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ABO-incompatible Kidney Transplantation

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Complications of ABO-incompatible Kidney Transplantation

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ABO incompatible kidney transplantation (ABOi KT) is getting increasingly popular all over the world in order to increase the living donor pool. Since the process involves desensitization one to four weeks prior to transplantation and increased immunosuppression at least for the first two weeks, the complications are higher than the regular kidney transplantation. The major complications include increased incidence of antibody-mediated rejection (ABMR), bleeding and infections. These complications are seen more in the early postoperative period rather than in the long term. The complications can start even before transplantation since the protocol of desensitization includes plasmapheresis (PE) and immunosuppression well before the transplantation. A national database study from the US reported in 2013 the early complications of ABOi KT between the years 2000 to 2007.[1] Unadjusted complication frequencies at 90 days after transplantation in the ABO incompatible (ABOi) recipients were significantly high for hemorrhage (13%), wound infections (12.1%), pneumonia (7.3%) and urinary tract infection (UTI) (34.1%). The corresponding figures for ABO compatible (ABOc) recipients were 6.7%, 7.3%, 3.8% and 22.2%, respectively (Table 1). The complications were not significantly different between 91 days and 365 days.

PRE-OPERATIVE COMPLICATIONS

The majority of the centers use a combination of triple immunosuppression including prednisolone, mycophenolate and tacrolimus 1–2 weeks before the transplantation. PE including double filtration plasma pheresis (DFPP) or

Table 1.
Frequencies of Complications at 90 Days (d) after Live Donor Kidney Transplantation, According to ABO Compatibility[1]

	Hemorrhage	Wound infection	Pneumonia	UTIs	Sepsis
	% at 90 d	% at 90 d	% at 90 d	% at 90 d	% at 90 d
ABOi	13%*	12%*	7.3%*	34.1%*	5.7%*
A2O#	6.7%	6.7%	0%	30%	3.3%
Compatible	6.9%	7.3%	3.8%	22.2%	4%

#A2O: Transplantation of A2 to O blood group.

*P < 0.05 vs compatible.

immunoadsorption (IA) are used to remove the anti-blood group antibodies. There is an increased chance of infection related to the lines used for pheresis treatment. There is not much of data on the preoperative infections and other complications since the transplantation is likely to be postponed whenever such a complication occurs.

INTRAOPERATIVE AND POSTOPERATIVE COMPLICATIONS

Bleeding

There is an increased incidence of intraoperative and postoperative bleeding due to depletion of the clotting factors Including fibrinogen by PE.[2] Low platelets and anticoagulation used during the pheresis treatment also contribute to the disorder. Regular PE using albumin as a replacement fluid produces more clotting disturbance than replacement with AB negative plasma. Splenectomy which was responsible for four times the risk of bleeding has virtually been given up in all the centers.[3] Plasma exchange can reduce the coagulation factors including fibrinogen by 60% even with a single session. According to the national database study from the US which reported the complications with the ABOi KT between the years 2000 to 2007, ABOi was associated with 72% higher risk of hemorrhage.[1] Blood transfusions were received more than twice compared to regular kidney transplantation. Naciri Bennani et al from France in a cohort of 44 patient reported 27.3% recipients with serious intraoperative bleeds including 2 patients who had intraoperative leakage of the renal artery anastomosis.[4] Post-transplantation large wound hematoma was observed in 16 patients. Two patients persisted with gross

