

CONTEMPORARY ANESTHESIA MANAGEMENT FOR LIVER TRANSPLANTATION

A Comparison of American and European Methods

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Abstract

This review article compares the organization of liver transplantation programs, anesthesia management and postoperative care in the United States and Europe.

Liver transplantation is a definitive treatment for end-stage liver disease. The procedure is extremely complex and requires excellent surgical technique and experienced anesthesiologists who are able to provide precise management. Liver transplantation programs, which first started in the United States and a few years later in Europe, have quickly been able to achieve remarkable results.

In the United States one organization, the United Network for Organ Sharing (UNOS) is responsible for the allocation of organs and data collection; in Europe there are various organizations with different levels of cooperation. The major difference between anesthesia management in the United States and Europe is the number of medications available for coagulation improvement. Substances such as prothrombin complex concentrate, fibrinogen, and antithrombin III allow for a greater flexibility in European anesthesia management. Thromboelastography, which is routinely used in the United States for overseeing coagulation, is now increasingly being used in Europe, and seems to be highly effective in providing precise information about coagulation. The overall ICU stay in Europe is longer than in the United States, and services such as maintenance of critical care, immunosuppression and nutrition are not separated in Europe.

Despite these differences in liver transplantation programs, overall one-year patient survival rate is similar in the United States and in Europe, exceeding 85% in both.

A brief history of liver transplantation

The history of solid organ transplantation started in 1954 in the United States with the first successful live-donor related kidney transplant. Dr. Joseph Murray performed the surgery at Brigham Hospital in Boston. The first liver transplant was done nine years later, again in the United States, on 1 March 1963 by Dr. Thomas

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Starzl in Denver, Colorado. Unfortunately, the patient (a 3-year-old child with biliary atresia) died a few hours after the procedure. By 1967, however, Dr. Starzl was successful in achieving long-term survival; an 18-month-old patient was alive one year after transplantation, which was unprecedented. The first European orthotopic liver transplantation was performed by Dr. Roy Calne in 1968 in the U.K., followed by Dr. Alfred Gütgemann, the head of the surgery department at the University of Bonn in 1969. About 40 doctors and nurses participated in the surgery, which lasted 5½ hours and was very successful. The patient survived seven months after the procedure, which was a very good result at the time. In 1972, Dr. Rudolf Pichlmayer, from Hannover, Germany, founded one of the biggest liver transplantation centers in Europe. Since then several transplantation programs have been established in various European countries, especially in Germany, France, England, Spain and Italy, where a large number of transplantations have been performed in different centers. The initial one-year survival rate of 24-30% was drastically improved to 70% in the 1980s, when the effectiveness of cyclosporine was confirmed for organ grafting. The shortage of donor livers forced the development of alternative procedures, such as partial liver transplantation. The first split liver transplants were performed at the same time in the United States and Europe in 1988. In 1989 the first live-donor related liver transplantation was completed by Dr. Russell Strong in Australia.

The competition between the United States and the European Union is ongoing, with the number of transplantations being similar, averaging about 5000-6000 per year (Table 1).

Table 1
Comparison of the total number of liver transplantations between Europe and United States from 1988 to 2007

To Date	Overall liver transplantation in the United States	Overall liver transplantation in Europe
1988	1713	1280
1989	2201	1720
1990	2690	2111
1991	2953	2508
1992	3064	2762
1993	3440	3000
1994	3652	3330
1995	3934	3629
1996	4084	3757
1997	4188	4038
1998	4516	4266
1999	4751	4587
2000	4997	4821
2001	5195	4945
2002	5332	5142
2003	5673	5095
2004	6171	5421
2005	6444	5475
2006	6651	5487
2007	6494	5624

2008	6319	4196
Overall	94,464	85,446

Based on OPTN data and ELTR data as of February 4, 2010.

