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Original Research

The new "Living Donor Liver Transplantation Program" Created by the Scientific Cooperation Between Malatya and Bishkek

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Abstract

Objectives: In countries that do not have legal regulations regarding organ donation and brain death, only living donor liver transplantation (LDLT) centers can be established. LDLT is a very difficult operation and consists of a series of complex surgeries. Establishing an LDLT center in underdeveloped or developing countries is only possible with a long-term, patience and devoted cooperation of a developed transplant center.

Methods: In this study, LDLT training between the new LDLT center planned to be established in Kyrgyzstan and Inonu University Liver Transplantation Institute (LTI), one of the world's leading institutes in LDLT, and the first 2 LDLTs at the center in Bishkek were presented. LTI's mentoring process started 9 years ago. The training process continued intermittently, but an intensive training program was implemented for the last two years. During this process, a total of 74 doctors or nurses, mainly general surgeons, received training on LDLT.

Results: At the end of the training process, a team of surgeons from both centers performed 2 LDLTs on 2 separate days in Bishkek, on June 10 and 11, 2024.

Conclusion: The purpose of this cooperation is to plan and implement joint programs between states, universities and LT centers and to obtain good results for patients. This study focused on the implications, results, and future expectations of this cooperation, which was written as the first LDLTs in the history of Kyrgyzstan.

Keywords: Living donor, liver transplantation, surgical experience

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Liver transplantation (LT) is the most effective treatment method for end-stage liver disease, acute liver failure, and some hepatic malignancies. The first deceased donor liver transplantation (DDLT) was performed in 1988, and the first living donor liver transplantation (LDLT) was performed in 1990 in Türkiye.[1] More than 80% of the LTs that occur between 1500-2000 per year are LDLT, and the organ donation rate is unfortunately less than 4 per million people. Inonu University is located in Malatya, a province with a population of amount 1 million, located in the west of the Eastern Anatolia Region of the country. The university, which has a history of approximately 50 years, established the School of Medicine in 1987 and opened the Turgut Ozal Medical Center (TOTM), one of the most

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expensive health investments in the country, in 1996. LT preparations at TOTM started in 1998, the first DDLT was performed in 2002, and the first LDLT was performed in 2005. The center, which exceeded its annual volume of 50 LTs in 2007, founded the Liver Transplantation Institute (LTI) in 2011 and built the Liver Transplantation Hospital in 2016. It is one of the only organ-specific university/institute hospitals in the world that has 156 patient beds, 36 intensive care beds, 12 operating rooms, conventional/interventional radiology, gastroenterology (endoscopy, ERCP etc.), and outpatient departments. It is the center that performs the most LDLT in Europe, including Türkiye, since 2008. Due to the transplantation team consisting of experienced and sufficient number of surgeons and anesthesiologists, medical tools, equipment and physical conditions, it is the center that performs the first 4-, 5-, 6-, 7-way liver paired exchange (LPE) transplants in the world.[2-4] The history of LT in Türkiye can be divided into 3 periods: initial stage (1988-1996), development stage (1997-2001) and rise and spread stage (2002-2023).[5] It is obvious that Inonu University Liver Transplantation Institute played the biggest role in the recent rise of LT activities in Turkey.

So far at LTI, a training was given to physicians from many centers such as Cambridge University, Warchaw University, Belgium Gent University, Giessen University, Russia St Petersburg University, and Novosibirsk State University. Among these countries, the Central Asian Turkish Republics have a special place due to the close origin of our nations. LTI has relations with Azerbaijan, Uzbekistan, Kazakhstan, Turkmenistan, and Kyrgyzstan in terms of training and operations related to LT. The Malatya - Bishkek story dealt with before but began mainly in September 2022, when Kyrgyz President Sadir Caparov requested the President of the Republic of Türkiye, Recep Tayyip Erdogan, to establish a LT program in Kyrgyzstan. Scientific cooperation began when President Erdoğan appointed the Rector of Inonu University, Prof. Dr. Ahmet Kizilay, through the Presidency of the Council of Higher Education, regarding this issue. In this study, the scientific, educational and operational aspects of Malatya-Bishkek cooperation were tried to be explained.