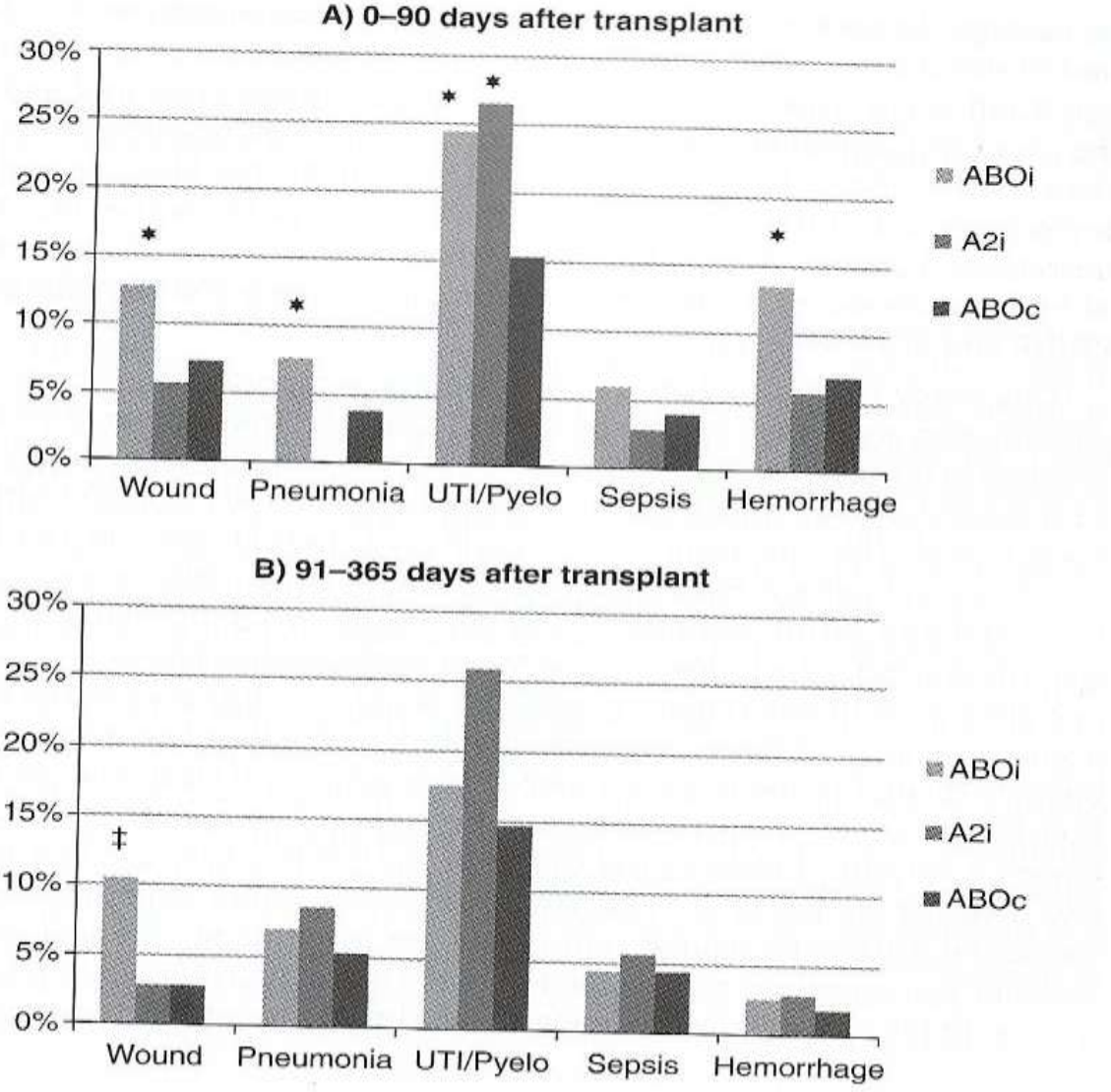

Figure 1. Pre-operative complications of the ABO-i transplantation. Kaplan-Meier estimates of infectious complications and hemorrhage frequencies over periods of 0–90 days and 91–365 days, according to blood type compatibility.[1]
ABOi: ABO incompatible; A2i: A2 incompatible; ABOc: ABO compatible.
P-values vs ABOc: *0.0001 to <0.05; ‡ <0.00010.

