Renal Function and Postsurgical Outcomes

Systematic Review Search Protocol

Review purpose and rationale.

To assess the relationship between a range of markers of renal damage and subsequent risk of major adverse outcomes in patients undergoing surgical procedures. The outcomes to be examined are: All cause mortality, composite and specific major cardiovascular events, and renal injury.

Background

The advent of a series of novel serum and urinary biomarkers has prompted research into their efficacy as diagnostic and prognostic tools. They hold potential as alternatives to current clinical use of serum creatinine as a marker of impaired renal function and damage. While the predictive value of biomarkers is being studied in a range of settings, a particular area of focus has been on individuals undergoing surgery as these people are at high risk of adverse outcomes. A number of studies have shown that renal biomarkers can predict adverse outcomes[1,2] although others have failed to detect a relationship[3,4]. Furthermore, the magnitude of any risk conferred by renal biomarkers, and the relative utility of different biomarkers has not been precisely defined.

Surgery is an integral component of treating some diseases and improving quality of life. An estimated 230 million people worldwide were considered to have undergone a

surgical procedure[5] in 2008. This is in the context of an ageing population with increasing comorbid disease burden[6]. Surgery also presents a unique clinical situation with significant physiological stress and injury[6]. In particular renal injury and failure are recognized complications of surgery with consequent impact on morbidity and mortality.

The etiology of renal failure post surgery is considered multifactorial, with patient and procedure based risks and potentially modifiable and nonmodifiable factors to minimize risk[7]. Damage can be caused by a range of prerenal, intrarenal and postrenal insults which ultimately result in tubular damage with impaired clearance of renal markers and reduced or absent urine production[8].

Cardiac surgery has a well recognized association with postoperative renal injury[8,9]. The incidence postcardiac surgery is dependent on the definition of acute kidney injury[10], as reflected in changes in serum creatinine, but is thought to affect up to 30% undergoing cardiopulmonary bypass[7]. The implications of renal failure in the postoperative period are significant with a relationship to morbidity and mortality. Renal dysfunction is recognized as an independent risk factor for progression to end stage kidney disease requiring permanent dialysis[8]. There is also an association with cardiovascular events, including mortality[11], as well as sepsis, respiratory failure, bleeding, and delirium[12]. Overall mortality rates are higher in patients with postcardiac surgical renal injury ranging between 15-30%[9]. This escalates where renal replacement therapy is required in the acute setting (around 1-5% of cases) to mortality rates of around 60%[8]. Even a small change in creatinine has been linked to a significant rise in mortality[13]. Noncardiac

surgery portends a lower though still significant risk of renal damage, estimated in one study at 0.8%, with 0.1% of cases requiring renal replacement therapy[14]. In the noncardiac surgical setting acute renal failure was also associated with increased mortality[14].The incidence of renal failure varies with the types of surgery, with gastrointestinal and vascular surgery conferring a greater risk[15].

Identification of patients prone to postsurgical events is currently limited. Preoperative risk assessment has involved various clinical models to predict mortality after cardiac surgery. The main models assessed by comparison include: Initial Parsonnet score; Cleveland Clinic score; French score; Euro score; Pons score; and Ontario Province Risk score[16]. To date there does not exist predictive models involving noncardiac surgery[14]. A comparative study in postcardiac surgical patients showed predictive values of mortality ranged between 70.1 to 78.6 (AUC-ROC), though morbidity prediction was poorer and ranged between 62.1 to 68.6 (AUC-ROC)[16]. This emphasizes their limitation in morbidity prediction in the preoperative setting.

