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Does an Additional Bile Duct Flush With Low-viscosity Preservation Solution Reduce Bile Duct Injury? A Single-blinded Randomized Clinical Trial

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Introduction. Biliary complications are a common cause of morbidity after liver transplantation and associated with bile duct injury. To reduce injury, a bile duct flush is performed with high-viscosity preservation solution. It has been suggested that an earlier additional bile duct flush with low-viscosity preservation solution may reduce bile duct injury and biliary complications. This study aimed to investigate whether an earlier additional bile duct flush would reduce bile duct injury or biliary complications. **Methods.** A randomized trial was conducted using 64 liver grafts from brain dead donors. The control group received a bile duct flush with University of Wisconsin (UW) solution after donor hepatectomy. The intervention group received a bile duct flush using low-viscosity Marshall solution immediately after the onset of cold ischemia and a bile duct flush with University of Wisconsin solution after donor hepatectomy. The primary outcomes were the degree of histological bile duct injury, assessed using the bile duct injury score, and biliary complications within 24 mo of transplant. **Results** . Bile duct injury scores were not different between the 2 groups. Similar rates of biliary complications occurred in the intervention group (31% [n = 9]) and controls (23% [n = 8]) (P = 0.573). No difference between groups was observed for anastomotic strictures (24% versus 20%, P = 0.766) or nonanastomotic strictures (7% versus 6%, P = 1.00). **Conclusions.** This is the first randomized trial to investigate an additional bile duct flush using low-viscosity preservation solution during organ procurement. The findings from this study suggest that performing an earlier additional bile duct flush with Marshall solution does not prevent biliary complications and bile duct injury.

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Biliary complications are a common cause of morbidity after liver transplantation and are associated with histological bile duct injury.[1-4] The etiology of bile duct injury is multifactorial and thought to be a combination of ischemic, immunological, and bile salt–related insults.[1-6] Intraluminal bile salts during organ preservation cause cholangiocyte injury because of cytotoxic detergent properties.[7] To mitigate this, the gallbladder is irrigated with saline during organ procurement, and later, after donor hepatectomy, the bile duct is flushed with preservation solution.[8-10] University of Wisconsin (UW) solution is a high-viscosity solution commonly used to preserve the liver and flush the bile duct.[9,10] However, an experimental study has suggested that low-viscosity preservation solution may improve the irrigation of small intrahepatic bile ducts and reduce bile duct injury.[11] Furthermore, it has also been suggested that performing 2 bile duct flushes may be superior to one[11] (Figure 1).

We hypothesized that performing an additional bile duct flush with low-viscosity preservation solution immediately after aortic cross clamp would be a simple technique to reduce bile duct injury and biliary complications. A randomized clinical trial was designed to compare our standard technique of bile duct flushing with an earlier additional bile duct flush using low-viscosity preservation solution. The 2 techniques