hematuria beyond day 5. Twelve of the patients needed a mean of 3.5 red cell transfusion on day 0 excluding the intraoperative period. They attributed the bleeding complication to the low value of fibrinogen, low platelet count and prolonged prothrombin time. The bleeding complications are not only restricted to PE, but also to IA. De Weerd et al from Netherlands reported the data in 65 ABOi KT using immunoadsorption and triple immunosuppression.[5] ABOi KT had more intraoperative blood loss and received erythrocyte transfusions twice as frequently as the controls in the first postoperative 48 hours. After the immunoadsorption, the platelet count decreased by 28% on

an average. This returned to normal 1 week after transplantation. The APTT and PT-INR did not differ from control groups. However, the drop in platelet count did not correlate with the number of transfusions required and the intraoperative bleeding. The ABOi patients lost more blood intraoperatively than controls (543 ± 65 ml vs 355 ± 34 ml, $P < 0.005$). The bleeding and the erythrocyte transfusion correlated to the number of IA treatments. They postulated a platelet dysfunction rather than thrombocytopenia as a cause of bleeding tendency. Coagulation abnormalities were not seen since the PT-INR and APTT were normal.

One study from a pediatric unit in Germany reported the results in 3 patients who underwent successful ABOi KT using IA.[6] The number of sessions required in these patients were 6, 10 and 11 to achieve a target antibody titer ≤1:4. Coagulation parameters were repeatedly monitored pre IA and within 4 hours post IA. The anticoagulation during IA consisted of heparin in 2 patients and citrate in 1 patient. Following the IA, the APTT and PT-INR were markedly increased and serum fibrinogen was decreased. No anticoagulation was given during transplantation surgery. Major postoperative bleeding occurred in 2 patients with one requiring repeated blood transfusions and the other a surgical revision 4 hours after transplantation. The bleeding disorder was possibly related to the large number of IA session to achieve low antibody titer. Several centers from Europe have also reported increased postoperative bleeding episodes following the use of IA.[4,6,11,12,16] This is in contrast to the low bleeding complications reported from Japan where large numbers of successful ABO-incompatible transplants are being done. The low rate of bleeding complications may be related to the use of less number of pheresis treatment (PE or DFPP) by accepting a high cut-off titer of 1 in 16 to 1 in 32.[7]

PREVENTION OF BLEEDING COMPLICATION

A. Restricting the number of plasma exchanges/IA.

   Since the bleeding complication correlate to the number of plasma exchanges or IA done prior to transplantation, it would be prudent to restrict the number of such sessions. This would possibly mean accepting higher titers of anti-A and anti-B antibodies like the Japanese centers.[8]

B. Replacement of clotting factors and fibrinogen after the last PE/IA.

C. Use of AB negative plasma as replacement fluid instead of albumin in the last exchange.

D. Replacement of heparin by nafamostat mesylate (NM) as an anticoagulant during PE may minimize the bleeding complication. Nafamostat mesylate

is a proteinase inhibitor with a short half-life of 5–8 minutes and it is easily removed by dialysis.[9,10]

E. Intraoperative administration of heparin should also be avoided and anticoagulation for prevention of thrombosis should be considered cautiously.

INFECTIONS

One of the major concerns in ABOi KT is the occurrence of infections due to aggressive immunosuppression in the initial perioperative period. Although infection can occur before the transplantation itself, there is a paucity of data concerning these infections since the transplantation would be postponed. Different centers have different protocols starting the immunosuppression even before 4 weeks of transplantation.[6] Majority uses Rituximab, PE/IA, and triple immunosuppression. Each of these procedures can make a patient susceptible to various infections. Wound infections, UTI, Viral infections, fungal infections have all been reported in patients with ABOi KT. The US national data of ABOi KT performed between the years 2000 to 2007 revealed a higher incidence of wound infections (12.5% vs 7.3%), pneumonia (7.3% vs 3.8%) and UTI (24.5% vs 15.3%) in the first 90 days in these recipients compared to the ABOc group.[1] A study by Naciri Bennani et al from France in 44 patients showed significantly high infectious complications of 72.7% cases as compared to the ABOc patients with 47.7%.[4] Similarly, Habicht et al from Germany in a cohort of 21 patients showed an incidence of 50% infections in ABOi group as compared to 21% to ABOc group.[11] Stefan Zschiedrich et al from Germany in a study of 100 patients showed infectious complications in 38% of patients with ABOi as compared to 35% of the ABOc group.[12] One of the additional dangers of infections in patients undergoing ABOi KT is the precipitation of ABMR.