Concentration of and changes in serum creatinine is currently relied upon as a marker of renal impairment, with an established relationship to morbidity and mortality in the postoperative surgical setting. However creatinine is limited in utility as a marker of renal damage due to time delay in changes and a range of nonrenal factors including those related to the operative and postoperative period, which affect the serum concentration[17]. Alternative and novel markers of renal damage have undergone recent evaluation to assess their utility in detection of renal damage and relationship to

morbidity and mortality in the surgical setting. Existing measures of renal function include estimated Glomerular Filtration Rate (eGFR)[2] and proteinuria[18]. Novel biomarkers indicative of renal damage include: tubular proteins dedifferentiated in renal injury (kidney injury molecule 1 or KIM-1); a tubular brush border enzyme (*N*-acetyl-β-D-glucosaminidase or NAG); an iron-siderophore-binding protein expressed in epithelial cell damage (neutrophil gelatinase associated lipocalin or NGAL); markers of impaired tubular protein absorption (cystatin c); and markers of inflammation in the proximal tubule (interleukin-18 or Il-18)[17].

A number of studies have found a relationship between alternative biomarkers and adverse outcomes. This includes change in eGFR as a predictor of mortality[2], and elevation in NGAL and cystatin c as early predictors of acute kidney injury[1] in the setting of post cardiac surgery. Conversely cystatin c was found not superior to creatinine for assessment of GFR and not predictive of outcome[4,19]. Similarly KIM-1 has been shown to be both a sensitive and specific marker of renal damage and predictor of acute kidney injury in a recent pilot study[20], though an earlier study found its predictive value of dialysis or death uncertain[3]. A key feature of the literature is that sample size tends to be small, potentially underpowering the results. With emerging evidence, a review of the literature is required to establish the significance and strength of the relationship of alternative and novel biomarkers to prediction and detection of renal injury and to associated outcomes.

This study aims to clarify the relationship between existing and novel markers of renal

damage and adverse outcomes post surgery. To achieve this we will perform a systematic review and meta-analysis of prospective observational cohort studies involving existing measures of renal function in clinical practice and emerging biomarkers which have undergone clinical trial. This will be in a population of patients, both adult and children, having undergone major surgery. The outcomes of interest will be: All cause mortality, composite and specific major cardiovascular events, and acute kidney injury.

Search strategy for identification of studies

Methods of the review

We will undertake a systematic review aiming to define the nature and strength of the relationship between a range of renal biomarkers and the risk of major adverse outcomes around cardiac and noncardiac surgery. The study will be conducted according to the PRISMA guidelines for meta-analyses of observational cohort studies.[21]

Criteria for selecting studies for this review:

Population:

- Patients (adults/children) undergoing surgical procedures. Both cardiac and noncardiac surgery will be included, with subanalyses to assess for different relationships. We will exclude studies directly involved with intervention on the

kidney, or primary kidney transplant, as the aim of the study is to observe incidental renal damage.

Comparison:

- Use of the following serum or urine markers to determine renal function or damage: Creatinine based eGFR, urinary proteinuria, cystatin c, NGAL, KIM-1, NAG and Il-18.

Outcome:

- Mortality from any cause (*i.e.*, undefined).
- Cardiovascular events include Acute Myocardial Infarction, Heart Failure, Cardiac Arrest, Cardiovascular death or Stroke, or as defined by authors.
- Acute Kidney Injury as defined by the presenting article

Search strategy

The primary data sources for this study will be cohort studies found by a search of the following medical literature databases: Medline (U.S. National Library of Medicine), EMBASE, CINAHL, and Cochrane central register of controlled trials will be queried using similar search strategies.

Search terminology will use both text-words and the Medical subject heading [MeSH] tool:

No restrictions will be placed on search terms including language restrictions to limit publication bias. Reference lists of retrieved studies will also be searched.

