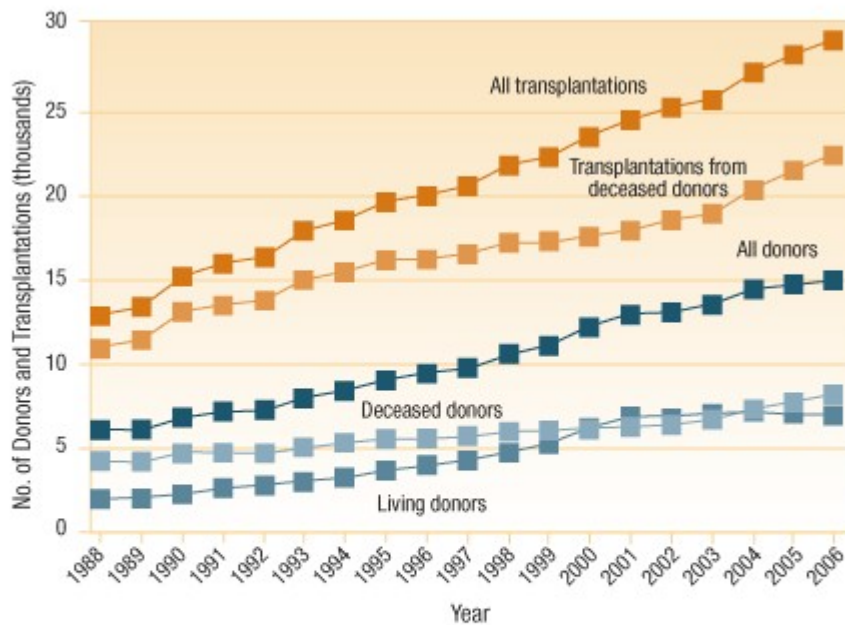


Figure 2

Organ donors and transplantations in the United States, 1988-2006. Data are from the Organ Procurement and Transplantation Network. Posted with permission from Steinbrook.⁷ Copyright ©2007 Massachusetts Medical Society. All rights reserved.

Two recent studies examined off-label use of (rVIIa) as “salvage therapy” for patients with nonsurvivable injuries who otherwise may have been ineligible for organ donation.^{8,13} Stein and colleagues conducted a retrospective review of deceased organ donors from a 6-year period at the R Adams Cowley Shock Trauma Center in Baltimore, Maryland, to compare donors who received rVIIa with donors who received conventional therapy.⁸

Study 1: Select Key Points

- 148 patients with devastating neurologic injury had organ recovery following declaration of brain death or withdrawal of care
- 29 patients received rVIIa; 119 patients received conventional therapy with plasma to reverse coagulopathy
- 21 of 29 rVIIa recipients were dosed before determination of nonsurvivability or plans for care withdrawal and were coagulopathic at time of rVIIa administration
- Indications for rVIIa administration included active hemorrhage (13 patients), enabling neurosurgical intervention (15 patients), and reversal of severe coagulopathy (1 patient)
- 8 patients administered rVIIa specifically as salvage therapy to permit donation

Based on a records review, researchers determined that patients treated with rVIIa, despite having sustained greater injury severity and physiologic compromise than the conventionally treated patients,

were able to donate organs at comparable rates: 101 organs were donated from the 29 rVIIa-treated patients versus 430 organs from the 119 patients who received conventional treatment (see **Table 1**).⁸ Moreover, the number of organs transplanted per donor were similar in the 2 groups (3.5 in the rVIIa group vs 3.6 in the conventionally treated group, $P=.7$). There also was nearly twice the rate of recovery of donated lungs in the rVIIa group ($P=.04$). Overall, the reviewers found that use of rVIIa facilitated donation in patients with devastating injuries who otherwise may not have been eligible for organ donation.⁸

Table 1. Percentage of Eligible Organs Transplanted

Group	n	SCD	DCD	ECD
rVIIa	29	17	11	1
No rVIIa	119	80	36	3

Group	Heart n (%)	Lung n (%)	Liver n (%)	Pancreas n (%)	Intestine n (%)	Kidney n (%)
rVIIa	9 (56)	15 (47)	19 (65)	11 (39)	1 (6)	43 (74)
No rVIIa	45 (56)	42 (26)	99 (83)	52 (43)	1 (1)	192 (81)

DCD=donation after cardiac death; ECD=extended criteria donors; rVIIa=recombinant factor VIIa; SCD=standard criteria donors. Data from Stein et al.⁸

The study results obtained by Stein and colleagues were observed on a much smaller scale by Aiyagari et al 4 years earlier.¹³ Investigators retrospectively reviewed the records of 3 patients who sustained gunshot wounds to the head with refractory bleeding. rVIIa was administered to reverse coagulopathy and stop bleeding following use of conventional treatment with blood products, including cryoprecipitate, fresh frozen plasma, and platelets.¹³

Study 2: Select Key Points

- All 3 patients had ongoing bleeding secondary to severe coagulopathy
- Active bleeding was refractory to standard replacement therapy
- At time of clinical presentation, patients' injuries were not known to be nonsurvivable
- rVIIa was administered in an attempt to achieve hemostasis and stabilize the patients to establish a diagnosis

Although investigators retrospectively determined that all 3 patients had nonsurvivable injuries, administration of rVIIa at the time of presentation resulted in rapid correction of abnormal coagulation parameters, arrest of bleeding, and reduction in transfusion requirements (see **Table 2**).¹³ Two patients went on to become successful deceased organ donors once hemodynamic stability was achieved.¹³