(a) Wound Infection

Wound infections are more likely to occur in ABOi KT because of the excessive bleeding either during surgery or in the postoperative period and the need for wound revision at times. The risk factors for wound infection are BMI, Diabetes, and elderly age. The US database showed a 3.5 times relative risk of wound infections even between 91 days and 365 days post transplantation.[1] Again the correlate of wound infections during this period included older recipient age, female sex, white race and higher BMI. The diabetic patient had 3 times more relative risk of wound infection in this period as compared to nondiabetic patients. Similarly, patients who received sirolimus-based immunosuppression had twice the risk as compared to those discharged with tacrolimus and MMF.

(b) Urinary Tract Infection (UTI)

Several studies have reported a higher incidence of UTI in ABOi KT recipients. The US database reported that ABOi KT recipients had significantly higher incidence of urinary tract infections and pyelonephritis (24.5% vs 15.3%) compared to ABOc kidney transplantation recipients in the first 90 days post transplantation.[1] The multivariate regression analysis including adjustment for baseline recipient, donor, and transplantation characteristics showed 55% higher risk of urinary tract infections and pyelonephritis in the ABOi group in the first 90 days post transplantation. The reasons for increased risk of infections are due to use of rituximab or splenectomy, duration, and type of pre-transplantation immunosuppressive medications including lymphocyte depleting monoclonal antibodies and more intensive post-transplantation immunosuppressive medications. Plasmapheresis increases the infection risk due to hypogammaglobulinemia and hypocomplementemia. Serum immunoglobulin levels can reduce by 60% even with one plasma exchange whereas DFPP reduces IgG by 40%. These reductions may persist for several weeks after multiple exchanges. Zschiedrich et al from Germany reported recurrent UTI in 18% of the patients as compared to 13% in the ABOc group.[12] Kahwaji et al from the US reported 50% UTIs which was similar in both the ABOi and ABOc group.[13] Similarly, Naciri Bennani et al from France reported acute pyelonephritis with similar prevalence in both the compatible and incompatible group.[4] Habicht et al from Germany reported urosepsis in 10% of the patients as against 6.3% in the compatible group.[11] Choi et al from Korea reported UTI in 14% of the patients as compared to 10.3% in the ABOc group.[14]

(c) Pneumonia

One of the life-threatening complications in the early postoperative period following kidney transplantation is pneumonia. According to the USRDS database, ABOi KT recipients had an incidence of 7.6% of pneumonia when compared to 3.8% of patients who underwent ABOc kidney transplantation.[1]

(d) Other Infections

Viral infections including CMV and BK virus, herpes viruses have been reported following ABOi KT. The incidence of these infections has been variable from different centers. Although some centers found the infection to be more in the incompatible group, others have found the incidence similar in both the groups.

Habicht et al reported the rate of viral infections including CMV, BKV, and herpes to be 50% compared to 21% in the ABOc group ($p = 0.038$) during a follow-up for 15.7 ± 8.3 months.[11] Baek et al reported that CMV infection was more common in the group treated with rituximab (16.4 vs 5.7%, p =

0.031), which raises the possibility of rituximab causing the increased risk.[15] However, there are other studies which do not substantiate the risk of rituximab. Though the cause of increased infections is not related to rituximab alone, the immunosuppressant dose needs to be reduced without the risk of rejections. Kahwaji et al from California reported a similar incidence of viral infections in the rituximab and non-rituximab group.[13] Cytomegalovirus infections were reported in 10% of the rituximab group and 15% of the non-rituximab group. According to them, BK virus was more common in patients who had received rituximab accounting for 40% of viral infections. Zschiedrich et al from Germany did not find any difference in the viral infections in the incompatible and compatible groups.[12] They did not find any difference in the hospitalization rates due to infections. Habicht et al from Germany found a higher incidence of viral infections including CMV, HSV, VZV, BKV in the ABOi group.[11] Cytomegalovirus infections occurred in 14% of the incompatible group as compared to 13% of the compatible group. One patient who has diagnosed CMV disease developed proximal urethral stenosis requiring surgical repair two months after transplantation. Three out of 21 patients developed HSV or VZV infection while only 2 HSVs were noted in 47 compatible patients. One patient in the ABOi group developed severe varicella meningitis 21 months after transplantation. According to them, the most common viral infection was BK virus leading to nephropathy in 5 of the 20 ABOi grafts. This was in comparison to 4 out of 47 in the compatible group. Interestingly BKN nephropathy was diagnosed within 3–6 months after transplantation by routine protocol biopsies in the absence of graft dysfunction.

