Systematic Review/Meta-analysis

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Graft function and renal protection with peritransplant systemic dexmedetomidine in kidney and liver recipients: systematic review and meta-analysis of randomized controlled trials

Martin Reichert, MD[a,*], Franziska Willis, MD[a], Christian Koch, MD[b], Anca-Laura Amati, MD[a], Jacqueline Braun, MD[a], Markus A. Weigand, MD[c], Michael Sander, MD[b], Hristos Karakizlis, MD[d], Martin Schneider, MD[a], Andreas Hecker, MD[a]

Background: By modulating inflammatory pathways and exerting sympatholytic effects, perioperative dexmedetomidine offers several benefits in non-transplant surgery. Its favorable impact on ischemia-reperfusion injury and perioperative renal function supports the potential role of dexmedetomidine as an adjunct in transplant surgery. The evidence within various settings of kidney (KT) and liver transplantation (LT) is systematically reviewed.

Methods: This systematic review evaluated randomized controlled trials investigating the efficacy of perioperative systemic dexmedetomidine in preventing allograft failure and/or kidney dysfunction in kidney and liver transplant recipients. Meta-analysis was performed using random or fixed effects model depending on the degree of statistical heterogeneity. Risk of bias and evidence quality were assessed.

Results: Ten randomized controlled trials tested perioperative systemic dexmedetomidine in recipients of living (n = 3) or deceased donor (n = 1) kidney transplants and living (n = 5) or deceased donor (n = 1) liver transplants. With moderate to high certainty, cardiocirculatory, pulmonary, or surgical complication rates did not differ between dexmedetomidine and control groups. Risk for delayed graft function was reduced with dexmedetomidine after deceased donor KT (risk ratio: 0.52 [0.26–1.01]; P = 0.05) and living donor LT (risk ratio: 0.35 [0.17–0.74]; P = 0.006), though this did not translate into improved long-term allograft survival within limited long-term follow-up. Rates of posttransplant acute kidney injury were decreased following these transplant modalities (risk ratio: 0.40 [0.18–0.90]; P = 0.03 and 0.69 [0.50–0.95]; P = 0.02, respectively). Early postoperative serum creatinine was improved after KT and living donor LT. After living donor LT, serum parameters indicating allograft function improved with dexmedetomidine on postoperative days 1, 3, and 5. However, no such improvements were observed after deceased donor LT.

Conclusions: Current evidence suggests that perioperative dexmedetomidine may reduce delayed graft function in deceased donor KT and living donor LT while supporting overall renal recovery. However, due to limited data and moderate certainty of evidence, further large-scale multicenter trials are needed to confirm clinical applicability and assess long-term efficacy.

Keywords: delayed graft function, dexmedetomidine, kidney, liver, renal protection, transplantation

Introduction

Kidney (KT) and liver transplantation (LT) for end-stage organ diseases remain challenging for physicians even in highly specialized transplant centers. Delayed graft function (DGF), characterized by early severe organ dysfunction after KT or LT, is a serious problem in transplantation medicine and a crucial risk factor for poor transplant outcomes and long-term allograft failure[1–7]. Besides careful donor-recipient selection, the investigation of additional strategies supporting stable early organ function postoperatively and thereby maintaining long-term allograft viability is essential, particularly in times of organ shortage.

DGF is closely related to ischemia-reperfusion injury (IRI) to the transplanted organ after both KT and LT[1–7]. During the first week after KT, DGF represents the clinical manifestation

[a]Department of General, Visceral, Thoracic, and Transplant Surgery, Giessen University Hospital, Justus-Liebig-University, Giessen, Germany, [b]Department of Anesthesiology, Intensive Care Medicine and Pain Therapy, Giessen University Hospital, Justus-Liebig-University, Giessen, Germany, [c]Department of Anesthesiology, Heidelberg University, Medical Faculty Heidelberg, Heidelberg, Germany and [d]Department of Internal Medicine II, Division of Nephrology and Renal Transplantation, Giessen University Hospital, Justus-Liebig-University, Giessen, Germany

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*Corresponding author. Address: Department of General, Visceral, Thoracic, and Transplant Surgery, Giessen University Hospital, Justus-Liebig-University of Giessen, Rudolf-Buchheim-Strasse 7, Giessen 35390, Germany. Tel.: +49 64198544701; Fax: +49 64198544709.
E-mail: martin.reichert@chiru.med.uni-giessen.de (M. Reichert).

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of severely impaired posttransplant renal function[8,9]. Kidney dysfunction in the postoperative period is also a relevant clinical problem after LT[10–13], and might indirectly be triggered by IRI to the liver transplant. Indeed, IRI with consecutive post-reperfusion syndrome after LT causes systemic effects inducing acute kidney injury (AKI), which in turn triggers the development of chronic kidney disease and leads to worse outcome in long-term follow-up[10–15].

Beneficial perioperative effects have been demonstrated for low-dose administration of the selective alpha-2 adrenoreceptor agonist dexmedetomidine as an adjuvant to intraoperative general anesthesia[16,17]. Furthermore, dexmedetomidine exerts protective effects in terms of perioperative inflammation and attenuation of IRI[18–21].

Overall, available clinical evidence from perioperative studies indicates potential renoprotective effects of dexmedetomidine[22,23]. Additionally, dexmedetomidine alleviates IRI in preclinical models[18–20,24] and in clinical contexts such as hepatectomy involving inflow occlusion[25,26].