Material and Methods

Before the decision of the Presidents of both countries on the establishment of a LDLT center in Kyrgyzstan, 4 Kyrgyz general surgeons and 1 Kyrgyz gastroenterologist received LT training for various periods between 2015-2019 in LTI. However, the planned training program started in September 2022. During this period, 34 general surgeons, 14 operating room nurses, 5 anesthesiologists, 3 radiologists, 2 pediatricians, 2 biochemistry specialists, 1 gastroenterologist, 1 pathologist, and 1 anesthesia technician received LDLT training in Inonu University LTI until July 2024, each for at least 3 months. Kyrgyz physicians and nurses were trained on the preparation of patients requiring LT, follow-up and treatment before and after LDLT, ICU, normal ward, and outpatient clinic in LTI. Very few of the Kyrgyz surgeons had some experience in hepatobiliary surgery. Major operations in Kyrgyzstan were mainly hepatic resections for echinococcus alveolaris.[6] They had no experience with DDLT or LDLT. The importance of a multidisciplinary team was emphasized during the training process and efforts were made to form a team in this direction. Training programs for Kyrgyz physicians as a multidisciplinary and routine:

1. Hepatocellular Carcinoma Council every Monday at 16:00
2. Biliary and Vascular Council where postoperative complications of transplant patients are discussed every Tuesday at 12:30.
3. Transplantation Council, where patients who are candidates for liver transplantation are discussed every Thursday at 13:30
4. Discussion of a topic planned as a symposium, seminar, or panel once a month (biliary atresia, renal problems in LT patients, LT in HBV cirrhosis, or pushing the limits of LT in HCC, etc.)

Surgically, all Kyrgyz surgeons and nurses were allowed to undergo surgery. The surgical training process included:

1. Participating as a second assistant in at least 10 living donors and 10 recipients
2. Participating as first assistant to at least 10 living donors and 10 recipients
3. Using CUSA (cavitron ultrasonic aspiration) to divide hepatic parenchyma in at least 3 living donors
4. Assisting the perfusion and reconstruction of the liver graft removed from the donor at least 5 times at the back table
5. Participating of nurses in at least 10 living donor, 10 recipient and 10 back-table procedures

Before starting the program, faculty members of the LTI, including the rector, visited the centers in Bishkek and Ochi at least twice to check the facilities, existing infrastructure, necessary surgical instruments, and equipment to perform LDLT in Kyrgyzstan, and they held meetings with managers, including the Kyrgyz president.

LTI faculty members decided that the proposed hospitals for LT in Bishkek and Ochi were not very suitable. There-

upon, it was decided to perform LDLT at the Turkish Kyrgyz Friendship Hospital in Bishkek, which was planned to be a cardiology-heart surgery center and where kidney transplants had been performed before. However, in this hospital or others, the Thompson Retractor, CUSA, operation-specific surgical sets (including vascular clamps) and synthetic vascular grafts to be used in vascular reconstruction, which are important instruments for LDLT and which were repeatedly requested to be provided, were not available.

Five of the Kyrgyz surgeons who were training at LTI went to Kyrgyzstan at the beginning of May 2024 and started the patient and donor preparation process. During this multidisciplinary preparation period, close contact with the faculty members of the institute continued. Evaluation of the vascular and parenchyma of donor livers, volumetry, and LT indication in the recipient were all carried out under the supervision of institute faculty members.

This study was approved by the Ethics Committee of the Inonu University, School of Medicine and was conducted in accordance with the declaration of Helsinki of 1996.