Study Type

1. “Studies, Cohort” [MeSH:exp]/or
2. “Follow-up-studies”[MeSH:exp]/or
3. “Prospective studies” [MeSH:exp]/or
4. “Evaluation studies” [MeSH:exp]/or
5. “Observation” [MeSH:exp]
6. Or/1-5
7. “Randomized controlled trial” [MeSH:exp]
8. 6 NOT 7

AND

Procedure

1. Surgery.tw/ or
2. Operation$.tw/ or
3. major surgery.tw/ or
4. surgical procedure.tw/ or
5. Cardiac Surgery.tw/ or
6. “Surgical procedures, operative”[MeSH:exp]
7. Or/1-6

AND

Biomarkers

1. Urinary biomarker$.tw
2. “glomerular filtration rate”[MeSH:exp]/ or

3. neutrophil gelatinase associated lipocalin.tw/ or
4. NGAL.tw/or
5. N-acetyl-β-D-glucosaminidase.tw/ or
6. NAG.tw/ or
7. cystatin c.tw/ or
8. proteinuria.tw/ or
9. Microalbuminuria.tw/ or
10. Albuminuria.tw/ or
11. interleukin 18.tw/or
12. Il 18.tw/ or
13. Kidney injury molecule-1.tw/ or
14. KIM-1.tw/or
15. Or 1-14

NOT

Randomized Controlled Trial

Methods of the review

The review will be carried out in three stages and in duplicate by two independent reviewers:

Round 1: Title and abstract review of records

Round 2: Whole article review of records remaining after round 1.

Round 3: Evaluation of articles remaining after round 2 using quality assessment tool

Rounds 1 and 2 will utilize the same inclusion and exclusion criteria:

Inclusion:

- Published prospective cohort observational study
- Reporting quantitative data with a measure of variance for the relationship between one or more of the renal biomarkers and one or more of the outcomes described above.

Exclusion

- Nonsurgical studies including sepsis, postcontrast, and emergency medicine
- Biomarkers that have not undergone clinical trial in humans
- Interventional trials, to avoid confounding of relationships by the selective use of interventions.
- Transplant surgery as they involve confounders, *e.g.*, calcineurin toxicity, infections.

Further articles will be sourced from bibliographies of selected articles and subject to the above inclusion and exclusion criteria.

Round 3 will involve use application of a quality assessment tool (appendix 1) to remaining articles. Resultant quality scores will be used to summarize effect estimates in the meta-analysis. Round 3 will also involve creation of an Excel database to store data extracted from the selected articles in a standardized format. The Excel database will include information related to the overall quality of the study such as year of study, sample size, patient characteristics including age, types of biomarkers used, outcome

measurement, and study quality. Where necessary additional information and/or data will be sought from the principal investigator of the trial concerned.

Where inclusion or exclusion of articles cannot be agreed upon by the reviewers, a third opinion will be sought to resolve any discrepancies regarding eligibility or quality of a study.

Analysis

Heterogeneity between studies is anticipated due to potential differences in patient selection and clinical setting, disease severity, specifics of the index and reference tests, and inter-observer variability. Therefore the I^2 statistic will be calculated to determine the proportion of between-study variation caused by heterogeneity. Subgroup analysis will be conducted to look for cause of heterogeneity and will include: surgery type (cardiac or noncardiac), prospective *versus* retrospective studies, and preexisting end stage renal disease. We will then observe the effect this has on the analysis.

Meta-analysis of the accumulated data will be performed by pooling results to construct odds ratio and confidence intervals to clarify any relationship between biomarker measurement and recorded outcomes. Publication bias will be tested for by use of sample size funnel plot.

References

1. Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Dragun D, Haase M: Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery: A prospective cohort study. Crit Care Med 2009; 37:553-60
2. Hillis G, Croal B, Buchan K, El-Shafei H, Gibson G, Jeffrey R, Millar C, Prescott G, Cuthbertson B: Renal function and outcome from coronary artery bypass grafting: Impact on mortality after a 2.3-year follow-up. Circulation 2006; 113; 1056-62
3. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, MacKinnon RW, Li L, Balakrishnan VS, Pereira BJ, Bonventre JV, Jaber BL: Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol 2007; 18:904–12
4. Heise D, Waeschle RM, Schlobohm J, Wessels J, Quintel M: Utility of cystatin c for assessment of renal function after cardiac surgery. Nephron Clin Pract 2009; 112:c107-14
5. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: An estimation of the global volume of surgery: A modelling strategy based on available data. Lancet 2008; 372:139-44
6. Mangano D: Peri-operative cardiovascular morbidity: New developments. Baillieres Clin Anaesthesiol 1999; 13:243-485
7. Karkouti K, Wijeysundera D, Yau T, Callum J, Cheng D, Crowther M, Dupuis J-Y, Fremes S, Kent B, Laflamme C, Lamy A, Legare J-F, Mazer C, McCluskey S, Rubens F, Sawchuk C,