OTHER COMPLICATIONS

(a) Lymphoceles

Wilpert et al from Germany reported a high incidence of lymphoceles requiring surgical intervention in patients undergoing ABOi KT.[16] This could possibly be related to the increased bleeding and immunosuppression. Three out of 43 (7%) of patients underwent surgical intervention for lymphoceles in the ABOc group, whereas 11 out of 40 (28%) in the ABOi group required surgical revision.

(b) Complications of Rituximab

Administration of rituximab itself is associated with a number of complications. Cytokine release syndrome can be produced by rituximab particularly in patients with lymphoma.[17] Generally, mild fever and chills related to the infusion are seen. Reactivation of hepatitis B virus is also a concern. Several studies have suggested that rituximab can increase the risk of infection including pneumocystis pneumonia, CMV disease, and fungal infection.

Rituximab-associated interstitial lung disease in nonrenal transplantation patients has been reported.[18,19] Progressive multifocal leukoencephalopathy (PML) is a rare serious demyelinating disease that occurs predominantly in severely immunosuppressed patient population.[20] Rituximab appears to be responsible for PML but the relationship is unclear. Disseminated intravascular coagulation (DIC) appears to be an extremely rare side effect of rituximab. An increased cardiovascular risk has been reported in renal transplantation patients receiving rituximab as induction therapy.[21]

(c) Neutropenia

According to Tanabe, 30% of rituximab-treated patients had neutropenia after surgery.[7] Most of the patients developed a sudden onset without anemia or neutropenia. This type of neutropenia was possibly caused by rituximab. But no patient experienced severe infections due to the neutropenia. It is recommended that complete blood count is monitored closely after transplantation.

STRATEGIES TO REDUCE INFECTIOUS COMPLICATIONS

Choi et al from South Korea analyzed their data of ABOi KT between the years 2009 to 2013.[14] A total number of 182 patients were studied. They analyzed the first 85 patients for postoperative infectious complications and amended the immunosuppressive regimes in the next 97 patients. The infectious complications reduced significantly with the reduction in the CMV antigenemia from 64.7% to 28.8%, BK viremia from 35.2% to 18.6%. The acute rejection rate and graft survival were similar in both the groups. Notably with the modified protocol, there were no deaths (8.2% vs 0%).

The following measures can help to reduce the infectious complications:

1. Reduced dose of rituximab (200 mg instead of 375 mg/ m^2).
2. Early reduction of dose of mycophenolate mofetil, after 2–3 weeks of transplantation.
3. Limiting the number of plasma exchanges to 3–5.
4. Long-term prophylaxis with cotrimoxazole and valganciclovir.

MALIGNANCY

There is an increased risk of cancer in organ transplantation recipients. The risk for stomach cancer is 1.5-fold and that for Kaposi's sarcoma is 61-fold more than the general population. The Transplantation Cancer Match (TCM) study