This systematic literature review evaluates current evidence on the effects of perioperative dexmedetomidine on posttransplant AKI and DGF following KT and LT, based on data from prospective, randomized controlled trials (RCTs)[8,27–35]. The meta-analysis investigates whether perioperative dexmedetomidine administration reduces the incidence of DGF in KT and LT. The underlying hypothesis proposes that dexmedetomidine exerts protective effects on graft function and promotes early posttransplant renal recovery. Subgroup analyses were conducted to distinguish between living and deceased donor transplants, aiming to explore potential differences in treatment effects, identify gaps in existing evidence, and provide a foundation for further research in perioperative transplant medicine.

HIGHLIGHTS

- Dexmedetomidine may reduce delayed graft function after deceased donor kidney transplantation and living donor liver transplantation.
- Potential renoprotective effects of perioperative dexmedetomidine administration may support renal recovery and improve early posttransplant kidney function.
- Subgroup analyses indicate that efficacy depends on donor type and transplant modality.
- Dexmedetomidine was well tolerated, with no increase in adverse events.
- Heterogeneity in study protocols, dosing strategies, and outcome definitions limits the certainty of evidence.
- Larger multicenter trials are needed to confirm clinical applicability and long-term benefits.

Methods

The study was prospectively registered in the *International Prospective Register of Systematic Reviews*. The protocol is available at: CRD42024538200. Systematic review and meta-analysis were performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[36], Assessing the methodological quality of systematic reviews guidelines[37] and Transparency in the reporting of artificial intelligence guideline[38].

Systematic literature search and data extraction

English or German literature was screened in *MEDLINE, CENTRAL*, and *Web of Science*. Further information was extracted from *ClinicalTrials.gov*. Prospective randomized-controlled trials investigating dexmedetomidine in the setting of KT or LT were identified using a predefined search strategy (Supplemental Digital Content 1, available at: http://links.lww.com/JS9/E589). Searches were performed on May 1, 2024 and finally updated on February 1, 2025.

Eligibility criteria for inclusion in the meta-analysis required that the study data be sourced from RCTs involving either living or deceased donor kidney or liver recipients and in whom dexmedetomidine was tested as peritransplant systemic experimental therapy against a control group with placebo, standard therapy, or no therapy. Studies lacking suitable comparators – for example, comparison with another pharmacologic intervention, studies failing to include transplant recipients, and trials with non-systemic experimental application of dexmedetomidine (e.g. isolated additive application in local or epidural anesthesia) were excluded from the meta-analysis.

The primary outcome was the incidence of delayed kidney or liver allograft function. DGF after KT was defined as the need for dialysis within the first week[8,28]. In LT, early allograft dysfunction was assessed through liver-specific laboratory parameters. Kwon *et al*[30] defined DGF after living donor LT by serum bilirubin levels >10 mg/dL or an international normalized ratio (INR) >1.6 on postoperative day 7. Yang *et al*[35] added serum aspartate aminotransferase or alanine aminotransferase >2000 U/L within the first 7 days to similar bilirubin and INR criteria. In the RCT by Fayed *et al*[33], the presence of severe lobular necrosis was used as an indirect marker of DGF after living donor LT.

Secondary outcomes were: General patient outcome measured by length of (posttransplant) stay (intensive care, in-hospital) as a surrogate parameter for patient general recovery; general allograft outcome, including incidence of (early) acute rejection and incidence of long-term allograft failure; incidence of posttransplant AKI, need for dialysis (beyond the respective definition of DGF after KT), incidence of furosemide therapy, kidney (dys-) function assessed by laboratory measurements and urine output; posttransplant liver injury, assessed by laboratory measurements of liver (dys-) function; patient reported outcomes, including patient satisfaction with treatment, quality of recovery and posttransplant (postoperative) pain; patient safety, including total incidence of complications, incidence of surgical complications > II° according to Clavien-Dindo classification[39], total incidence of cardiac complications (especially incidence of hypotension, incidence of bradycardia), total incidence of pulmonary complications, incidence of hypoxemia or prolonged invasive ventilation and incidence of delirium.

Two reviewers independently screened the titles and abstracts of studies retrieved using the search strategies outlined above and those from additional sources for potential inclusion. Full texts of potentially eligible studies were retrieved and again independently assessed for final inclusion into the meta-analysis by two reviewers (see PRISMA flow diagram in Supplemental Digital Content 2, available at: http://links.lww.com/JS9/E590). Data for quality assessment and evidence synthesis were extracted from the studies and included into a standardized form by two

reviewers. At any stage disagreements between the two primary reviewers were resolved by an independent third party.

If relevant data were missing from the published manuscript or other sources, these were requested from study authors three times in a row with a minimum of 1 week apart. Other potential sources for obtaining comprehensive datasets were open registries for clinical trials. Otherwise, if only the median was provided or standard deviation of means was lacking, conversion from median to mean and standard deviation was carried out using the method described by Wan *et al*[40].

Data synthesis and statistical analysis

When comparable data from multiple RCTs were available, data synthesis and statistical analysis were performed using the Cochrane Collaboration's Review Manager (RevMan Version 5.4). Heterogeneity of each data synthesis was tested using Cochran's *Q* statistic and I^2 test (I^2 = 0%–40%: low; I^2 = 41%–74%: moderate; I^2 = 75%–100%: high) as described before[16].

For dichotomous outcomes, risk ratios (RR) were calculated: RR <1 favors the experimental pharmacologic intervention with dexmedetomidine. For continuous parameters, mean differences (MD) between the two groups were calculated. For each data synthesis, the appropriate statistical model (fixed or random effects) was selected individually based on the degree of heterogeneity assessed by I^2 test (low heterogeneity: fixed effects model; moderate to high heterogeneity: random effects model). Results are reported in forest plots with 95% confidence intervals. If no meta-analysis could be performed, results of the individual studies are reported narratively. *P* values < 0.05 were considered statistically significant.