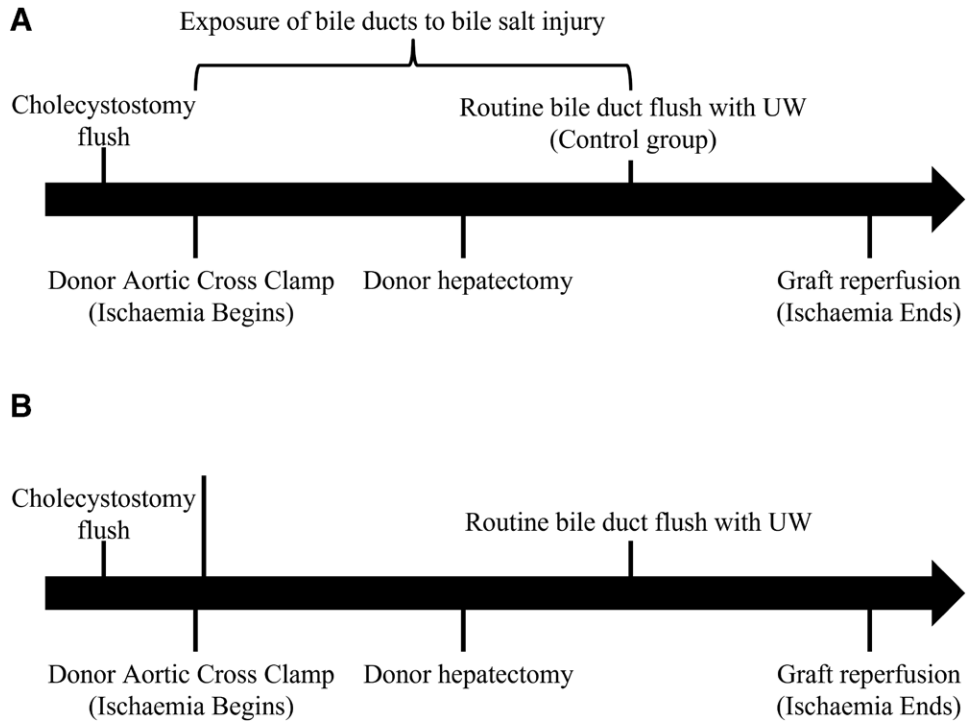

FIGURE 1. Timeline of organ procurement and ischemia. A, Current practice, in which the bile ducts are exposed to bile salt injury. B, The role of an additional and earlier bile duct flush to significantly reduce bile salt injury. UW, University of Wisconsin.

were compared in terms of histological injury and biliary complications.

MATERIALS AND METHODS

A prospective randomized trial was performed at the Australian National Liver Transplantation Unit (ANLTU) from March 2016 to June 2017. Written informed consent was obtained from each enrolled recipient, and the study was performed in accordance with the ethical guidelines of the 2000 Declaration of Helsinki. Brain dead donor livers procured and transplanted in adult recipients within New South Wales, Australia, were eligible. Donors were randomized just before organ procurement to either the control or intervention group using random number generation by the primary investigator who was not involved in donor recruitment (M.L.) (Figure 2). Allocation was disclosed to the donor surgical team but not to the liver transplant team or the recipient.

The control group received our standard protocol for biliary flushing with an antegrade cystic duct flush with normal saline via cholecystotomy during the warm phase of organ procurement followed by a single retrograde bile duct flush on the back table after donor hepatectomy with 75 mL of UW solution (Belzer UW, Bridge to Life) (Figure 1A).

The intervention group received the antegrade cystic duct flush via cholecystotomy followed by 2 retrograde bile duct flushes. The first (additional) bile duct flush was performed immediately after aortic cross clamp with 60 mL of cold Marshall solution (Soltran, Baxter, United Kingdom) using a silastic infant feeding catheter and 60-mL syringe via a distal choledochotomy. The additional bile duct flush was performed after aortic cross clamp because of the high potassium content of Marshall solution and to reduce bile salt injury during cold ischemia. Marshall solution was chosen as the low-viscosity bile duct flush because of availability at our center. Sixty milliliters was the largest volume in a single syringe and chosen as the flush volume. The second bile duct flush was performed as in the control group, after donor hepatectomy with 75 mL of cold UW solution (Figure 1B). The viscosity of UW is significantly higher than Marshall solution because of the addition of raffinose, glutathione, allopurinol, adenosine, pentafraction, and lactobinoic acid.[12] Otherwise, standard organ procurement techniques as previously described by the ANLTU were used in both groups.[13,14]

Outcomes

For histological assessment, a cross-sectional sample of distal donor bile duct was taken at the end of cold ischemia just before liver implantation. Specimens were processed in 10% neutral buffered formalin and stained in hematoxylin and eosin. They were examined independently by 2 blinded hepatobiliary pathologists, and discrepancies in scores were resolved with multiheader consensus. Bile duct injury was scored using a bile duct injury scoring system as described by Op den Dries et al.[4] This is a semiquantitative systematic histological scoring system for bile duct injury that examines the biliary epithelium, mural stroma, vascular plexus, peribiliary glands, inflammation, bleeding, and thrombosis within bile duct samples. This histological scoring system has been shown to correlate with biliary complications.[4]

Recipients were managed intraoperatively and postoperatively in the standard fashion at the ANLTU. Recipients were followed up for 24 mo, and medical records were comprehensively reviewed for outcome data. The clinical endpoint was biliary complications occurring within 24 mo from transplantation. Biliary complications were diagnosed by clinical or biochemical suspicion, and routine imaging was not performed