which is a linkage between Scientific registry of transplantation recipients (SRTR) and US population-based cancer registries identified 7 cancers among ABOi KT recipients, including non-Hodgkin's lymphoma, Merkel cell carcinoma (rare neuroendocrine tumor of skin caused by Merkel cell polyoma virus), gastric adenocarcinoma, hepatocellular carcinoma, papillary thyroid carcinoma, pancreatic carcinoma and testicular seminoma.[22] The time to cancer diagnosis was 0.9–9.2 years (median 3.6 years). Several studies have demonstrated that the risk of cancer did not differ in the ABOi and ABOc kidney transplantation recipients. The risk of cancer is likely to be lower with lower immunosuppressive doses which are followed recently compared to the earlier protocols. Yamamoto who published their research data in 252 live related transplantation analyzed, retrospectively for various malignancies.[23] Eleven incidence of malignancy was observed during a median follow-up of 48 months. The incidence rates in the ABOc and ABOi group were 4.2% and 4.8%, respectively. There was no statistical difference in the event-free survival for malignancy between the two groups. They included patients who had undergone splenectomy and received cyclophosphamide for incompatible transplantation.

ACUTE REJECTIONS

Acute antibody-mediated rejection (AMR) is the leading cause of graft failure in ABOi KT recipients.[24,25] Antibody-mediated rejection occurred in 17.9–30% of ABOi KT patients. Antibody-mediated rejection usually occurs 2–7 days after transplantation and usually does not occur after 1 month. Once accommodation is established AMR does not occur and the graft function is stable. The treatment of acute rejection is likely to increase the complications of ABOi KT. Rejection has been covered in detail in the previous chapter.

MISCELLANEOUS COMPLICATIONS

De novo post transplantation diabetes mellitus has been reported in a similar incidence as compatible kidney transplantation. Naciri Bennani et al reported 4 out of 44 patients developing de novo diabetes.[4]

THE INDIAN SCENARIO

One of the biggest concerns in a country like India is the increased prevalence of infections like tuberculosis, gastroenteritis, and parasitic infections more than the western world. Additionally, precise diagnosis of the causative organism may not be possible resulting in mortality or loss of graft function due to the de-escalation of immunosuppression.

Several centers have reported successful ABOi KT in India. Joshi et al from Mumbai reported a high incidence of mortality in patients undergoing splenectomy prior to the transplantation.[26] Out of the 19 recipients who underwent splenectomy, 4 expired, 2 due to septicemia following community-acquired pneumonia post transplantation. One expired due to flaring up of underlying B-cell lymphoma within a week after transplantation. One patient had a cardiac event 1 year after transplantation. One recipient had severe post-transplantation coagulopathy, which was managed with intravenous coagulation factors. Five out of the 19 patients had subclinical pancreatitis which was suspected due to prolonged paralytic ileus following surgery which was confirmed by raised amylase and lipase levels. The same center reported much better results once rituximab replaced splenectomy. Out of the 6 recipients, one expired due to community-acquired pneumonia. Ravichandran et al reported a single center experience in 2012 in 13 patients who have undergone ABOi KT.[27] Two patients lost the graft due to ABMR. One patient developed UTI and another patient developed CMV infection both of which were successfully treated. The same center reported in 2015 their overall experience of 35 patients who had undergone ABOi KT.[28] Two patients were lost 1 due to excessive postoperative bleeding and another due to pulmonary aspergillosis 3 months after successful transplantation. The complication rates after 1 year (average follow-up 36.7 months) were similar both in the ABOi and ABOc groups.[29] Out of the 18 patients followed, gastroenteritis was reported in 4, CMV infection in 1, tuberculosis in 2 and UTI in 4 patients. The patient with tuberculosis presented with a miliary form but was successfully treated with conventional antituberculous drugs. The complication rates were comparable with the ABOc group which had 21 patients followed up for an average of 38.9 months. Jha et al from Haryana reported their experience in 20 patients undergoing ABOi KT.[30] One patient developed BKV infection and pneumonia. One patient was lost due to sepsis and CMV infection.

CONCLUSION

ABOi KT has been associated with increased incidence of complications in the immediate perioperative period especially related to bleeding. Infections also occur at a higher rate due to the intense immunosuppression in the early period after transplantation. However, the long-term results in terms of both patient and graft survival have been excellent and possibly better than that of compatible transplantation. With experience and de-escalation of desensitization protocols, it is possible to reduce the complications and make blood group incompatible kidney transplantations more popular and successful.

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