Post-operative Aspirin in preventing early renal allograft thrombosis: A Meta-Analysis

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ABSTRACT

Background: Kidney transplantation (KT) remains to be the preferred mode of renal replacement therapy as it offers the best clinical outcomes, a better quality of life, and lesser complications compared to dialysis. However, KT still carries a number of complications, one of which is graft thrombosis. Despite advancements in treatment, graft thrombosis is still an important cause of early graft loss. Prevention therefore, is of significance. A growing number of evidence suggests that low-dose aspirin has a role in the primary prevention of allograft thrombosis.

Research Question: Among renal transplant recipients, does postoperative aspirin prevent early renal allograft thrombosis?

Objective: To conduct a meta-analysis to determine the effect of postoperative aspirin on preventing renal allograft thrombosis.

Methods: A systematic search of PubMed, Google Scholar, CENTRAL, and clinicaltrials.gov was done by two independent authors. All randomized and non-randomized studies determining the effect of postoperative aspirin on renal vein/allograft thrombosis were reviewed for eligibility and quality assessment. Studies on both adult and pediatric kidney transplant recipients were included.

Results: Five non-randomized cohort studies (3 in adults, 2 in children) with a total of 2,393 patients were included. Using the Newcastle-Ottawa scale, two studies were found to have good quality, while three had poor quality. In a fixed-effects meta-analysis, aspirin was associated with a reduced risk for renal allograft thrombosis in adults (RR 0.13; 95% CI 0.06, 0.28; I^2 22%) and children (RR 0.11; 95% CI 0.03, 0.40; I^2 0%).

Conclusion: Post-operative aspirin was associated with reduced risk for renal allograft thrombosis in both adults and children. However, the best available evidence is limited to observational studies. A well-designed randomized controlled trial is needed to confirm this finding.

Keywords: aspirin, renal vein thrombosis, renal allograft thrombosis

INTRODUCTION

Chronic kidney disease (CKD), along with its complications, is one of the leading causes of morbidity and mortality in the Philippines. According to the National Kidney and Transplant Institute (NKTI), one Filipino is diagnosed with CKD every hour with a great fraction detected in the late stages of the disease, often needing renal replacement therapy through either dialysis or transplantation.[1] Consequently, general physicians and nephrologists alike are caring for an increasing number of dialysis and transplant patients.

Kidney transplantation (KT) remains to be the preferred choice in terms of renal replacement therapy as it offers a better quality of life and lesser complications compared to hemodialysis. Despite this, only a scant number undergo the procedure because the proportion of patients needing organs greatly outnumbers the available organs listed for donation. In the National Capital Region alone, there are more than 200 patients waiting for a suitable kidney donor. Moreover, nationally, there are about 7,000 end-stage renal disease (ESRD) patients on the waiting list, which continue to grow each year.[2] Because of this, donor kidneys remain to be a very scarce healthcare commodity.

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Due to the rigorous and tedious process of KT, from screening, acquisition of organs and surgical transplantation, it is crucial that utmost care and surveillance be given to graft recipients. KT, despite its numerous benefits, still carries several complications during and after the procedure. Pathological complications include rejection, infection, and cardiovascular events, while surgical complications involve vascular and urological complications, wound infection, and herniation.[3] Standard measures through guideline-based therapy are essential components to prevent and minimize these events. Novel ways to target infection, rejection and failure are also being currently investigated. In line with this, several new studies are focusing on the management of graft thrombosis that continues to threaten renal allografts.[4-7]

Graft thrombosis is an important cause of early graft loss following KT. The cause of this may be due several factors such as technical and anatomical problems, clotting disorders, diabetes, cyclosporine use, but is often difficult to define.[8] Clinical findings of thrombosis include anuria accompanied by tenderness and excruciating pain over the graft region. A suspicion of graft thrombosis warrants immediate investigation, as it may be potentially reversible.[9] Management options range from lysis with heparin or anti-fibrinolytic agents to endovascular techniques. Response to treatment, however, still varies and most cases generally succumb to irreversible loss of renal function.[9]

Compared to the morbidity that comes with graft thrombosis and bleeding complications from available treatment, it is worthwhile to investigate options for prevention as it is responsible for 2-7% of early renal graft loss. Whether it is advisable to give routine anticoagulation or antiplatelet therapy to transplant recipients at a low risk of thrombosis is still debatable.[9] Antithrombotic agents including warfarin, heparin, low-molecular weight heparin and aspirin have been used to prevent and treat thrombotic complications after transplantation.[10] Some centers have even incorporated these drugs to standard prophylactic regimens to prevent renal allograft thrombosis.[11,12] An example of such treatment regimen was illustrated by Ponticelli et al, in their review. They proposed an algorithm which stratifies patients by their thrombotic risk using clinical history and thrombophilia work-up. The protocol recommended the use low-molecular weight heparin and aspirin for both standard and intensive prophylaxis groups, with the intensive group receiving longer duration of treatment.[9] To date, however, no standard prophylactic regimen exists, and practices widely differ among institutions.[12] Even in the Philippines, the decision to administer prophylaxis, including the choice of drug, varies in clinical practice.