Results

While the mentoring program continued, a total of 8 patients, 5 from Bishkek and 3 from Ochi, were prepared for LT from 2 separate centers in Kyrgyzstan as of the beginning of May 2024. These patients were discussed in online meetings. Finally, 2 patients with end-stage liver disease were selected for LT, which will be described in detail below. These patients had 2 suitable living donors. Five days before the operation, a faculty member transplant surgeon from the institute was sent to Bishkek to perform all the checks. Preparations were made for this surgeon's impressions there. The operations would be performed at the Turkish-Kyrgyz Friendship Hospital in Bishkek. Operating rooms and intensive care conditions (mechanical ventilators, hepafilter etc.) were suitable. However, surgical instruments, Thompson retractors, CUSA, and synthetic vascular grafts were not available. In other words, unfortunately, the essential elements of LDLT could not be provided.

This problem was solved with the initiatives of the rector of Inonu University (Prof. Dr. Ahmet KIZILAY) on the government. The Ministry of Customs and Trade and Turkish Airlines allowed the international movement of surgical sets, Thompson retractors, CUSA and other equipment weighing over 100 kg. In addition to the faculty member previously sent to Bishkek, a team of 7 people, including 3 transplant surgeons, 1 transplant anesthetist and 2 transplant nurses, headed by the rector, flew to Bishkek on June 9, 2024. The team arrived in Bishkek at 04.30 am on June 10, 2024. After a few hours of rest, the first LDLT operation was launched around noon. Donor and recipient informations for 2 separate LDLTs are presented below.

a. First LDLT (June 10, 2024)

Living donor: 20-year-old female, patient's daughter, height 155 cm, weight 65 kg, blood type: A Rh(+), right lobe: 500 cc, left lobe: 300 cc (remnant lobe 33%).

Recipient: 51-year-old female patient, height 147 cm, weight 52 kg, blood type: A Rh(+). The patient has severe tense ascite. Meld Na score was 20. ANA and ASMA are positive, with diagnosis cirrhosis due to otoimmune hepatitis. During the operation, 15 liters of ascitic fluid was drained from abdominal cavity of the patient. The liver was highly cirrhotic and atrophic. Right lobe LDLT was performed. Graft-to-recipient weight ratio was 0,96 %. Segment 5 hepatic vein was extended to the left hepatic vein stump with an 8 mm Dacron synthetic vascular graft. Right hepatic vein and portal vein anastomosis was normal. The graft hepatic artery had narrow diameter (<2mm). Hepatic artery anastomosis was repeated twice. The right hepatic artery of the graft was anastomosed to the arteria hepatica propria of the recipient with X8.5 magnitude loop and 8/0 prolene sutures according to the technique we described previously.[7] The bile ducts of the graft consisted of two ducts close to each other. Two duct to duct anastomoses were performed with interrupted, 6/0 prolene sutures. The patient's donor was discharged on the 12th postoperative day. On the 20th postoperative day, recipient's clinical and all laboratory parameters were normal and discharged. Triple immunosuppressive prophylaxis consisting of tacrolimus, mycophenolate mofetil, and corticosteroid is applied.

b. Second LDLT (June 11, 2024)

Living donor: Twenty six-year-old female, patient's daughter, height 161 cm, weight 50 kg, blood type 0 Rh(+), right lobe: 500 cc, left lobe 290 cc (remnant left lobe 32%).

Recipient: Fifty-years-old, female patient, height 148 cm, weight 50 kg, blood type 0 Rh (+). The patient had esophageal variceal bleeding twice and variceal ligation was performed for this. On CT, there were multiple nodules in the liver parenchyma, the largest of which was 2 cm in size. The liver had the appearance of chronic liver disease but was not severely cirrhotic. Nodules in the liver were evaluated as dysplastic nodules. MELD Na score was 10. During the operation, multiple nodular lesions were detected in the non-cirrhotic liver. Graft-to-recipient weight ratio was 1 %. Right lobe LDLT was performed. Hepatic vein and portal vein anastomoses were normal. The graft hepatic artery was anastomosed to the recipient arteria hepatica propria, as previously defined.

[7] The graft had one bile duct. Duct to duct anastomosis was performed and a transanastomotic feeding tube was placed through the cystic duct. At the end of the operation, cholangiographic images was normal. The patient's donor was discharged on the 10th postoperative day. On the 21th postoperative day, recipient's clinical and all laboratory parameters were normal and discharged. Triple immunosuppressive prophylaxis consisting of tacrolimus, mycophenolate mofetil, and corticosteroid is applied.