Organization of the transplantation network

Soon after the first successful steps in transplantation and the establishment of transplantation centers, it became clear that the procedures had to be coordinated on a regional or national level in order to procure and distribute organs. Gathering transplantation dates and dealing with legal issues became an additional responsibility of these national and international organizations. In the United States, the Southeast Organ Procurement Foundation (SEOPF) was established in 1968 to integrate all transplant programs and to coordinate the research in this field. SEOPF introduced many innovations: in 1977 it initiated the first computer-based organ matching system, and in 1982 it established the kidney center with 24-hour assistance. In 1984 the United Network for Organ Sharing (UNOS) separated from SEOPF and received a federal contract for operating the Organ Procurement and Transplantation Network. Now UNOS operates the computer-based system for organ matching, gathers all information about transplantations, and publishes reports of mortality and survival for all US-active transplant centers. In 2002, UNOS introduced the MELD (Model for End-Stage Liver Disease) scoring system, which changed the organ allocation system in the United States. UNOS was also one of the organizations that took part in the founding of Donate Life America to explain the importance of organ donation to the public. Thanks to UNOS, the idea of organ donation has become more acceptable in all segments of society. Today UNOS coordinates 253 transplant centers with 908 different transplant programs (128 programs for liver transplants, with currently more than 16,000 patients on the waiting list (based on OPTN data 2009). UNOS also provides information about the average waiting time and survival ratio for different organs in different regions.

In Europe, transplant services are organized slightly differently. The structure of transplantation services is more complicated. Depending on the country in Europe, there are several organizations responsible for transplantation.

Founded in 1967 by Dr. Jon J. van Rood, Eurotransplant is the largest organization, with its main office in Holland. The aim of Eurotransplant is similar to that of UNOS: to register all patients who need organ transplants and to improve the matching system. The organization started with the allocation of 11 kidney grafts in the first year and 60 in the following year. About 75 transplantation centers currently participate in Eurotransplant (36 for liver transplantation), and more than 15,000 patients are on the waiting list (about 2500 for liver transplant). The other European national transplantation organizations were founded at about the same time and have the same purpose as Eurotransplant. Balttransplant is the only new organization that has recently been added in order to coordinate transplantation activity in Estonia, Latvia and Lithuania.

The development of liver transplantation programs in Eastern Europe has been relatively slow. In 9 out of 19 former communist countries, early attempts were made to start liver transplantation with very low numbers of procedures and survival rates, below those of the established programs. In the 1980s and 1990s, Hungary, Poland, and in particular the Czech Republic began successful programs with a one-year survival rate of about 90%¹. In Poland there are currently 5 adult-liver transplantation programs and 1 pediatric liver transplantation program, with about 400 patients on the waiting list and a mean waiting time of 200 days.

In 1985, the European Liver Transplant Registry (ELTR) was founded at the meeting of the European Society for Organ Transplantation in Munich. This step was important for the coordination of procedures, data gathering, and coordinating research between the different transplantation programs in various European countries. Initially, 32 European centers participated in the ELTR. With currently 137 centers from 23 countries, ELTR harbors an enormous scientific potential. ELTR has collected data regarding more than 70,500 transplantations performed in Europe, including data about indications for transplantation, donors' (including living donors') and recipients' blood group compatibility, data about a variety of surgical techniques, mortality reports, graft survival data, data about immunosuppression therapy and recipient survival rates (Table 2 and 3).

Table 2
Recipient survival rates in Europe

Year	Survival overall	1 Year Survival %	5 Year Survival %	7 Year Survival %	10 Year Survival %
1985	519	34	22	20	18
1985-1989	4129	64	53	50	46
1990-1994	12.007	77	65	61	56
1995-1999	18.162	82	71	66	
2000-2004	22.945	85	74		
After 2004	18.786	87			

European Liver Transplant Registry (ELTR). Data analysis as of December 2007. Available at: <http://www.eltr.org>. Accessed February 4, 2010.