Assessment of bias and quality of evidence

Risk of bias was assessed independently for each study included into the meta-analysis by two investigators and a third party, if necessary, using the Cochrane Collaboration´s risk-of-bias tool-2 (available at: www.methods.cochrane.org; version from August 22, 2019; Supplemental Digital Content 3, available at: http://links.lww.com/JS9/E591 depicts results of risk of bias assessment). Quality of evidence was assessed using "Grading of Recommendations, Assessment, Development and Evaluations" (GRADE software GRADEpro GDT; available at: www.gradepro.org). The respective certainty of evidence (CoE) is given at each calculation included into the main manuscript: very low ⨁, low ⨁⨁, moderate ⨁⨁⨁, high ⨁⨁⨁⨁. Summary of findings from GRADE are presented in Supplemental Digital Content 4, available at: http://links.lww.com/JS9/E592.

Results

Study characteristics

The systematic review identified ten RCTs investigating the effects of systemic dexmedetomidine as a perioperative intervention in 1217 transplant recipients in the context of KT and LT. Three RCTs focused on recipients of living donor kidney transplants; 110 patients in the dexmedetomidine intervention groups, and 110 patients in control groups[27–29]. One RCT involved 56 dexmedetomidine-treated and 55 placebo-controlled patients undergoing KT from deceased donors, specifically donation after cardiac death[8]. In LT, 5 RCTs examined the effects in living donor recipients; 283 patients in dexmedetomidine groups and 283 patients in control groups[30–34]. One RCT included 160 deceased donor liver transplant recipients in both the dexmedetomidine and placebo group[35].

Perioperative administration protocols varied across studies, with dexmedetomidine administered intraoperatively at infusion rates of up to 0.8 µg/kg/h. In four studies, dexmedetomidine administration was continued postoperatively at lower doses[8,29–31]. Supplemental Digital Content 5, available at: http://links.lww.com/JS9/E593, and Supplemental Digital Content 6, available at: http://links.lww.com/JS9/E594, provide detailed summary of individual study characteristics, administration protocols, and reported outcomes. In most RCTs, dexmedetomidine was compared with placebo. However, one study by Wang *et al* compared dexmedetomidine to standard care, and another study by Negi *et al* to standard analgesic care, rendering it altogether questionable whether blinding was adequate in these RCTs[27,29]. In this regard, results from risk of bias assessment are listed in Supplemental Digital Content 3, available at: http://links.lww.com/JS9/E591.

Allograft outcome after KT

Two RCTs assessed DGF after KT. While the meta-analysis did not confirm an effect on DGF after living donor KT, the subgroup analysis indicated a reduced incidence of DGF in recipients of deceased donor kidney transplants with dexmedetomidine, with borderline significance (RR: 0.52 [0.26–1.01]; *P* = 0.05; Fig. 1A).

Three RCTs reported no difference in early acute rejection rates between dexmedetomidine and control groups following KT (RR: 0.91 [0.53–1.57]; *P* = 0.74; Supplemental Digital Content 7, available at: http://links.lww.com/JS9/E595)[8,28,29]. Additionally, Shan *et al*[8] reported on the incidence of acute rejection beyond the initial posttransplant in-hospital stay and detected no differences between both groups during the one-year follow-up.

Although Shan *et al*[8] reported a nonsignificant trend (*P* = 0.08) toward reduced 1-year allograft failure rate in deceased donor kidney recipients after dexmedetomidine intervention, the meta-analysis revealed no disparity in long-term allograft failure (RR: 0.62 [0.03–12.79]; *P* = 0.75; Fig. 1C). Despite the moderate CoE in this regard, it is worth noting that follow-up in these trials was heterogeneous and very limited – ranging from 6[28] to 12 months post-transplant[8], with mostly small sample sizes.

Posttransplant kidney function

Posttransplant kidney dysfunction was furthermore assessed by rates of perioperative furosemide therapy, incidence of post-transplant AKI beyond the DGF definition, urine output as well as laboratory markers for kidney function.

No difference in the incidence of furosemide therapy was reported perioperatively by Shan *et al*, Park *et al*, and Wang *et al*[8,28,29] during KT or the first week thereafter (RR 0.90 [0.78–1.05]; *P* = 0.17; I^2 = 0%). Consistently, Park *et al* and Shan *et al*[8,28] described equal dosages of postoperative furosemide in recipients after deceased and living donor KT.

One RCT with recipients of living donor kidneys and one RCT with recipients of deceased donor kidneys reported rates of post-transplant AKI or the need for dialysis beyond the respective definition of DGF after KT[8,28]. Although this was reduced following dexmedetomidine intervention in deceased