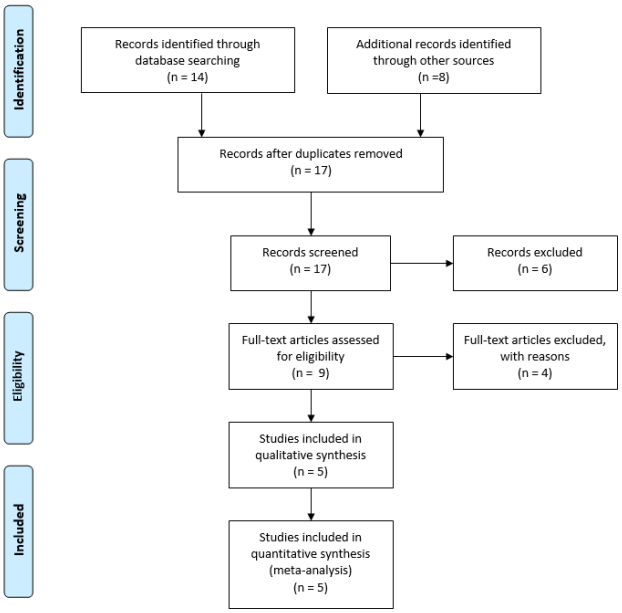

Figure 1. Flow Diagram of Study Selection

Of particular interest is the emerging evidence of low dose aspirin alone as a means of primary prevention for allograft thrombosis. The wide availability and low cost of the drug make it appealing as a standard add-on therapy to costly transplant protocols. In the clinical setting, perhaps the most comprehensive review thus far is a meta-analysis by Cheungpasitporn et al. which looked into the several benefits of aspirin in kidney transplant patients. In their review, they found that aspirin reduced the risks of allograft failure and mortality. Two studies were included in a meta-analysis which had allograft thrombosis as the outcome which also yielded encouraging results. Low dose aspirin was noted to reduce allograft thrombosis with a pooled RR of 0.11 (CI 0.02-0.53).[5] Since then, several small cohort studies have come out which are worthwhile to look into to strengthen the current available evidence.

Given these data, we aim to conduct a review of recent studies to investigate whether low-dose aspirin reduces the risk of renal allograft thrombosis in children and adults undergoing kidney transplantation.

METHODS

Search Strategy and Study Selection

The conduct of the study was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched by two independent authors using the following terms: "aspirin," "aspirin Mesh," "''renal transplant,'' "kidney transplantation Mesh," "renal allograft thrombosis," and "renal vein thrombosis." Any unpublished trial was sought using the database *clinicaltrials.gov*. Manual search of cross-referenced materials was also done. Only full-text articles were considered for inclusion. Efforts were made to obtain full-text articles of abstracts, including correspondence with authors. Disagreements were resolved by a third reviewer and mutual consensus.

Table I. Included Studies

Study (Year)	Design	Population	Size	Immunosup-pression	Exposure	Outcomes
Robertson (2000)	Retrospective cohort	Adult renal transplant recipients (living-related & cadaveric)	955	Cyclosporine, Azathioprine / Mycophenolate Mofetil, Prednisolone	Aspirin 75 mg/day for 1-month post-KT (> 1 month for high-risk; 150 mg/day if with previous renal artery/vein thrombosis)	Incidence of renal vein thrombosis
Murphy (2001)	Retrospective cohort	Adult renal transplant recipients (cadaveric)	226	Cyclosporine Prednisolone with or without Azathioprine	Aspirin 150 mg/day for 3 months post-KT, Heparin 5000 units before and 5000 units 2x/day for 5 days post-KT	Allograft thrombosis rates Delayed graft function, acute rejection, GFR at 1 year Aspirin complications
Stechman (2007)	Retrospective cohort	Adult renal transplant recipients (living-related & cadaveric)	697	*No details*	Aspirin 75 mg/day for 28 days post-KT	Renal transplant vein thrombosis
Esfandiar (2012)	Prospective cohort	Pediatric renal transplant recipients (living-related and unrelated donors)	87	*No details*	Heparin 50 U/kg every 8 hours for 7 days post-KT AND Aspirin 5 mg/kg, 3x/week from Day 3 to 3 months post-KT	Vascular thrombosis Serum creatinine at 1 year, survival rate, allograft failure
Midani (2019)	Retrospective cohort	Pediatric renal transplant recipients (living-related & cadaveric)	328	Cyclosporine / Tacrolimus, Azathioprine, Prednisolone	Aspirin 1 mg/kg/day (Maximum dose 75 mg/day) for 1-month post-KT, Heparin 3000-7500 U/day 3x/day until 7-10 days post-KT	Renal allograft thrombosis Hemorrhagic complications