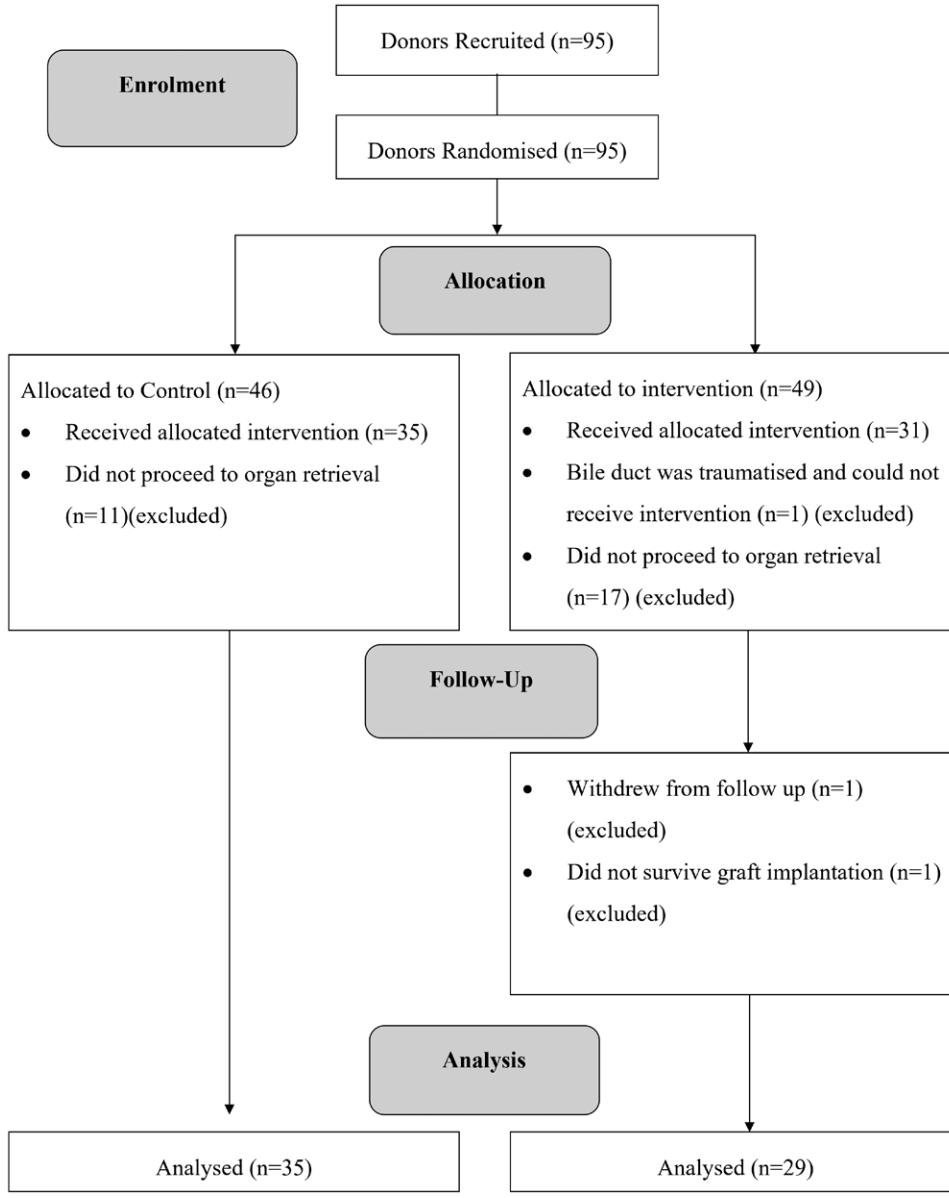

FIGURE 2. CONSORT guidelines flow chart.

because of low diagnostic yield in asymptomatic patients.[15] No threshold for liver biochemistry was used to trigger biliary investigation. Biliary complications included biliary strictures and bile leaks. Biliary strictures were defined as any narrowing of the donor biliary tree on magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography.[16,17] Not all cases of biliary strictures underwent endoscopic retrograde cholangiopancreatography because of anatomic location or severity of clinical symptoms. Biliary strictures were subcategorized into anastomotic strictures (AS) and non-AS (NASs). AS was defined as strictures localized to the biliary anastomosis. NAS was defined as any stricture in the donor biliary tree away from the biliary anastomosis. Bile leak was defined as the presence of bilirubin in the posttransplant drain or extravasation of bile on biliary imaging.

This trial was prospectively registered on the Australian and New Zealand Clinical Trials Registry (U1111-1179-9801) and approved by the Sydney Local Health District Ethics Review Committee (Approval Number X15-0444).

Statistical Analysis

Statistical analysis was performed with SPSS 23 (IBM Corporation, NY). Categorical variables were analyzed with Fisher exact testing. Continuous variables were analyzed using the Mann-Whitney U test. Time to event analysis was performed using log-rank Kaplan-Meier survival analysis. Statistical significance was defined as a P value <0.05. Because of limited clinical evidence on the effect of an additional low-viscosity bile duct flush, a reduction in severe mural stromal necrosis by 29% was considered necessary for a meaningful histological difference to prevent biliary complications.[4] As such, a sample size of 62 donors was required ($\alpha = 0.05$, $\beta = 0.2$), and recruitment ceased at 65 donors to account for loss to follow-up and dropout.