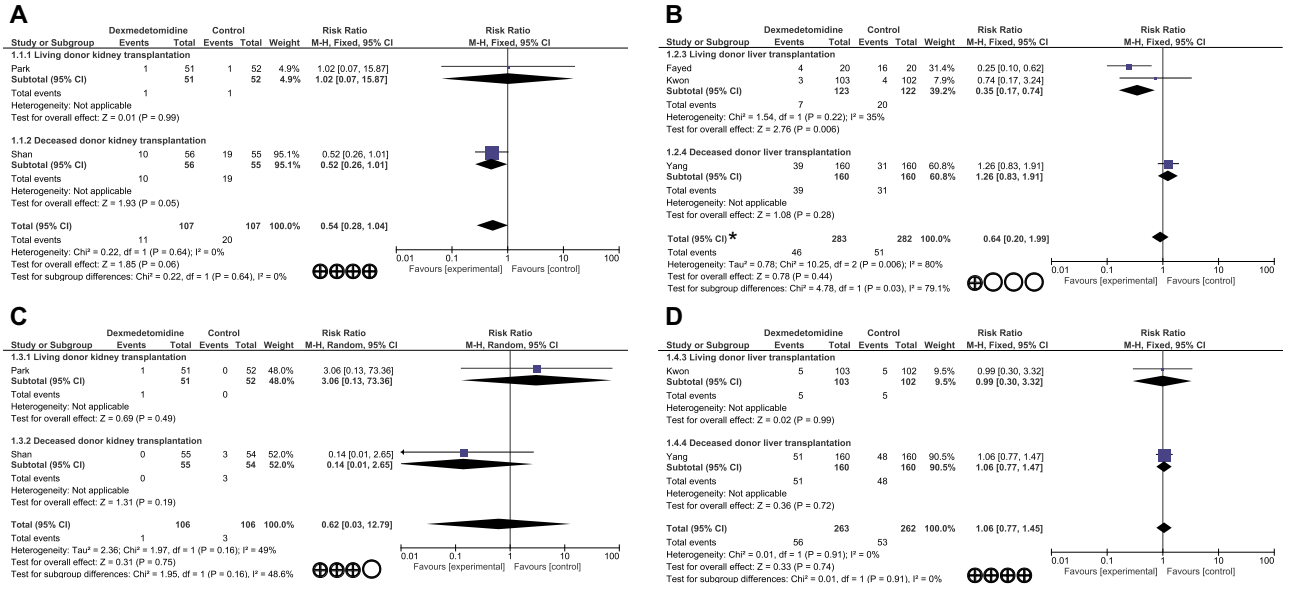

Figure 1. Allograft outcome. Effect of pharmacologic intervention with dexmedetomidine on outcomes of kidney and liver allografts versus comparator. Results are given as risk ratio and 95% confidence interval (95% CI). (A) Incidence of posttransplant delayed graft function after kidney transplantation. (B) Incidence of posttransplant delayed graft function after liver transplantation. (C) Long-term allograft failure or loss (6–12 months posttransplant) after kidney transplantation. (D) Long-term allograft failure or loss (12 months posttransplant) after liver transplantation. Certainty of evidence: very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕. *Random effects model used for calculation of overall effects.

donor KT (RR: 0.40 [0.18–0.90]; P = 0.03), the meta-analysis failed to confirm this effect across all KTs (Fig. 2A).

Creatinine clearance (MD: 8.21 [1.66–14.76] ml/min; p = 0.01) and estimated glomerular filtration rate (MD: 6.79 [0.67–12.91] ml/h/1.73 m^2; P = 0.03) were higher on postoperative day 1 with dexmedetomidine after both living and deceased donor kidney recipients, although urine output improvements until day 7 did not reach significance (Supplemental Digital Content 8–10, available at: http://links.lww.com/JS9/E595). Serum creatinine was lower on

