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Joint Liver-Kidney Transplantation for Primary Hyperoxaluria and Other Metabolic Conditions: A Review Paper

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Abstract

Combined liver-kidney transplantation (CLKT) represents a pivotal therapeutic advancement in the management of metabolic disorders, particularly primary hyperoxaluria type I (PH-I), a rare autosomal recessive condition resulting in systemic oxalosis and end-stage renal disease (ESRD). This review synthesizes clinical evidence from key studies, including the University of Kansas Medical Center and international registries, to assess the efficacy, outcomes, and current management strategies associated with CLKT in PH-I and other metabolic diseases. CLKT effectively corrects the underlying hepatic enzymatic deficiency and restores renal function, significantly improving patient and graft survival rates compared to kidney-alone transplantation, which is often compromised by recurrent oxalate deposition. The review outlines perioperative management strategies such as intensive dialysis, high-volume diuresis, and pyridoxine therapy, and highlights critical considerations like timing of transplantation, oxalate mobilization, and immunosuppressive regimens. Despite ongoing challenges, including persistent post-transplant hyperoxaluria and risk of graft rejection, CLKT remains the gold standard for pyridoxine-unresponsive PH-I. Emerging approaches such as gene therapy, improved diagnostic tools, and personalized treatment protocols offer promising avenues for future care.

Keywords: Combined liver-kidney transplantation, therapeutic advancement, metabolic disorders, hepatic enzymatic deficiency, risk of graft rejection,immunosuppressive.

Introduction: Combined liver-kidney transplantation (CLKT) has emerged as a critical therapeutic strategy for patients with metabolic disorders, particularly primary hyperoxaluria type I (PH-I), where hepatic enzyme deficiencies lead to systemic oxalosis and end-stage renal disease (ESRD). This review synthesizes findings from key studies, including the experience of the University of Kansas Medical Center (KUMC) and other institutions, to evaluate the efficacy, outcomes, and management strategies for CLKT in metabolic disorders[1-2]. This guideline supersedes prior recommendations from the British Society for Haematology (BSH).Antiphospholipid syndrome (APS) is an autoimmune disorder marked by thrombotic events (affecting venous, arterial, or microvascular systems) and/or pregnancy-related complications, alongside persistently elevated antiphospholipid antibodies (aPL). APS

may present as primary APS (occurring independently) or secondary APS (associated with other autoimmune conditions, most frequently systemic lupus erythematosus [SLE] or rheumatoid arthritis).To diagnose APS, both clinical and laboratory criteria must be met: Clinical evidence of at least one thrombotic event (objectively confirmed) or pregnancy morbidity & Laboratory confirmation of persistently positive aPL (lupus anticoagulant [LA], IgG/IgM anticardiolipin [aCL], and/or IgG/IgM anti-β2 glycoprotein-1 [aβ2GPI]) on two separate occasions, spaced at least 12 weeks apart[3-5].aPL are heterogeneous and primarily directed against phospholipid-binding proteins, the best recognized being β2GPI (primarily domain-I of the open form of the molecule) and prothrombin. Their presence is necessary but insufficient for the development of the thrombotic manifestations of APS. It is hypothesized that this requires a second trigger, such as infection, pregnancy or surgery, which leads to a more pronounced thrombo-inflammatory response[6-7].

BACKGROUND AND RATIONALE

Primary hyperoxaluria type I (PH-I) is an autosomal recessive disorder caused by a deficiency in the hepatic enzyme alanine:glyoxylate aminotransferase (AGT), leading to excessive oxalate production. Oxalate is primarily excreted by the kidneys, and its accumulation results in nephrolithiasis, nephrocalcinosis, and eventually ESRD. Without intervention, systemic oxalosis can lead to multi-organ failure and death. Traditional kidney-alone transplantation has been largely unsuccessful in PH-I due to recurrent oxalate deposition in the graft. The introduction of CLKT in the 1980s aimed to correct the underlying metabolic defect by replacing the liver while simultaneously addressing renal failure.