Table II. Newcastle-Ottawa Scale for Non-Randomized Studies

	Selection	Comparability	Outcome	Quality of Study
Robertson et al (2000)	3	0	2	Poor
Murphy et al (2001)	3	1	2	Good
Stechman et al (2007)	3	0	2	Poor
Esfandiar et al (2012)	3	1	3	Good
Midani et al (2019)	3	0	2	Poor

Eligibility Criteria

All studies available for review during the conduct of the meta-analysis (until December 2019) that satisfy the following criteria were eligible for inclusion: (1) adults or pediatric kidney transplant recipients, (2) aspirin prophylaxis given post-transplant, and (3) renal vein thrombosis/renal allograft thrombosis as an outcome (primary or secondary). Only studies written in English (or with corresponding English translation) were included. Papers presented as abstracts only were excluded.

Study Quality Assessment

The Newcastle-Ottawa Scale, a tool that evaluates cohort studies, was used in the meta-analysis. It has three subscales on selection, comparability, and outcomes. A good quality study should have all of the following minimum scores: 3 in the selection domain, 1 in the comparability domain, 2 in the outcome domain.

RESULTS

Study Selection & Study Characteristics

Twenty-two studies were found in the electronic search (*Figure 1*). After screening out duplicates, abstract-only publications, and articles failing to meet the eligibility criteria, five studies were included in the final meta-analysis.

The characteristics of the included studies are summarized in Table 1. All studies were non-randomized cohorts involving the use of aspirin for prophylaxis against early renal allograft thrombosis. Three studies

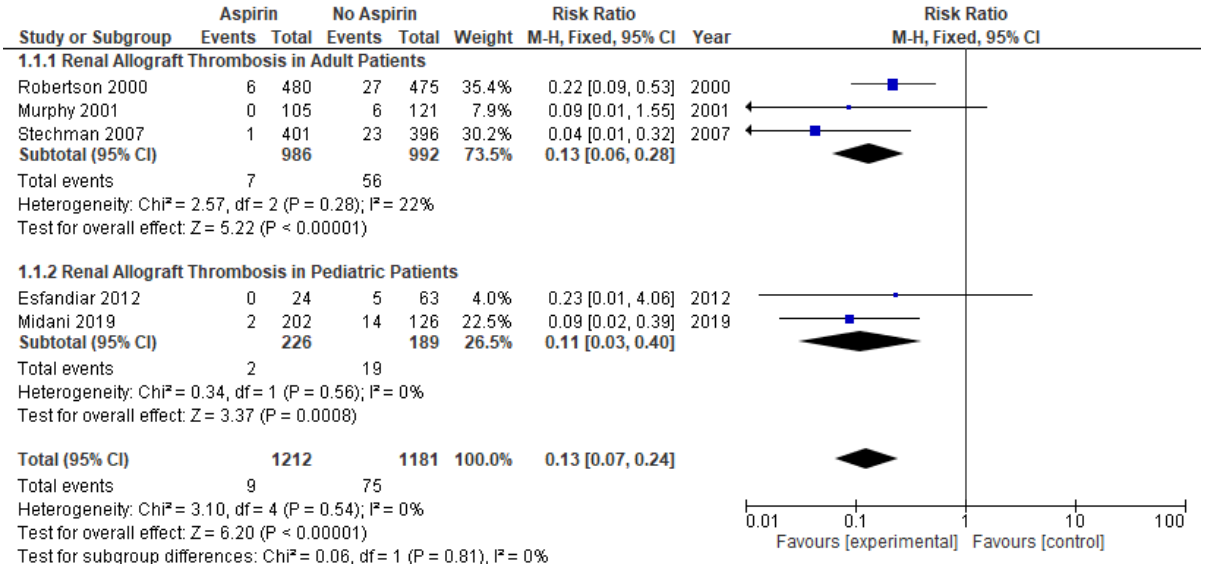

Figure 2. Forest plot of all included studies comparing risk of allograft thrombosis in kidney transplant recipients who received aspirin vs. control; square data markers, RR; horizontal line, 95% CIs, with marker size reflecting statistical weight of study using fixed-effects meta-analysis; diamond data markers, overall RRs and 95% CIs for outcomes of interest