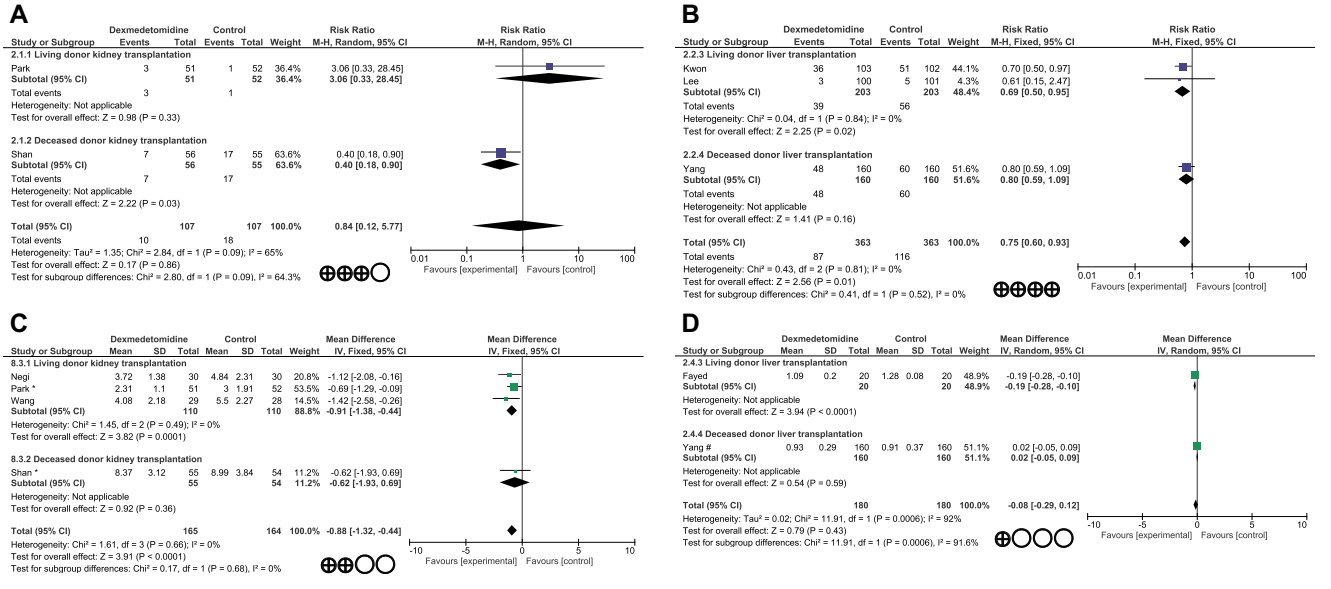

Figure 2. Posttransplant renal function. Effect of pharmacologic intervention with dexmedetomidine on posttransplant renal function. Results are given as risk ratio or mean difference and 95% confidence interval (95% CI). (A) Incidence of posttransplant acute kidney injury or need for dialysis beyond the definition of delayed graft function after kidney transplantation. (B) Incidence of posttransplant acute kidney injury or need for dialysis after liver transplantation. (C) Serum creatinine on posttransplant day 1 [mg/dl] after kidney transplantation. (D) Serum creatinine on posttransplant day 1 [mg/dl] after liver transplantation. *Primary data obtained from corresponding author. #Data estimated from publication graphs. Certainty of evidence: very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕.

postoperative day 1 and showed a nonsignificant trend toward improvement on day 2 after KT under dexmedetomidine intervention (MD: –0.88 [–1.32 to 0.44] mg/dl; $P < 0.0001$ and –0.21 [–0.43 to 0.02] mg/dl; $P = 0.08$; Supplemental Digital Content 11, available at: http://links.lww.com/JS9/E595). Although only limited data are available in the current literature, no differences between intervention and control groups were observed in serum cystatin C values (Supplemental Digital Content 12, available at: http://links.lww.com/JS9/E595). The single study analysis by Shan *et al*[8] indicates some potential benefits in serum neutrophil gelatinase-associated lipocalin values in the dexmedetomidine group after deceased donor KT; however, this was confirmed in the meta-analysis only as a trend on postoperative day 3 (MD: –105.00 [–218.17 to 8.17]; $P = 0.07$; Supplemental Digital Content 13, available at: http://links.lww.com/JS9/E595)[8].

Allograft outcome after LT

Improvements in early allograft function were primarily observed in the subgroup meta-analysis of results from two studies including living donor liver recipients (RR: 0.35 [0.17–0.74]; $P = 0.006$), while deceased donor liver transplant recipients did not experience similar benefits. The certainty of this evidence was graded as very low primarily due to publication bias and heterogeneity in the definition of DGF across the individual trials (Fig. 1B).

Data on acute liver allograft rejection rates were not available in the literature.

Long-term allograft failure rates were reported in two RCTs (until 12 months posttransplant) in recipients of living as well as deceased donor liver transplants[30,35], with no differences observed between the dexmedetomidine and control groups (RR: 1.06 [0.77–1.45]; $P = 0.74$; Fig. 1D).

Posttransplant liver function

Posttransplant liver injury and dysfunction were assessed by laboratory serum markers[30,31,33,35]. Dexmedetomidine was found to improve laboratory indicators of liver damage (including decreased serum aspartate aminotransferase and alanine aminotransferase) and function (including decreased serum total bilirubin and increased INR) on postoperative days 1, 3, and 5 compared to placebo following living donor LT. However, similar effects were not observed after deceased donor LT (Supplemental Digital Content 14–17, available at: http://links.lww.com/JS9/E595). These contrasting findings contribute to significant heterogeneity and are based on single study results.

Post-liver transplant kidney injury

Information on the incidence and dosages of furosemide therapy following LT was unavailable; however, rates of AKI or need for dialysis after LT were markedly decreased after dexmedetomidine intervention (RR: 0.75 [0.60–0.93]; $P = 0.01$; Fig. 2B). Similarly, detailed data on perioperative serum markers of renal function were scarce, although beneficial effects were observed on postoperative serum creatinine values in recipients following living-related liver donation with perioperative dexmedetomidine intervention (Fig. 2D, Supplemental Digital Content 11, available at: http://links.lww.com/JS9/E595).

Overall outcome and complications

None of the RCTs evaluated patient-reported outcomes, including satisfaction with treatment or subjective quality of recovery. Postoperative pain was recorded in the studies by Negi *et al* as well as Shan *et al* until postoperative day 1 after living donor as well as postoperative day 2 after deceased donor KT, respectively[8,27]. Here, a narrative report suggested advantages for patients undergoing dexmedetomidine intervention during the first 24 hours after surgery[8,27]. Accordingly, Sayed and Yassen as well as Fayed *et al* reported lower dosages of opioids and anesthetic agents with dexmedetomidine during living donor LT[32,33]. In contrast, postoperative use of analgesics and sedatives was comparable between intervention and placebo groups in the RCT conducted by Yang *et al*[35]. The heterogeneous data format prevented incorporation of these findings into the meta-analysis.

The incidence of posttransplant delirium was reported by two RCTs in recipients of living donor liver transplants with no differences between intervention and placebo in the meta-analysis[31,34] (Table 1).

The overall complication rates were unavailable, even after reaching out to the study authors. Data on complications relevant to intervention with dexmedetomidine were synthesized in the meta-analysis (Table 1). Certainty of evidence regarding them was consistently moderate to high. The risk of surgical complications >II° according to the Clavien-Dindo classification[39] was comparable between both groups.