Table 3
Recipient survival rates in the U.S.A

Liver Donor Type	Years Post Transplant	Number of Functioning Grafts	Survival Rate	95% Confidence Interval
Cadaveric	1 Year	13,057	86.3	(85.7, 86.8)
Living	1 Year	823	90.1	(88.1, 92.1)
Cadaveric	3Year	12,823	78.0	(77.4, 78.6)
Living	3 Year	1066	82.7	(80.6, 84.7)
Cadaveric	5 Year	10,402	72.0	(71.3, 72.7)
Living	5 Year	505	77.9	(74.7, 81.0)

1 year survival based on 2002-2004 transplants, 3 year survival based on 1999-2002 transplants, 5 year survival based on 1997-2000 transplants. Based on OPTN data as of February 4, 2010.

Cost Issues

Liver transplantation is one of the most expensive medical procedures performed. It is, therefore, of interest to compare cost variations of liver transplantation between the United States and other countries. The Organization for Economic Cooperation and Development (OECD), which includes 24 European countries, USA, Canada, Japan, Korea, New Zealand and Australia, recently published a report (van der Hilst et al., 2009)

about expenses in this field. The estimated mean cost of a liver transplantation in the United States (in 2005 dollars) was \$163,438 (\$145,277-\$181,598) compared to \$103,548 (\$85,514-\$121,582) for other OECD countries². Patient characteristics, disease characteristics, quality of health care provider, and methodology could not explain this cost difference. Health system characteristics differed between the United States and other OECD countries. Cost differences in liver transplantation between these two groups may be, therefore, largely explained by health system characteristics. It is interesting that within each center the factors having a major influence on cost were: etiology of liver disease, patient status at the time of transplantation, necessity of re-transplantation, and duration of hospital stay³. It is unlikely that differences in anesthesia management contribute to the described differences; as based on the United States experience, anesthesia costs are responsible for only a fraction of the total liver transplantation bill. Instead, the higher cost of liver transplantation in the United States is in line with other health costs, including the higher price of hospital stays, physician services, and pharmaceuticals.

Intraoperative Anesthesia Management

The general management of anesthesia for liver transplantation is similar in the United States and in Europe. In summary, different transplantation centers have slightly different standards, but overall, general endotracheal anesthesia (GETA) is the standard of care. Epidural anesthesia is not used because of the compromised coagulation and platelet function⁴. Most centers in Europe no longer float a pulmonary catheter (Swan Ganz catheter) in order to monitor cardiac output, pulmonary pressure, and central venous pressure for several reasons: the patient selection process has been improved, the catheters are expensive, and the procedure is invasive and often leads to complications. In the United States, use of the Swan-Ganz (SG) catheter remains relatively common, but there is a clear trend towards a reduction in its use by most centers both in Europe and the United States. Transplant anesthesiologists have instead begun measuring central venous pressure (CVP), as well as using different non-invasive methods for cardiac output estimation and the relay of certain biochemical parameters (e.g., base deficit or lactate level) for volume management during the liver transplantation. In both the United States and Europe, keeping the CVP low during liver transplantation seems to be critical for anesthesia management. Although there is no clear evidence for its ideal level, the CVP is generally kept between 5 and 10 cm H₂O. However, it is important to note that lower CVP values could be a reason for hypotension and deterioration of microperfusion in grafts. A CVP significantly higher than 10 cm H₂O is a cause of liver congestion, deterioration of liver function, and substantial coagulopathy. This is one of the reasons for relatively restrictive volume management, using blood products (FFP or PRBCs units) and albumin to increase colloid osmotic pressure, with only limited infusion of normal saline.

New modalities for volume and cardiac status monitoring include increasing the use of TEE intraoperatively instead of a SG catheter. The role of non-invasive cardiac output devices (e.g., esophageal Doppler, arterial line pulse contour analysis, etc.) is continually increasing.