Table 2. Serial Hematologic Parameters Before and After Administration of rVIIa

	Time after admission (h:min)	Hematocrit (%)	Platelets (10 ³ /mm ³)	PPT (s)	PT (s)	INR	Fibrinogen (mg/dL)
Case 1							
Before rVIIa	0:00	34.8	171	42.6	20.6	1.89	48
	3:00	22.8	97	51.1	24.0	2.31	
After rVIIa	5:30	30.0	107	36.0	14.7	1.22	227
	9:00	29.1	94	31.4	13.1	1.05	
	16:00	38.5	111			1.89	
Case 2							
Before rVIIa	0:00	16.4	139	>150.0	>106.0	>15.94	<20
	2:00	20.1	115	>150.0	>106.0	>15.94	
	3:00	22.9	67	107.3	30.5	3.16	
After rVIIa	8:30	25.9	27	36.5	12.6	1.00	199
	13:00	21.8	71	32.2	13.1	1.05	
	20:30	26.9	105	34.2	14.0	1.15	
	29:30	26.5	81	34.0	15.4	1.30	
Case 3							
Before rVIIa	0:00	43.3	134	85.8	24.0	2.31	53
	4:30	30.5	131	85.8	29.5	3.02	
After rVIIa	8:00	37.4	203	40.8	13.8	1.13	
	10:45	35.6	203	36.9	15.1	1.27	

INR= international normalized ratio; PPT=partial prothrombin time; PT=prothrombin time; rVIIa=recombinant factor VIIa. Reprinted from Journal of Critical Care, Vol 20, Aiyagari V, Menendez JA, Diringier MN, Treatment of severe coagulopathy after gunshot injury to the head using recombinant activated factor VII, pages 176-180, ©2005, with permission from Elsevier.¹³

In both retrospective reviews, investigators determined from outcomes data that recovered organs were successfully transplanted, with no adverse effect on graft function in recipients and no significant ischemic damage from intravascular coagulation in the organs, despite administration of rVIIa.^{8,13}

Both studies, despite their limitations in size and design, demonstrated that off-label use of rVIIa facilitated organ donation in patients with severe coagulopathy and fatal injuries who otherwise may have been unlikely candidates for donation.

Financial and Ethical Concerns

Both teams of investigators, in achieving hemostasis in their patients with nonsurvivable injuries through the off-label use of rVIIa, were able to preserve the possibility of organ donation and potentially increase the donor pool. Nevertheless, the use of such methods to do so has raised financial and ethical concerns that center on the question of whether clinicians are engaging in experimentation and acting irresponsibly when a treatment modality used to save lives is used to preserve lives.

Fairfax and colleagues, in response to the retrospective study conducted by Stein et al, question

whether the high cost of rVIIa justifies its use as salvage therapy, specifying that the charge for one dose of rVIIa for a 70-kg patient is \$7961 USD.¹⁵ Indeed, Stein and colleagues note that a single large weight-based dose of the agent costs nearly \$10,000 USD.⁸

“Recombinant factor VIIa is expensive, but its use is justified if the organ donor supply can be increased.”⁸

Addressing the issue of cost, Aiyagari et al determined that it may be more economically advantageous to use rVIIa, considering the rising costs of transfusion in the United States and the fact that in the clinical situations presented, transfusion requirements would have significantly increased if rVIIa had not been used.¹³ Additionally, administration of rVIIa in lieu of blood products for certain patients may be a more viable solution because not all institutions have unlimited availability of blood products at all times.

Another argument raised concerns the administration of experimental substances to patients who are unable to give informed consent.¹⁴ Although the approved indications for rVIIa include hemophilia A and B, acquired hemophilia, and certain factor deficiencies,¹⁶ its off-label use for managing the coagulopathy of trauma is well documented.¹⁷⁻²¹ In all or many of the clinical situations described by the Stein and Aiyagari research teams, rVIIa was administered before determination of nonsurvivability to reverse coagulopathy and maintain hemostasis, ^{8,13} a context for the agent that may be off-label but cannot be considered experimental.

As Aiyagari and colleagues note, although rVIIa cannot be considered experimental in the context in which it was used, viewpoints differ regarding whether consent should be obtained when administering an approved drug for a nonapproved use. However, it is the prescribing physician's responsibility to determine the most appropriate drug for each patient, and given the exigencies of a trauma situation, when patients cannot speak for themselves and their families are not immediately available, consent becomes secondary to the stabilization of refractory, life-threatening hemorrhage and doing what is best for the patient.¹⁴ As Aiyagari and investigators state, “There appears to be a point at which nonapproved uses of drugs become acceptable without prior consent. It is up to the treating physician to determine when that line is crossed.”¹⁴ Moreover, consent is not required for off-label indications if the drug is used as part of an institution's local standard of care.

Conclusion

The idea of employing methods that routinely have been used as life-saving devices to facilitate organ donation among deceased donors is relatively novel, and like all novel ideas, must be put to the test of time, debate, and continued discussion. Physicians need not be advocates of organ donation,

necessarily, but as Stein and colleagues have indicated, they should regard donation as an integral part of end-of-life care for patients and their families.⁸ It is the physician's responsibility to abide by a patient's/family's end-of-life wishes, even if those wishes include organ donation. To do otherwise and allow patients to exsanguinate would leave no possibility for donation and, perhaps, the opportunity to save a life elsewhere.

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