The meta-analysis found no differences in the incidence of bradycardia. Although not reported in the original publication, the primary data from Park *et al*[28] were provided upon request. Data from Wang *et al*[29] following living donor KT as well as from Fayed *et al*, Kwon *et al*, and Sayed and Yassen[30,32,33] following living donor LT could not be included in the meta-analysis due to inappropriate data formats; at least Fayed *et al*[33] observed uncomplicated bradycardia more frequently with dexmedetomidine. Similarly, the incidence of hypotension was equal with dexmedetomidine compared to control patients in the meta-analysis of results from three RCTs[8,28,31]. Data on hypotension from 6 RCTs could not be included in the meta-analysis[27,29,30,32–34], wherein no major differences between the groups were narratively reported. Fayed *et al*[33] described no differences in mean blood pressures between the dexmedetomidine and placebo groups, however, they reported higher catecholamine dosages needed in order to maintain adequate mean blood pressure in patients receiving dexmedetomidine, with dose reduction of dexmedetomidine due to hypotension in three of these patients.

The rate of pulmonary complications was reported in three RCTs[8,31,35] and original data were provided by Park *et al*[28], showing no differences between perioperative dexmedetomidine and control. Additionally, the meta-analysis of two RCTs found no differences in rates of severe hypoxemia and prolonged mechanical ventilation[31,35]. Kwon *et al* and Shan *et al*[8,30] reported no differences in posttransplant mechanical ventilation duration, while Fayed *et al* and Xu *et al*[33,34] showed reduced durations with dexmedetomidine compared to placebo.

The meta-analysis found that post-liver transplant stays at the intensive care unit were shorter with dexmedetomidine intervention (MD: –0.41 [–0.81 to 0.00] *d*; $P = 0.05$), but there were no differences in total hospital stay, as a surrogate for overall postoperative recovery (Fig. 3).

Table 1

Summary of safety outcomes and perioperative complications following systemic dexmedetomidine administration in kidney and liver transplantation.

	Incidence of surgical complications > CD II	Incidence of bradycardia	Incidence of hypotension	Incidence of pulmonary complications	Incidence of hypoxemia or post-transplant (prolonged) MV	Incidence of delirium
Effect	↔	↔	↔	↔	↔	↔
Risk ratio	0.97	1.57	1.09	1.02	1.14	0.78
95% confidence interval	0.60–1.74	0.83–2.99	0.68–1.75	0.83–1.25	0.47–2.77	0.23–2.60
P value	0.92	0.17	0.71	0.84	0.77	0.68
Effects model	Fixed	Fixed	Random	Fixed	Random	Random
Certainty of evidence	⊕⊕⊕⊕	⊕⊕⊕⊕	⊕⊕⊕◯	⊕⊕⊕⊕	⊕⊕⊕◯	⊕◯◯◯
Number of RCTs:						
• Living donor kidney Tx	1 RCT	1 RCT	1 RCT	1 RCT	–	–
• Deceased donor kidney Tx	–	1 RCT	1 RCT	1 RCT	–	–
• Living donor liver Tx	2 RCTs	1 RCT	1 RCT	1 RCT	1 RCT	2 RCTs
• Deceased donor liver Tx	1 RCT	–	1 RCT	1 RCT	1 RCT	–
Number of patients [*n*]	829	415	735	735	521	281
Heterogeneity [I^2]	24%	0%	63%	0%	56%	74%

This table summarizes findings from secondary dichotomous outcomes related to complications and safety parameters, as reported in RCTs evaluating perioperative dexmedetomidine use. These outcomes include perioperative events such as bradycardia, hypotension, hypoxemia, and postoperative delirium. Effect of experimental pharmacologic intervention versus comparator (no effect through experimental dexmedetomidine intervention: ↔ (whether positive or negative effects were observed through the experimental intervention). — signifies that the outcome was not assessed in the respective studies. CD refers to the Clavien-Dindo classification of surgical complications[39]; MV indicates mechanical/invasive ventilation. The certainty of evidence regarding Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was assessed using GRADEpro GDT software (available at: www.gradepro.org). The certainty of evidence is indicated as follows: very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕. RCT stands for randomized controlled trial. From the study by Yang *et al*[35], rates of pneumonia and rates of acute lung injury were used for the incidences of pulmonary complications and hypoxemia, respectively.

Discussion

The present systematic review and meta-analysis synthesize current evidence on perioperative systemic dexmedetomidine in recipients of kidney and liver transplants. It categorizes interventions across different transplantation modalities and highlights potential benefits of dexmedetomidine in two specific settings: deceased donor KT and living donor