University of Kansas Medical Center (KUMC) Experience:

The KUMC study reviewed 16 patients with PH-I who underwent CLKT or kidney-alone transplantation. The results demonstrated that CLKT effectively corrected the metabolic defect, with plasma oxalate levels decreasing significantly post-transplantation. However, hyperoxaluria persisted for several months to years due to the mobilization of tissue oxalate stores.

Patient survival rates were 78% for CLKT and 89% for kidney-alone transplantation. Renal allograft survival rates at 5 years were 52% for CLKT and 36% for kidney-alone transplantation, highlighting the challenges of recurrent oxalosis in kidney-alone grafts. The PT or aPTT is prolonged in about 50–60% of cases of DIC at some point during the course of illness.This is mainly attributed to the consumption of coagulation factors but impaired synthesis, due to abnormal liver function, vitamin K deficiency or loss of the coagulation proteins, due to massive bleeding, may also play a role[8-9].

European and U.S. Registry Data:

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European registry data (1984-1997) reported 1-, 2-, and 5-year patient survival rates of 88%, 80%, and 72%, respectively, for CLKT in PH-I. Renal allograft survival was 62% at 5 years.

U.S. registry data (1984-1996) showed similar patient survival rates for CLKT (69%) and kidney-alone transplantation (74%), with no significant difference in renal allograft survival between the two groups.

Management Strategies:

Pretransplantation: Intensive dialysis to reduce plasma oxalate levels is critical. Hemodialysis or continuous venovenous hemodiafiltration (CVVHDF) is recommended to maintain plasma oxalate levels below 20 µmol/L.

Posttransplantation: High-volume diuresis, neutral phosphate therapy, and pyridoxine (for pyridoxine-responsive patients) are essential to prevent calcium oxalate crystallization and stone formation. Close monitoring of urine oxalate levels and renal function is necessary to detect early signs of graft dysfunction.

INDICATIONS FOR TRANSPLANTATION

CLKT: Recommended for patients with PH-I who are pyridoxine-resistant, have significant systemic oxalosis, or have previously failed kidney-alone transplantation. CLKT is also indicated for patients with prolonged dialysis duration (>1 year) or those awaiting cadaveric organs with expected long waiting times.

Kidney-Alone Transplantation: Suitable for pyridoxine-responsive PH-I patients and those with PH-II, which has a milder clinical course. Kidney-alone transplantation may also serve as a bridge to CLKT in patients with available living donors.

CHALLENGES AND CONSIDERATIONS

Timing of Transplantation: Early transplantation before the development of significant systemic oxalosis is crucial. However, predicting the clinical course of PH-I is challenging, and preemptive liver transplantation in asymptomatic patients remains controversial due to the risks of immunosuppression and surgical complications.

Oxalate Mobilization: Post-CLKT, hyperoxaluria can persist for years due to the slow mobilization of tissue oxalate stores. Intensive dialysis and high fluid intake are necessary to prevent graft damage during this period.

Immunosuppression: The risk of acute and chronic rejection remains a concern, particularly in kidney-alone transplantation. Tailored immunosuppressive regimens are essential to balance graft survival and minimize complications.

FUTURE DIRECTIONS

Gene Therapy: Advances in gene therapy may offer a curative approach by correcting the underlying enzyme deficiency without the need for organ transplantation. However, challenges related to transfection efficiency and long-term efficacy need to be addressed.

Improved Diagnostics: Enhanced genetic testing and biomarkers for early detection of PH-I and PH-II could facilitate timely intervention and improve outcomes.

Personalized Medicine: Tailoring transplantation strategies based on individual patient characteristics, such as pyridoxine responsiveness and genetic mutations, may optimize outcomes.

CONCLUSION

Combined liver-kidney transplantation has revolutionized the management of primary hyperoxaluria type I, offering a curative approach by addressing both the metabolic defect and renal failure. While challenges remain, including persistent hyperoxaluria and graft rejection, advancements in transplantation techniques, immunosuppression, and supportive care have significantly improved patient outcomes. Future research into gene therapy and personalized medicine holds promise for further enhancing the quality of life for patients with metabolic disorders.

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