RESULTS

Ninety-five donors met inclusion criteria and were randomized before organ procurement surgery. Twenty-eight

grafts were deemed nontransplantable during donor surgery and not retrieved (17 in the intervention group and 11 in the control group). One donor that was randomized to the intervention group, however, had trauma to the bile duct unrelated to the intervention procedures and did not receive the intervention. This case was excluded from analysis. One recipient did not survive until graft implantation, and another withdrew from the study within the first month posttransplant. The final analysis was performed on 64 liver transplants. This resulted in 29 cases in the intervention group and 35 cases in the control group (Figure 2).

Donor and recipient demographic characteristics were similar in both groups (Table 1). Trauma, as a cause of donor death, was more prevalent in the control group (odds ratio [OR] 0.5, 95% confidence interval [CI] 0.4-0.6, P = 0.013). Alcoholic liver disease was more prevalent in the intervention group (OR 3.9, 95% CI 1.25-12.3, P = 0.027). Both groups had similar cold and warm ischemia times (P = 0.451 and 0.479, respectively).

Clinical Outcomes

All recipients received 24 mo of follow-up. One-year graft survival was 93% in the intervention group and 91% in the control group (log rank P = 0.565). There were no significant differences in the rates of biliary complications, biliary strictures, or bile leaks. Overall, biliary complications occurred in 31% of recipients (n = 9/29) in the intervention group and 23% of recipients (n = 8/35) in the control group (OR 1.5, 95% CI 0.5-4.6, P = 0.573) (Table 2). These included 1 bile leak in the intervention group (3%) and 3 in the control group (9%) (OR 0.4, 95% CI 0.04-3.9, P = 0.620), and 9 (31%) biliary strictures in the intervention group and 8 (23%) in the control group (OR 1.5, 95% CI 0.5-4.6, P = 0.573). ASs occurred in 24% (n = 7/29) of recipients in the intervention group and 20% (n = 7/35) of recipients in the control group (OR 1.3, 95% CI 0.4-4.2, P = 0.766). NASs occurred in 7% (n = 2/29) of the intervention group compared with 6% (n = 2/35) in the control group (OR 1.2, 95% CI 0.2-9.3, P = 1.00). The time to identification of biliary complications was similar between groups (P = 0.530) with a median of 0.8 mo for the control group and 3.8 mo for the intervention group. Likewise, there was no significant difference between groups for the time to identify ASs (P = 0.743) or NASs (P = 0.847).

TABLE 1.

Demographical information

	Control group (n = 35)		Intervention group (n = 29)		*P*
	Number/median	%/IQR	Number/median	%/IQR	
Donor age	56	48–64	56	46.7–66	0.697
Donor BMI	25.4	23.4–28.7	26.7	21.4–28.7	0.451
Donor risk index	1.679	1.413–1.837	1.581	1.363–1.962	0.802
Donor cause of death					0.027
Trauma	7	20%	0	0%	
CVA	17	49%	20	69%	
Hypoxia	11	31%	9	31%	
Recipient age	58	49.4–62.4	59.3	50.9–61.9	0.802
BMI	27.8	24.6–33.7	29.5	24.3–35.5	0.451
Primary transplant	32	91%	25	86%	0.692
MELD	22	15–28.5	19	15.3–23.5	0.284
Cause of recipient liver disease					
ETOH	6	17%	13	45%	0.027
HCC	8	23%	9	31%	0.573
HCV	9	26%	11	38%	0.417
HBV	1	3%	1	3%	1.00
NASH	7	20%	6	21%	1.00
CIT	314	251–392	326	265–382	0.451
WIT	41	33–59	43	34–57	0.479

CIT, cold ischemic time; CVA, cerebrovascular accident; ETOH, alcoholic liver disease; HBV, hepatitis B virus cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus cirrhosis; IQR, interquartile range; NASH, nonalcoholic steatohepatitis; WIT, warm ischemic time.

TABLE 2.

Clinical outcomes

	Control group (n = 35)		Intervention group (n = 29)		*P*
	Number	Percentage	Number	Percentage	
Bile leaks	3	9	1	3	0.620
Biliary strictures	8	23	9	31	0.573
NAS	2	6	2	7	1.00
AS	7	20	7	24	0.766

AS, anastomotic stricture; NAS, nonanastomotic stricture.