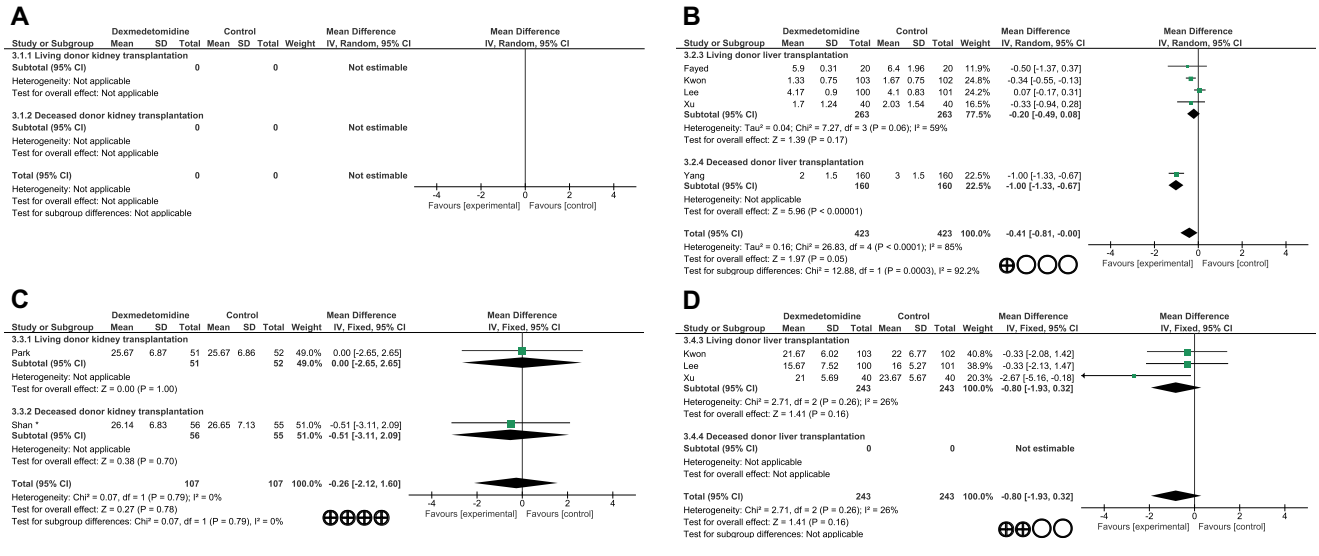

Figure 3. Posttransplant length of stay. Results are given as mean difference and 95% confidence interval (95% CI). (A) Length of posttransplant stay at intensive care unit after kidney transplantation [*d*]. (B) Length of posttransplant stay at intensive care unit after liver transplantation [*d*]. (C) Total posttransplant in-hospital stay after kidney transplantation [*d*]. (D) Total posttransplant in-hospital stay after liver transplantation [*d*]. *Primary data obtained from corresponding author. Certainty of evidence: very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, high ⊕⊕⊕⊕.

LT. Consequently, it provides valuable insights for future research and clinical practice in perioperative transplantation medicine.

Early allograft dysfunction and renal injury remain major concerns in patients following KT and LT[1–9]. Renal function is closely linked to the allograft after KT[8,9], while systemic effects of IRI and hepatorenal syndrome, as seen in delayed hepatic allograft function[5,7,10–15], contribute to the pathogenesis of AKI after LT[10–13]. Post-liver transplant AKI increases the long-term risk of chronic kidney disease[10–14]. Conversely, DGF is strongly associated with ischemia duration and severity of IRI[10–14], posing a substantial risk for irreversible organ damage and long-term allograft failure[41].

Given these challenges, the development of strategies to mitigate IRI-related organ dysfunction is of utmost importance in transplantation medicine to ensure long-term stable allograft function, particularly amid global organ shortages. While machine perfusion has significantly reduced DGF by minimizing IRI through oxygenated perfusate and has shown potential to improve long-term allograft survival compared to standard cold storage in both KT[42,43] and LT[44–48], its widespread adoption remains limited due to technical complexity, high costs, and logistical challenges. This highlights the ongoing relevance of pharmacological strategies as a more accessible approach. Among potential candidates, dexmedetomidine – a selective alpha-2 adrenoreceptor agonist – has shown promising anti-inflammatory and anti-oxidant effects in experimental models[18,20,24]. Furthermore, perioperative clinical studies outside the transplant setting suggested renoprotective effects[23], attributed to anti-inflammatory and antioxidant pathways, analgesic effects with reduced nephrotoxic medication and improved hemodynamics with enhanced renal perfusion through alpha-2 agonism[23,49]. These benefits suggest that dexmedetomidine may serve as a valuable adjunct in peritransplant medicine. Therefore, perioperative renal function can be directly or indirectly affected by IRI in KT or LT settings, respectively. Consecutively, maintaining optimal perioperative renal function significantly impacts on long-term outcomes of the patients[8–14]. These renoprotective effects have been systematically investigated in our meta-analysis of data from RCTs, which categorizes the findings by transplant modality (liver and kidney) and donor type (living and deceased donor).

In the present meta-analysis, perioperative dexmedetomidine administration was found to be safe, particularly with regard to hemodynamic and respiratory complications, which are relevant concerns in dexmedetomidine intervention[50,51]. Dexmedetomidine improved early allograft function, notably by reducing DGF rates after deceased donor KT ($P = 0.05$) and living donor LT ($P < 0.006$). These beneficial effects were not consistently observed in other transplant modalities, which may be explained by generally shorter ischemia times in living donor compared to deceased donor transplantation as well as lower ischemia tolerance of liver grafts compared to kidneys. Whether these early functional improvements translate into better long-term allograft survival remains uncertain, given the limited follow-up periods of 6–12 months in the small sample-sized individual studies. Nevertheless, Shan *et al*[8] reported a trend toward improved 1-year allograft survival with dexmedetomidine following KT from donation after cardiac death, suggesting a potential long-term benefit that warrants further investigation.

Despite the observed clinical benefits, precise mechanisms by which dexmedetomidine exerts protective effects in solid organ transplantation remain incompletely understood. However, preclinical studies suggest several potential pathways. Activation of alpha-2 adrenergic receptors leads to sympatholysis and improved microcirculation[29,52]. In preclinical models, attenuation of IRI has been demonstrated through modulation of key intracellular signaling cascades including the Toll-like receptor 4/nuclear factor kappa B (TLR4/NF-κB), Janus kinase/signal transducers and activators of transcription (JAK/STAT) and Sirtuin 3 pathways[15,53–55]. These mechanisms are associated with anti-inflammatory, anti-apoptotic, and anti-ferroptotic effects and enhancement of mitophagy[20]. As systematically reviewed by Hou *et al*, activation of these pathways leads to reductions in the release of pro-inflammatory cytokines and oxidative stress[20,56,57]. However, it must be emphasized that most mechanistic insights to date derive from preclinical ischemia-reperfusion models. Translational studies specifically investigating these pathways in clinical transplantation settings, as well as potential interactions with modern immunosuppressive regimens, are currently lacking.