Kyrgyzstan Minister of Health Alim Kadir was involved in all of these operations at certain times. Because he was also a professor of general surgery.

On Wednesday, June 12, 2024, the patients' physical examinations, laboratory parameters and vascular anastomoses with Doppler US were normal. Subsequently, on Thursday, June 13, 2024, a meeting was held with the surgeons and anesthetists who would follow up the patients (Fig. 1), and the Turkish transplantation team of 8 people (Fig. 2) left Bishkek with the equipment brought.

Figure 1. The team that performed the first liver transplants in Kyrgyzstan.

Figure 2. Kyrgyz and Turkish physicians after transplantations.

Discussion

To put forward a model for establishing a new LDLT center through mentorship from an university with transplantation expertise is not an easy project. There are extremely heterogeneous publications on this subject.[8-10] It is obvious that Kyrgyzstan, with its population of 7 million, needs one or two liver transplant centers. Bishkek and Ochi are the 2 largest cities of Kyrgyzstan, and the infrastructure of health institutions is more developed in the capital Bishkek. However, in this country where there is no legal regulation regarding deceased donor organ donation, unfortunately there are no health institutions suitable for LDLT. Turkish-Kyrgyz Friendship Hospital in Bishkek was specially prepared in this regard, and 2 LDLTs were performed for the first time in the history of Kyrgyzstan. It is really difficult today to answer the question of whether this program will continue. This article will mainly focus on the rules, measures and remedies required for the continuity of this program.

Establishing a new LT program in underdeveloped countries will make significant contributions to better recognition of liver patients requiring LT in that country and the development of hepatobiliary surgery. However, since the learning curve tends to be long in complex surgeries such as LDLT, graft and patient survival rates may be low in the first LTs.[11] According to Addeo et al., surgeons performing LT have three learning curves. The first phase covers the first 70 procedures, the 2nd phase covers 70-100 LTs. After this, when the surgical time and blood transfusion requirement stabilize, the third stage is reached.[12] What path should be followed in LDLT? In Kyrgyzstan, it will take a long time to achieve even numbers of 10s rather than numbers of 70s and 100s.[13] For this reason, rather than the institutions' learning curve in Bishkek, the surgery and anesthesia team will need to complete the learning curve in an experienced center.

Multidisciplinary approach is the key to achieving good results in the new center. In the previous visits of Inonu University faculty members, they visited intensive care, operating rooms and patient wards and held many meetings with the teams there. In fact, these visits also revealed the obstacles to establishing such a program and led to studies on how to overcome these obstacles.

The structured training program for transplant surgeons in Türkiye is regulated by the Ministry of Health. The criteria that the responsible transplant surgeon must have for the opening of any new liver transplant center can be summarized as follows: Such as having at least 50 LTs per year for at least 1 year within the last 5 years and having articles on LT in journals within the scope of SCI. In addition, Inonu University LTI has 4-year doctoral programs under the name of LT surgery and anesthesia. However, it was impossible to

implement such programs for Kyrgyz surgeons or anesthesiologists. We focused on an accelerated training program in Malatya and the obligation to accompany transplants in Kyrgyzstan for approximately 1 year. We also suggested that 5-10 transplant surgeons and 2 transplant anesthetists should continue their education at Inonu University LTE for a more intensive training program. It would probably be necessary to train donor and recipient surgeons separately and more specifically. On the other hand, in some centers, donor and recipent surgery was given as training to the same surgeon. Training programs of over 40 hours for LT theory and over 100 hours for LT surgery have also been defined.[14]

Liver transplantation surgery requires to be highly skilled, with great expertise and vast experience. With accelerated training programs in a short time at Inonu University, efforts were made to help young Kyrgyz surgeons improve their surgical techniques and gain mastery and experience by teaching an optimized LT surgery.

Disclosures

Ethics Committee Approval: This study was approved by Inonu University Ethics Committee (Date: 11/09/2024, Number: 2024/6397).

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