Beattie, W: Acute kidney injury after sardiac surgery: Focus on modifiable risk factors. Circulation 2009; 119:495-502

8. Rosner MH, Okusa MD: Acute kidney Injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006; 1:19-32
9. Thakar CV, Worley S, Arrigan S, Yared JP, Paganini EP: Influence of renal dysfunction on mortality after cardiac surgery: Modifying effect of preoperative renal function. Kidney Int 2005; 67:1112–9
10. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, Dent C, Devarajan P, Edelstein CL: Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 2006; 70:199-203
11. Muntner P, He J, Hamm L, Loria C, Whelton PK: Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002; 13:745–53
12. Levy EM, Viscoli CM, Horwitz RI: The effect of acute renal failure on mortality: A cohort analysis. JAMA 1996; 275:1489-94
13. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M: Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. J Am Soc Nephrol 2004; 15: 1597-1605
14. Kheterpal S, Tremper K, Englesbe M, O'Reilly M, Shanks A, Fetterman D, Rosenberg A, Swartz R: Predictors of postoperative acute renal failure after non-cardiac surgery in patients with previously normal renal function Anesthesiology 2007; 107:892-902

15. Sear JW: Kidney dysfunction in the post-operative period. Br J Anaesth 2005; 95:20-32
16. Geissler HJ, Hölzl P, Marohl S, Kuhn-Régnier F, Mehlhorn U, Südkamp M, de Vivie ER: Risk stratification in heart surgery: Comparison of six score systems. Eur J Cardiothorac Surg 2000; 17:400-6
17. Parikh CR, Devarajan P: New biomarkers of acute kidney injury. Crit Care Med 2008; 36:S159-65
18. Mikkelsen MM, Andersen NH, Christensen TD, Hansen TK, Eiskjaer H, Mogensen CE, Hjortdal VE, Johnsen SP: Microalbuminuria and short-term prognosis in patients undergoing cardiac surgery. Interact Cardiovasc Thorac Surg 2009; 9:484-90
19. Ahlstrom A, Tallgren M, Peltonen S, Pettilä V: Evolution and predictive power of serum cystatin C in acute renal failure. Clin Nephrol 2004; 62:344-50
20. Liangos O, Tighiouart H, Perianayagam M, Kolyada A, Han WK, Wald R, Bonventre J, Jaber J: Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. Biomarkers 2009; 14:423-31
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009; 151:W65-94

Appendix 1:

POSTSURGICAL RENAL FAILURE SYSTEMATIC REVIEW:

QUALITY ASSESSMENT TOOL

Observational Studies

1. How did the study define renal injury/ damage or failure, and in what time frame?
    a. Yes
    b. No
2. Did the study define a particular adverse outcome, and in what time frame? *E.g.,* AMI at 30 days.
    a. Yes
    b. No
3. Did the study define a specific end-point, *e.g.*, mortality, dialysis dependence?
    a. Yes
    b. No
4. Which fluid was used to sample biomarkers?
    a. Urine
    b. Serum
    c. Both
5. Was there a series of biomarkers taken prior to surgery?
    a. Yes
    b. No

6. Was this in comparison to a standard measurement (*i.e.*, creatinine)?
    a. Yes
    b. No
7. Did the study include people with existing renal disease?
    a. Yes
    b. No
8. Was this accounted for/ adjusted for?
    a. Yes
    b. No
9. Were other preexisting comorbidities, *e.g.*, cardiovascular disease accounted for?
    a. Yes
    b. No
10. Did the study draw comparison with a current predictive clinical model?
    a. Yes
    b. No