Correction of Coagulation

Keeping the CVP in the desired range is very difficult in cases where there is both coagulopathy and a need to administer blood products. In the United States, the blood products available for correction of intra- or postoperative coagulopathy include FFP, platelets, and cryoprecipitate. In Europe there are some additional

treatment possibilities that are not currently available in the United States due to a lack of FDA approval. Prothrombin complex concentrate (PCC; also called PPSB in Germany and Beriplex P/N in the UK) can significantly improve coagulation with only minimal volume expansion. It was first successfully applied in 1959. Since then, this agent has frequently been used in situations of extensive coagulopathy. The medication consists of a combination of balanced coagulation factors (Factor II Protrombin, Factor VII Proconvertin, Factor X Stuart-Prower-Factor, Factor IX antihemophilic Factor, Protein C, Protein S, Protein Z, AT III [15-30 U], and Heparin [250 U]). Depending on the situation, a dose of 1200 U-3000 U is necessary for significant improvement of coagulation. Every 600 U must be dissolved in 20 ml fluid. This means that volume exposure is 40-100 ml for the optimization of coagulation. The alternative to PCC is giving FFP units with extensive amounts of volume (each unit is about 250 ml). The use of PCC is very favorable, especially in situations where there is already a high CVP level. PCC can significantly improve coagulation in a very short period of time, which is desirable in many clinical situations^{5,6}.

This is a major reason why PCC is used in Europe as widely as it is; not only for liver transplantation, but also for a variety of specific clinical situations in which coagulation is compromised and it is necessary to quickly prepare a patient for surgery. Use of the medication is safe when applied according to recommendations. The possibility of thrombosis is a major complication of this medication. The first report about DIC after using PCC was published in 1959. Other possible thrombotic complications are: deep vein thrombosis, myocardial infarction, and lung embolism⁷. Allergic reactions were described after application of PCC as well. An additional problem with this medication is its extremely high cost: for this reason, only a senior hematologist may prescribe this medication in the UK.

A further difference between Europe and the United States is the availability of fibrinogen for transfusions in the former but not in the latter. The medication is not FDA approved in the United States, and thus the transfusion of cryoprecipitate is the only possibility to adjust fibrinogen levels. Cryoprecipitate is available in Europe as well, but an infusion of fibrinogen is preferred because it allows administration of the medication in a more precise, faster manner, and with less volume exposure. Fibrinogen is available in powder form, and the volume amount that is necessary for infusion is comparable with PCC. The adverse effects after administering fibrinogen are similar to those after administering PCC: thrombosis and allergic reactions. With careful use, and taking into account all advantages and disadvantages, the administration of fibrinogen is safe and has been widely used in European countries for correction of impaired coagulation.

Aprotinin has been used for many years in liver transplantation. There are many publications that demonstrate blood product transfusions can be reduced with a prophylactic infusion of a low dose of aprotinin. Generally, the prophylactic use of antifibrinolytics is very controversial. Nowadays, its use in veno-venous bypass for liver transplantation is very rare, and we no longer expect the activation of plasmin and fibrinolytic cascade. Discussion about the prophylactic use of this group of medications has existed for several years, and we currently have no clear answer. Aprotinin was withdrawn from the market in 2008 in the United States and Europe and can be used only for studies on cardiopulmonary bypasses. Different centers in the United States and Europe have started the use of tranexamic acid and epsilon aminocaproic acid, which have a mechanism of action similar to aprotinin. Although the publications show a slightly higher evidence of arterial and venous thrombosis in patients with tranexamic acid and epsilon aminocaproic acid treatment in comparison to those where aprotinin was applied, its impact on clinical practice is not completely clear⁸.

The use of thromboelastography (TEG) for coagulation management, both in the United States and in Europe, constitutes the more recent trend in coagulation monitoring. The method is relatively old and was first