In addition to reducing DGF, dexmedetomidine also decreased the overall incidence of posttransplant AKI (beyond DGF in KT). Similarly, this effect was particularly pronounced after deceased donor KT and living donor LT. Peritransplant laboratory parameters for kidney and liver function should be interpreted with caution due to limitations and heterogeneities in the available published data. Nonetheless, the meta-analysis indicates improvements in kidney function early after transplantation. Even after living donor LT single study results reveal improvements in posttransplant liver damage (indicated by serum aspartate aminotransferase and alanine aminotransferase) and liver function (indicated by INR and serum total bilirubin). These findings are consistent with previous observations from hepatectomy using inflow occlusion, further supporting the biological plausibility of dexmedetomidine's protective effects on hepatic IRI[25,26].

The presented systematic review and meta-analysis provide an updated and refined synthesis of the effects of systemically administered dexmedetomidine on allograft function and perioperative renoprotection following KT and LT. Thereby the analysis centers on the shared pathophysiology of renal dysfunction[58–60], primarily attributable to IRI of the allograft, which plays a critical role not only in KT but also in the development of renal impairment after LT[1–14]. To ensure a high level of methodological quality and minimize the risk of confounding, only RCTs were included, with observational and retrospective studies systematically excluded. Recognizing the inherent physiological and clinical differences between living versus deceased organ donation, outcomes were stratified by donor type wherever feasible. Subgroup analyses were conducted to account for these variations, enabling a differentiated assessment of dexmedetomidine's potential benefits across distinct transplant settings.

This approach enables a comprehensive, high-quality evidence synthesis with relevant clinical implications. Despite the strengths of the present work, certain limitations must be acknowledged. The included studies were monocentric with small sample sizes and lacked extended long-term follow-up, restricting the ability to assess durable transplant outcomes. Definitions of key outcomes, such as DGF, varied substantially across trials, particularly in LT, contributing to clinical heterogeneity. Furthermore, substantial

variability in dexmedetomidine administration protocols and dosing regimens was observed, ranging from intraoperative-only use to prolonged perioperative administration. The choice of control interventions also differed markedly among studies, thereby complicating direct comparisons (Supplemental Digital Content 5, available at: http://links.lww.com/JS9/E593). While subgroup analysis by transplant modality and donor type was possible and carefully applied to avoid bias, stratification by recipient age was not feasible. No randomized trials on pediatric transplant recipients were available, and the lack of individual patient data prevented further stratification into younger or elderly adult cohorts. However, single retrospective studies in pediatric KT and LT have suggested also potential benefits of dexmedetomidine in reducing IRI and supporting postoperative renal function[61,62]. In addition, the predominance of studies from Asian countries may limit the generalizability of the findings due to differences in patient populations, healthcare systems, and clinical transplantation practices. Although these factors introduced statistical and clinical heterogeneity, the analytical strategy accounted for this variability by applying fixed-effects or random-effects models based on the degree of heterogeneity assessed via I^2 statistics. Despite certain indications of publication bias and imprecision, the present work provides a structured and transparent synthesis of the best available randomized evidence. These findings provide a promising basis for future research in perioperative transplantation medicine and underscore the urgent need for larger, multicenter RCTs with standardized protocols and extended follow-up to validate and expand upon these observations.

In conclusion, current evidence suggests that perioperative dexmedetomidine may improve early transplant outcomes, particularly by reducing DGF and supporting posttransplant kidney and liver recovery, in specific settings, notably deceased donor KT and living donor LT. These effects were not consistently observed across all transplant modalities. Given the moderate certainty of evidence, small sample sizes, and limited follow-up durations of the included trials, the clinical application of dexmedetomidine in transplantation appears promising but requires further validation through multicenter RCTs to confirm these findings and assess their long-term clinical impact in this vulnerable patient cohort.

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Author contributions

All authors substantially contributed to the manuscript, all authors were involved in drafting the work, manuscript writing or revised it critically for important intellectual content. All authors have read the final version of the manuscript and gave final approval of the version to be published. All authors agree to be accountable for the authors own contributions and to ensure that questions related to the integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in literature. Study concept: M.R., C.K., M.A.W., M. Sander, H.K., M. Schneider, A.H.; data collection: M.R., F.W., A.-L.A., J.B., A.H.; data analysis: M.R., F.W., A.-L.A., J.B., A.H.; data interpretation: M.R., C.K., M.A.W., M. Sander, H.K., M. Schneider, A.H.; resources: M. Schneider, A.H.; supervision: C.K., M. Schneider, A.H.; validation: F.W., A.-L.A., C.K., H.K.; visualization: M.R.; writing – first draft: M.R., F.W., A.-L.A., J.B.; writing – critical revision: C.K., M.A.W., M. Sander, H.K., M. Schneider, A.H.

Conflicts of interest disclosure

Not applicable.

Research registration unique identifying number (UIN)

The study was prospectively registered in the *International Prospective Register of Systematic Reviews* (PROSPERO 2024 CRD42024538200). The protocol is available at: CRD42024538200. Systematic review and meta-analysis were performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, Assessing the methodological quality of systematic reviews (AMSTAR-2) guidelines and Transparency in the reporting of artificial intelligence (TITAN) guideline.

Guarantor

Martin Reichert.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

The authors report no conflicts of interest related to this work.

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