TABLE 3.

Bile duct injury characteristics stratified into bile duct Injury scores

	Control group (n = 32)		Intervention group (n = 26)		*P*
Grade (score)	**Cases**	**%**	**Cases**	**%**	
Biliary epithelial injury					0.374
Low (0–1)	10	31	5	19	
High (2)	22	69	21	81	
Mural stromal necrosis					0.767
Low (0–1)	23	72	20	77	
High (2–3)	9	28	6	23	
Vascular injury					0.346
Low (0–1)	23	72	22	85	
High (2–3)	9	28	4	15	
Periluminal peribiliary gland injury					0.517
Low (0)	7	23	4	15	
High (1–2)	23	77	22	85	
Deep peribiliary gland injury					0.223
Low (0)	6	20	9	38	
High (1–2)	24	80	15	63	

Histological Assessment

Bile duct samples were available in 89% (n = 26) of the intervention group and 91% (n = 32) of the control group. Failure to collect samples was due to staffing issues. All bile duct samples had varying degrees of biliary epithelial injury, and >50% epithelial injury was present in 81% (n = 21) of the intervention group compared with 69% (n = 22) controls (OR 1.9, 95% CI 0.6-6.5, P = 0.374). All bile duct injury domains were similar between groups (all $P \geq 0.05$). Further subgroup analysis was performed for bile duct injury domains, which were previously demonstrated to have clinical relevance for biliary complications. Peribiliary vascular injury and mural stromal necrosis were stratified into low- and high-grade injuries (grades 0–1 versus 2–3, respectively) (Table 3; Figure 3). No significant difference was demonstrated between groups for peribiliary vascular injury (OR 0.5, 95% CI 0.1-1.7, P = 0.346) or mural stromal necrosis (OR 0.8, 95% CI 0.2-2.5, P = 0.767). Peribiliary gland injury was stratified into the presence or absence of injury (grade 0 versus 1–2) (Table 3), which did

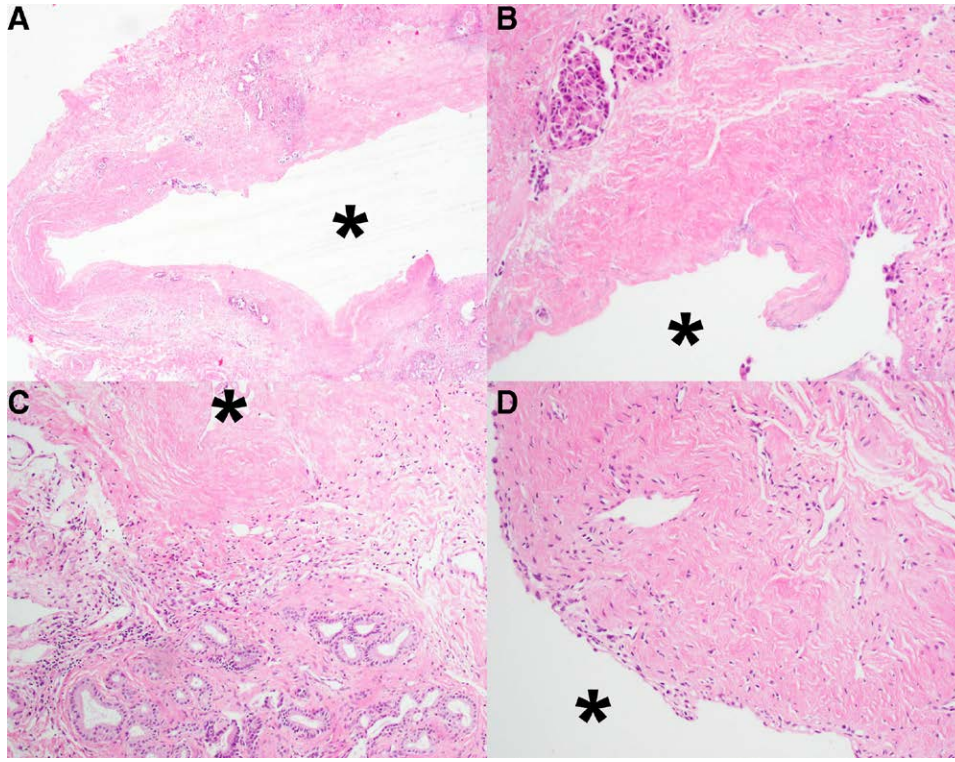

FIGURE 3. Histological images of bile duct biopsies. A, ×40 magnification of bile duct with high-grade biliary epithelial loss, mural stromal necrosis, vascular injury, and inflammation. B, ×200 magnification of (A) that demonstrates high-grade mural stromal necrosis and epithelial loss. C, ×100 magnification demonstrating inflammation underlying an area of mural stromal necrosis. D, ×200 magnification of low-grade mural stroma necrosis. The asterisk indicates the luminal surface.

not demonstrate significant difference between groups for periluminal peribiliary gland (OR 1.7, 95% CI 0.4-6.5, P = 0.517) or deep peribiliary gland injury (OR 0.4, 95% CI 0.1-1.4, P = 0.223).