described by the German researcher Helmut Hartert in 1948⁹. In contrast to traditional coagulation studies, TEG is a relatively simple procedure to analyze clot formations under dynamic conditions. TEG measures the viscoelastic properties of blood as it is induced to clot under a low shear environment resembling sluggish venous flow. The patterns of changes in shear elasticity enable the determination of the kinetics of clot formation and growth as well as the strength and stability of the formed clot¹⁰. This procedure allows the exact determination of coagulopathy. TEG has not been implemented in clinical practice for many years. In 1980, anesthesiologists in the United States began using the procedure routinely for liver transplantations. In Europe, the application of thromboelastogram is not the standard of care. In Germany, TEG has been on the market since about 2000, and many transplantation centers have begun its use in special clinical situations. A large number of publications have shown that thromboelastography can recognize coagulation problems faster, more specifically, and sometimes in situations when the coagulation profile is still normal¹¹. TEG was a significantly better predictor (87% accuracy) of postoperative hemorrhages and the need for reoperation than the activated clotting time ACT (30% accuracy) or coagulation profile (51% accuracy)¹⁰. Our expectation is that TEG will be the routine standard of care in the near future for liver transplantation.

Postoperative Care for Liver Transplantation Patients

The organization of postoperative care for liver transplantation patients in the United States is somewhat different than in Europe. In the United States, surgeons are the usual care providers, and anesthesiologists (and other specialists) are involved in the postoperative care for transplant patients only occasionally, in particular in the big centers. In Europe the main emphasis in the education of anesthesiologists is placed on critical care; consequently, the majority of SICUs are run by anesthesiologists. Teams on the transplantation SICU usually consist of up to 50% of anesthesiologists and 50% of surgeons, and we believe that this cooperation might significantly improve the quality of care. The next significant difference between the United States and Europe is the absence of separate care for different services (i.e., in Europe the same team is usually responsible for maintenance of postoperative care, nutrition, ventilation, antibiotic therapy and immunosuppression). This approach requires additional training for the SICU team members but enables them to provide care more consistently and improves the flow of information.

In the United States discharge from the intensive care unit occurs much faster in uncomplicated cases (less than 24 hours) than in Europe, where the ICU stay is five days and more.

Early extubation became the gold standard in Europe in order to prevent postoperative pulmonary infections in patients with a high level of immunosuppression, as well as to improve hemodynamic stability and to facilitate easier neurologic monitoring of patients. Certainly, early extubation requires closer observation and monitoring of patients especially on the first and second day after the operation, but involvement of anesthesiologists in ICUs with expertise in the area of airway management makes the process easier. In the United States the extubation of transplant patients in the operating room at the end of surgery is becoming more and more popular but, unfortunately, does not have widespread acceptance, especially among surgeons.

It is important, however, to note that even if centers in the United States have a shorter length of stay than centers in other countries, this does not translate into overall lower costs.

Conclusion

Liver transplantation has become a remarkably successful project, offering critically ill people a new chance to achieve a good quality of life. With the improvement of surgery and anesthesia techniques and the use of newer medications for immunosuppression, patient and graft survival have been vastly improved. Currently, the longest patient survival rate is more than thirty years after a successful liver transplantation. Liver transplantation is an example of how an extremely complex procedure requires close cooperation between different specialties.

The United States and Western Europe have some of the biggest transplantation centers in the world. The development of transplantation programs on both continents took slightly different paths, but with very similar final results. Many countries that were not very active in this area now recognize the ethical and financial advantage of liver transplantation and have started, or are about to start, their own programs with the aim of achieving established standards.

Despite different program lengths and experiences, the anesthesia management for liver transplantation is becoming increasingly convergent. The difference in the structure of the transplantation service, the transplantation procedure and postoperative care do not have a major influence on the final outcome. Few differences in anesthesia management, none of them in critical areas, have been observed. In Europe, the wider choice of medications, especially for coagulation adjustment, allows the transplant anesthesiologist more flexibility in the management of transplantation patients but it does not improve results significantly.

In the United States, the cost of liver transplantation is higher despite a significantly shorter postoperative hospital stay. At the same time, the outcomes in the United States are similar to Europe, with a patient survival rate of 88% at one year and 72% at five years. In the current financial situation, both continents are claiming a reduction in costs, but it is very likely that expenses in the United States will be higher in comparison to Europe due to the structure of the health care system and the significantly higher price of medications. It is expected that the process of unification in the management of liver transplantations will further progress, and with recent pressure on reducing health care costs, the difference between the United States and Europe will gradually diminish even further.

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