involved adult kidney transplant recipients while two studies involved the pediatric age group.[8, 13-16]

Study Quality Assessment

The Newcastle-Ottawa Scale was used to evaluate the quality of the included studies. This tool is used for meta-analysis of observational studies. It has three subscales: selection, comparability, and outcomes. A score of at least 6 without a zero point in any subscale is needed to qualify as a good quality study (Appendix A).

As summarized in *Table II*, only two studies were assessed to have good quality.[13,15] The other studies suffered in the comparability domain either from lack of sufficient details or significant differences found in the baseline characteristics between the cohorts with possible confounding.[8,14,16] Details on the follow-up of cohorts on the retrospective studies were also lacking. Because of the small number of studies identified, a test for funnel plot asymmetry to detect publication bias cannot be made.

Aspirin and Renal Allograft Thrombosis

In a fixed-effects meta-analysis (*Figure 2*), post-operative aspirin was associated with a reduced risk for renal allograft thrombosis (RR 0.13; 95% CI 0.07, 0.24; I^2 0%). On post hoc subgroup analysis, the effects are similar with adults (RR 0.13; 95% CI 0.06, 0.28; I^2 22%) and children (RR 0.11; 95% CI 0.03, 0.40; I^2 0%). If the studies that used short courses of heparin were excluded aspirin was still associated with reduced thrombosis risk (RR 0.14; 95% CI 0.06, 0.30; I^2 58%).[13,15,16]

Aspirin-related complications

Two studies reported complications related to aspirin. Among adult patients, aspirin was tolerated well with only a 1.9% discontinuation rate due to prior peptic ulcer disease.[13] In the same study, aspirin did not significantly increase the incidence of macroscopic hematuria following renal allograft biopsy (9% in aspirin group vs. 7% in control group). In the study involving the pediatric group, bleeding complications requiring surgical re-exploration was found in 1% (2 of 202) taking aspirin.[16] One patient (0.5%) had renal allograft loss from hemorrhage.[16]

DISCUSSION

Kidney transplant procedures are increasingly performed each year. Despite improved practices, surgical techniques and better transplantation technology, complications still occur with some leading to devastating consequences. Vascular complications are one of the most serious and dreaded because a vast majority of these cases eventually result in graft loss. Up to 2–7% of early allograft loss in adults and 35% in pediatric patients are due to renal allograft thrombosis.[7,17] Apart from early graft loss, these patients were also noted to have higher mortality rates due to risk of graft rupture and other embolic complications.[18] Prompt diagnosis and urgent treatment are essential but often unsuccessful. Because of this, studies on possible interventions to prevent renal graft thrombosis have continuously been an area of interest to significantly reduce its incidence and negative outcomes post transplantation.

Several factors may be linked with the development of renal graft thrombosis. There are studies suggesting that

the presence of genetic coagulation abnormalities, hypercoagulable states, age of both donor and recipient, presence of atherosclerosis, vascular abnormalities, hypovolemia, surgical or technique error, long cold ischemia time and delayed graft function recovery are some of the factors that has been shown to increase the risk of developing graft thrombosis.[9,19-21] Some immunosuppressive medications used to prevent rejection might also contribute to the development of this complication. Cyclosporine-treated patients were observed to have moderately increased levels of plasminogen activator inhibitor activity causing decreased fibrinolysis thus predisposing to increased thrombogenicity.[22-23] Studies however reported no correlation between cyclosporine levels and increased occurrence of post-transplant thrombosis.[21, 23] The use of monoclonal antibody OKT3 with high dose methylprednisolone was also explored because of their ability to stimulate tissue factor-mediated procoagulant activity and the inhibition of fibrinolytic system.[24,25] Although these medications were noted to have a procoagulant effect in vivo, to date there are still no well powered trials comparing these medications to other immunosuppressive treatments to prove that these medications indeed increase the risk of graft thrombosis.