DISCUSSION

The presence of intraluminal bile during organ procurement causes significant necrosis of the bile duct stroma and epithelium.[3,9] As a consequence, the removal of bile from the biliary tree is important to prevent biliary complications.[18,19] In standard practice, the gallbladder is incised and flushed with saline during the warm phase of organ procurement, prior to aortic cross clamp.[20] Although the gallbladder flush removes bile from the cystic duct and distal bile duct, the proximal intrahepatic biliary tree may remain unflushed.[9,10] Subsequently, many transplant centers also perform a bile duct flush with preservation solution after graft hepatectomy.[10] Flushing the bile ducts with UW has been shown to preserve the biliary tree during graft storage and transport.[9-11] However, an animal study has suggested that an additional bile duct flush with low-viscosity preservation fluid may reduce bile duct injury.[11] This study investigated whether an earlier additional bile duct flush with low-viscosity preservation solution immediately after the onset of cold ischemia could reduce bile duct injury or biliary complications.

To our knowledge, no clinical trial has previously investigated bile duct flushing in liver transplantation. This study did not demonstrate any significant difference in histological bile duct injury between the intervention and control. Similarly, there was no difference in the incidence of biliary complications between the 2 groups. The histological findings of bile duct injury in this study are similar the reported literature.[2,4] All bile ducts had evidence of bile duct injury, particularly biliary epithelial loss (Figure 3). These findings suggest that performing an additional bile duct flush with low-viscosity preservation solution after the onset of ischemia does not reduce bile duct injury or biliary complications compared with the standard bile duct flush with UW performed at our center.

There is no firm consensus on the ideal volume and type of solution used to flush the biliary tree during organ procurement. As per our unit practice, the bile duct flush in the control group was 75 mL of UW solution after donor hepatectomy (Figure 1). In published clinical practice, volumes between 50 and 200 mL have been used.[10,18,21,22] This study demonstrates that 75 mL is equivalent in the prevention of bile duct injury and biliary complications compared with the total 135 mL used in the intervention group. Furthermore, an animal study suggested that a low-viscosity preservation solution (eg, histidine-tryptophan-ketoglutarate, Marshall solution) reduced bile duct injury compared with high-viscosity solution alone (eg, UW), possibly because of the ability for low-viscosity solutions to penetrate smaller intrahepatic ducts.[11] Low-viscosity Marshall solution was used in the intervention group; however, this did not result in a significant reduction of histological bile duct injury. Thus, a bile duct flush with 75 mL of UW seems reasonable for the reduction of bile duct injury and biliary complications.

A limitation of this study was that only biopsies of the distal bile duct were analyzed. However, Op den Dries et al demonstrated that assessment of the distal bile duct was predictive of intrahepatic biliary strictures.[4] In addition, despite the use of randomization, demographic differences in donor and recipient factors between groups may have confounded the results of this study. Trauma as a cause of donor death was more prevalent in the control group; however, a large national registry study did not demonstrate an association between donor cause of death and biliary complications.[23] In addition, it should be acknowledged that all donors in this study were retrieved and transplanted in the New South Wales, Australia, which may impact the external validity of the study. This was to ensure adherence of the study protocol by the organ procurement team. Furthermore, although larger studies have not shown any correlation between alcoholic liver disease and biliary complications, the intervention group had a higher prevalence of alcoholic liver disease and may act as a confounding factor to outcomes in this study.[24,25] A further limitation of the study was the use of clinical indicators to determine the need for biliary interventions and imaging rather than protocolized magnetic resonance cholangiopancreatography, which means that some clinically insignificant biliary strictures have been missed.

This is the first prospective randomized trial investigating the effect of bile duct flushing during liver transplantation on humans. Our findings suggest that there is no significant advantage to performing an earlier and additional bile duct flush with low-viscosity preservation solution in terms of histological or clinical outcomes.

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