Prostaglandin E1 analogs do not improve renal function among either transplant or nontransplant patients: no further trials required

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Authors' objectives
To assess whether prostaglandin E1 analogs have a role in either reducing renal allograft rejection or improving renal function among both transplant and non-transplant patients.

Searching
A detailed search of the literature was conducted by one author using OVID MEDLINE between 1981 to December 1997. All search results were limited to clinical trials conducted on humans, published in the English language, and with an available abstract. The references from each trial were also read to identify any nonindexed trials.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), either non-blinded or double-blinded, and with or without crossover.

Specific interventions included in the review
Studies that met the following inclusion criteria were accepted:

1. Prospective design with randomisation of patients to either treatment or control arms.
2. Administration of an oral or intravenous prostaglandin (PG) as the main intervention.
3. Utilisation of an objective measure of change in renal function (eg: serum creatine level, creatine clearance (CrCl), or glomerular filtration rate (GFR)) from before to after PG therapy.
4. Inclusion of either nontransplant patients exposed to a potential nephrotoxic agent, or renal or liver transplant patients receiving cyclosporine (CsA). Included trials examined the effects of PGE1 among renal transplant patients or among hepatic transplant recipients. Within all trials CsA was used early after transplant, usually along with corticosteroids and other immunosuppressive agents. The dose of CsA ranged from 1.5 mg/kg/day up to 14 mg/kg/day. The active therapy was either oral misoprostol, enisoprost or intravenous alprostadil.

Participants included in the review
Transplant and non-transplant patients who have been treated with prostaglandin E1 analogs for improving renal function.

Outcomes assessed in the review
The outcome of interest was the combined rate of acute renal graft rejection or renal dysfunction. Acute renal graft rejection was broadly defined as an increase in serum creatinine level after ruling out the possibility of CsA nephrotoxicity or urological complications and was confirmed by either graft biopsy or an improvement in renal function after the initiation of antirejection therapy (eg high-dose steroids OKT3). Acute renal dysfunction was defined as a rise in serum creatinine level unresponsive to intravenous fluids or diuretics, either due to acute rejection or CsA nephrotoxicity. The latter was based on a deterioration in renal function, with subsequent improvement 1 week after reducing the CsA dose. Because of the difficulty in separating renal graft rejection from acute dysfunction, both events were analysed together as a single, clinically meaningful outcome. The mean change in GFR was determined either by way of direct measurement or by using the pre- and posttransplant serum creatinine (SeCr) levels, according to the Cockroft-Gault (1976) equation: CrCl = ((140-age)x weight(kg))/(SeCr (Mumol/L)x0.80). Direct measurement of GFR, using radiolabeled isotope scans or inuline clearance, were otherwise used whenever possible.

How were decisions on the relevance of primary studies made?
The author does not state how the papers were selected for the review, or how many of the reviewers performed the selection.

**Assessment of study quality**
The author does not state that they assessed quality.

**Data extraction**
The author does not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

**Methods of synthesis**

How were the studies combined?
For dichotomous data of acute rejection/dysfunction, the unadjusted odds ratio (OR) was calculated for each study and then pooled using a random-effects model by DerSimonian and Laird (1986). A 95% confidence interval (CI) for the summary OR was calculated using the same method. The pooled prevalence of acute graft rejection/renal dysfunction in the control population, called the weighted control event rate, was determined using the random-effects method, as was the weighted treatment event rate for the treatment groups.

How were differences between studies investigated?
Heterogeneity across all studies was assessed by visual inspection and by using the Breslow and Day (1980) test for statistical heterogeneity. Rejection of the hypothesis that the studies were not heterogeneous occurred at a 2-sided P value less than 0.10.

**Results of the review**

Nineteen studies met all inclusion criteria. Seven trials examined the effects of PGE1 among renal transplant patients, whereas three were performed on hepatic transplant recipients. Nine trials were conducted among a variety of nontransplant patients.

Within the 10 transplant trials, renal transplant rejection or renal dysfunction was not significantly reduced with prostaglandin E1 (OR=0.91, 95% CI: 0.64,1.28), 2-sided P=0.58; weighted control event 66.9%, 95% CI:50.5,80.0). The GFR was estimated within nine transplant studies, with a minimal positive gain in renal function with PGE1 (mean difference 2.3 ml/min, 95% CI: 1.6,3.1). Nine other randomised, double blinded trials evaluated the effect of PGE1 on renal function among a variety of nontransplant patients. No significant change in the in the GFR was observed between PGE1 and placebo arms (mean difference 0.5 ml/min in favour of placebo, 95% CI -2.8,1.8). However these studies were very heterogeneous.

**Authors' conclusions**

Among both transplant and nontransplant populations, PGE1 does not seem to preserve or improve renal function.

**CRD commentary**
The inclusion criteria are described clearly and completely. Only one electronic database (MEDLINE) was used for the literature search and the search was restricted to English language articles. The quality of the included studies was not reported, nor was the way data were extracted from primary studies. The synthesis of results was clear and appropriate.

**Implications of the review for practice and research**
According to the authors, further research is unlikely to demonstrate superiority of PGE1 in the context of cyclosporine or nonsteroidal anti-inflammatory drug use.
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Other publications of related interest

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.