Aspirin has been used traditionally for prevention of cardiovascular events. It has been already used among liver transplant recipients and has resulted in reduction in rates of allograft thrombosis.[20] However, data on renal transplant recipients is still unclear. Aspirin has been introduced as a prophylaxis against RVT post-renal transplant in 1991 in some centers.[8] Unfortunately, studies to date have different conclusions regarding the effect of aspirin in RVT reduction.

A meta-analysis published in 2017 involving two studies on adult kidney transplant patients showed that aspirin resulted in reduction of allograft failure and risk of allograft thrombosis compared to those who did not receive treatment.[5] Our meta-analysis adds newer studies and includes pediatric transplant patients. Our findings agree with the previous review that aspirin is associated with reduced risk for renal allograft thrombosis. The proposed mechanism is through inhibition of platelet function by acetylation of the platelet cyclooxygenase (COX), reduction in the production of thromboxane A_2 which is a potent platelet aggregator and vasoconstrictor and subsequent deceleration of transplant vasculopathy.[26]

Aspirin prophylaxis is not without side effects. There is still concern on the risk of bleeding among CKD patients. Compared to heparin however, patients who were given aspirin after renal transplantation had lower incidence of perioperative bleeding complications (1–2%).[8] In the studies which investigated pediatric KT patients, surgical re-exploration from bleeding complication was noted in 1% and renal allograft loss from hemorrhage in only 0.5%.[15.] Moreover, bleeding was not significant in KT recipients receiving antiplatelet agents compared to those without.[27] Balancing the benefit from the risk of bleeding in these patients is still of utmost importance.

Our meta-analysis has certain limitations. First, heparin was combined with aspirin in 3 studies.[13,15,16] However, when these studies were excluded, aspirin use was still associated with reduced risk for thrombosis. Among pediatric patients, aspirin has a significantly lower incidence of renal allograft thrombosis (1%) compared with heparin (9%) (OR 0.17; 95% CI 0.04 – 0.75; p-value 0.020 for Aspirin).[16] Previous studies which examined the effects of heparin prophylaxis on renal allograft thrombosis also showed no significant reduction.[28-29] Another study involving 401 transplant recipients showed that aspirin administration is sufficient for prophylaxis against renal vein transplant thrombosis in those patients where heparin is contraindicated.[14]

Another limitation identified is that the studies included were not randomized controlled trials and used a historical control group. Because of this, a causal relationship cannot be established from this meta-analysis. A large multicenter randomized trial would be valuable to be able to determine the safety, efficacy, and optimal duration of the therapy with aspirin for the prevention of kidney allograft thrombosis. In the absence of a prospective RCT, this data provides the best evidence available to date that showed the value of aspirin in reducing the incidence of renal allograft thrombosis.

CONCLUSION

The use of aspirin post-kidney transplantation was associated with reduced risk for renal allograft thrombosis in both adult and pediatric populations. The best available evidence however, is supported only by cohort studies of equivocal quality. Despite these limitations, randomized controlled studies exploring the effect of aspirin on renal allograft thrombosis are definitely worth pursuing.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest on the development of this meta-analysis.

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APPENDIX

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1. Representativeness of the exposed cohort
    a. Truly representative (one star)
    b. Somewhat representative (one star)
    c. Selected group
    d. No description of the derivation of the cohort
2. Selection of the non-exposed cohort
    a. Drawn from the same community as the exposed cohort (one star)
    b. Drawn from a different source
    c. No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure
    a. Secure record (e.g., surgical record) (one star)
    b. Structured interview (one star)
    c. Written self report
    d. No description
    e. Other
4. Demonstration that outcome of interest was not present at start of study
    a. Yes (one star)
    b. No

Comparability

1. Comparability of cohorts on the basis of the design or analysis controlled for confounders
    a. The study controls for age, sex and marital status (one star)
    b. Study controls for other factors (list) _____ (one star)
    c. Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1. Assessment of outcome
    a. Independent blind assessment (one star)
    b. Record linkage (one star)
    c. Self report
    d. No description
    e. Other
2. Was follow-up long enough for outcomes to occur
    a. Yes (one star
    b. No

Indicate the median duration of follow-up and a brief rationale for the assessment above: _____

3. Adequacy of follow-up of cohorts
    a. Complete follow up- all subject accounted for (one star)
    b. Subjects lost to follow up are unlikely to introduce bias – number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
    c. Follow up rate less than 80% and no description of those lost
    d. No statement

<u>Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)</u>

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection