Abhishek Trehan

Medical Sciences Division, University of
Oxford, Lincoln College, Oxford, UK

Comparison of Off-Clamp Partial Nephrectomy and On-Clamp Partial Nephrectomy: A Systematic Review and Meta-Analysis

Key Words

Nephrectomy · Partial nephrectomy · Ischaemia · Renal clamping · Renal tumours

Abstract

Objective: To compare peri- and postoperative variables, surgical complications, oncological outcomes and renal outcomes of off-clamp partial nephrectomy (PN) and on-clamp PN. **Methods:** A systematic search of the electronic databases, including MEDLINE, Embase and Cochrane Library, was performed. The pooled estimates of tumour size, operative time, estimated blood loss, length of stay, overall complications, transfusion rates, urinary leaks, positive surgical margins and eGFR were calculated. **Results:** 14 studies were included. There was no significant difference between off-clamp PN and on-clamp PN in terms of tumour size, operative time, estimated blood loss, length of stay, overall complications, transfusion rates, urinary leaks, and positive surgical margins. However, a non-statistically significant trend towards increased blood loss ($p = 0.12$) and transfusion rates ($p = 0.07$) in those undergoing off-clamp PN was noted. Off-clamp PN was associated with a significantly lower reduction in eGFR than on-clamp PN (standardised weighted mean difference 0.27, 95% CI 0.14, 0.40, $p < 0.0001$). **Conclusions:** Off-clamp PN may be associated with im-

proved long-term renal outcomes when compared to on-clamp PN with no difference in in peri- and postoperative variables, surgical complications and oncological outcomes. However, the meta-analysis was limited by the design of the underlying studies, and hence further work is necessary.

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Introduction

In light of the increasing evidence to suggest that when compared to radical nephrectomy, partial nephrectomy (PN) is associated with similar oncological outcome, reduced incidence of chronic kidney disease (CKD) and increased overall survival, PN is increasingly gaining popularity over radical nephrectomy [1–3].

A recent area of particular interest with regard to PN is whether or not clamping of the renal hilum should be undertaken. On the one hand, clamping of the renal hilum during PN is traditionally undertaken with the intention of minimising blood loss and allowing for bloodless dissection, which would be hoped to improve visualisation and hence reduce the incidence of positive surgical margins and aid in renorrhaphy [4]. On the other hand however, it has been suggested that renal ischaemia can impair renal function on both a short- and long-term ba-

Fig. 1. Flow diagram of studies identified, included and excluded.

sis. Perhaps the most compelling evidence in support of this was presented by Thompson et al. [5] who, in their observational study with multivariate analysis, found that longer warm ischaemia time is associated with both acute renal failure (ARF) and CKD, leading to the conclusion that ‘every minute [of renal hilum clamping] counts’.

In a bid to mitigate these potentially negative effects on renal function, performing PN in the absence of renal ischaemia by not clamping the renal pedicle has been advocated. The aim of this meta-analysis is to compare off-clamp PN to on-clamp PN.

Methods

A systematic search of the electronic databases MEDLINE and Embase was performed using the OVID SP interface and of The Cochrane Library using the PubMed interface. The following search query of all available fields was utilised: nephrectomy AND (clamp* OR ischaemia).

The inclusion criteria for this meta-analysis were comparative studies comparing off-clamp to completely on-clamp PN. Studies involving partial/segmental renal artery clamping were not included. The following exclusion criteria were used: (i) conference abstract; (ii) case report, letter or review; (iii) off-clamp PN non-comparatively described; (iv) does not meet the inclusion criteria. Where two studies were published by the same group with overlapping patient populations, the most recent study was used. The following information was extracted from each study: first author,

year of publication, number of patients, warm ischaemia time (WIT), means of group allocation, surgical approach, estimated blood loss, operative time, length of hospital stay, overall complications (including transfusions), transfusions, urinary leak, positive surgical margins, recurrence, and renal function outcomes.

A meta-analysis comparing off-clamp to on-clamp PNs was undertaken. The risk ratio (RR) was used for binary outcomes and weighted mean difference (WMD) or standardised weighted mean difference (SWMD) for continuous variables. RRs were calculated as off-clamp risk relative to on-clamp risk; thus $RR > 1$ indicates greater risk in off-clamp group, and $RR < 1$ indicates greater risk in on-clamp group. Mean differences were calculated as off-clamp minus on-clamp; thus positive mean differences reflect a greater off-clamp value for that variable, and negative mean differences reflect a greater on-clamp value for that variable. A random effects model was utilised throughout in light of study heterogeneity ($I^2 > 50\%$ for most variables). Data analysis was performed with Review Manager (RevMan 5.2, Cochrane Collaboration, Oxford, UK). Where outcomes which were continuous variables were stated as medians and range, the methods described by Hozo et al. [6] were utilised in order to estimate the mean and standard deviation. Estimates of standard deviation were not made for continuous variables where no measure of data spread was provided.

Results

A total of 1,604 search results were retrieved, of which 14 studies were included in this meta-analysis (fig. 1). The characteristics of the included studies are shown in table 1. All studies were observational cohort studies other than Kondo et al. [10], which was stated to allocate patients randomly although no further details on this allocation were provided in the study.

Meta-Analysis of Tumour Size

There was overall no significant difference in tumour size between patients undergoing off-clamp and on-clamp PN (WMD -0.25 cm, 95% CI $-0.52, 0.03$, $p = 0.08$) (fig. 2).

Meta-Analysis of Peri- and Postoperative Variables

Both groups had similar operative time (WMD 1.69 min, 95% CI $-17.93, 21.32$, $p = 0.87$) (fig. 3), estimated blood loss (WMD 89.76 ml, 95% CI $-23.70, 203.23$, $p = 0.12$) (fig. 4), and length of stay (WMD 0.31 days, 95% CI $-0.89, 1.50$, $p = 0.61$) (fig. 5).

Meta-Analysis of Surgical Complications

Both groups had similar overall complication rates (RR 0.87, 95% CI 0.51, 1.46, $p = 0.59$) (fig. 6), transfusion rates (RR 1.49, 95% CI 0.97, 2.28, $p = 0.07$) (fig. 7), and incidence of urinary leaks (RR 0.55, 95% CI 0.24, 1.27, $p = 0.16$) (fig. 8).

Table 1. Characteristics of included studies [7–20]

Reference (first author)	Number of patients off-clamp/on-clamp	Mean WIT, min	Group allocation	Surgical approach	Assessment of renal function	Renal outcomes reported	Mean follow-up, months
George, 2013 [7]	150/289	25.5 (5–60)	surgeon preference and off-clamp cases converted to on-clamp on demand	laparoscopic	serum [creatinine]	1. change in [creatinine] (mg/dl and %); 2. change in eGFR (ml/min and %)	6
Guillonneau, 2003 [8]	12/16	27.3±7 (15–47) [†]	not stated	laparoscopic	serum [creatinine]	1. change in [creatinine] (mg/dl)	1
Kobayashi, 2008 [9]	13/7	35 (25–40)	not stated	laparoscopic	serum [creatinine] and MAG3 renal scintigraphy	1. change in [creatinine] (mg/dl); 2. change in renal scan (%)	NA for [creatinine]; renal scan <3 months
Kondo, 2002 [10]	10/24	NA [†]	random selection (details not specified)	open	DMSA renal scintigraphy	1. postoperative DMSA uptake (%)	NA
Koo, 2010 [11]	11/10	28.9±8.07 (21–45) [*]	on-clamp if the depth of tumour invasion was >50% of the renal parenchyma on CT or MRI	laparoscopic	serum [creatinine]	1. postoperative [creatinine] (mg/dl)	NA
Kopp, 2012 [12]	64/164	24.5±4.6	not stated	open	serum [creatinine]	1. number of patients with eGFR <60	off-clamp 24.7; on-clamp 53.6
Martin, 2012 [13]	4/32	32±10 (14–53)	not stated	laparoscopic and robotic	serum [creatinine] and renal scan (method not defined)	1. change in eGFR (ml/min); 2. change in renal scan (%)	13.7
Nadu, 2005 [14]	16/29	28 (20–43)	tumour characteristics	laparoscopic	–	–	–
Petrasz, 2012 [15]	13/25	18.4 (3–35)	all cases began off-clamp; converted to on-clamp on demand	laparoscopic	serum [creatinine]	1. postoperative [creatinine] and change in [creatinine] (mg/dl)	NA
Porpiglia, 2012 [16]	41/76	20.90±9.27	tumour characteristics	laparoscopic	serum [creatinine]	1. postoperative [creatinine] (mg/dl); 2. postoperative eGFR and change in eGFR (ml/min)	at discharge
Smith, 2011 [17]	192/116	23 (15–29)	not stated	open, laparoscopic and robotic	serum [creatinine]	1. postoperative eGFR and change in eGFR (ml/min)	12
Tanagho, 2012 [18]	29/29	14.7± 6.2	retrospectively matched 29 off-clamp patients with 29 on-clamp patients with identical nephrometry scores and comparable baseline Charlson Comorbidity Index	robotic	serum [creatinine]	1. postoperative [creatinine] and change in [creatinine] (mg/dl); 2. postoperative eGFR and change in eGFR (ml/min)	off-clamp: 9.5; on-clamp: 8.6
Thompson, 2010 [19]	96/362	21 (4–55)	not stated	open and laparoscopic	serum [creatinine]	1. number of patients with ARF; 2. number of patients with CKD	acute NA; chronic 39.6
Wszolek, 2011 [20]	75/29	25±14 (8–60)	surgeon preference	open	serum [creatinine]	1. change in eGFR (%)	early 0–3.3; late 3.3–12

[†] Cold ischaemia. ^{*} Renal artery only (not vein) clamped.

Fig. 2. Meta-analysis of tumour size.

Fig. 3. Meta-analysis of operative time.

Meta-Analysis of Oncological Variables

Both groups had a similar incidence of positive surgical margins (RR 0.61, 95% CI 0.34, 1.08, $p = 0.09$) (fig. 9). Only 1 study reported recurrence rates and this was similar in both groups ($p = 0.60$) [17].

Meta-Analysis of Renal Outcomes

SWMD was used to assess renal outcomes as the studies varied in their time of follow-up, and 1 study reported change in eGFR in terms of a percentage not absolute

units. There was a significantly lower reduction in eGFR associated with off-clamp than on-clamp PN (SWMD 0.27, 95% CI 0.14, 0.40, $p < 0.0001$) (fig. 10).

When repeating tumour size analysis for only the 6 studies included in this eGFR analysis, there was no significant difference in tumour size between groups (WMD -0.43 cm, 95% CI -0.92, 0.07, $p = 0.09$) (fig. 11).

The meta-analysis only included 6 of the 14 studies included in this study due to 1 study not assessing renal function and the remaining 7 studies not providing suf-

Fig. 4. Meta-analysis of estimated blood loss.

Fig. 5. Meta-analysis of length of stay.

ficient data for analysis or using outcome measures not amenable to combined analysis with change in eGFR. Key renal outcomes from these 7 studies are shown in table 2.

Discussion

This meta-analysis included 14 studies comparing off-clamp PN with on-clamp PN. No significant difference was found between off-clamp and on-clamp PN in terms of operative time, estimate blood loss, length of stay, overall complications and urinary leak. One of the main potential drawbacks of off-clamp PN is a theoretic

cal risk of increase in blood loss and hence transfusion rates; whilst not statistically significant, the meta-analysis demonstrated a trend towards increased blood loss ($p = 0.12$) and transfusion rates ($p = 0.07$) in the off-clamp group. Impaired visualisation due to bleeding is noted as a potential disadvantage associated with off-clamp PN; the present meta-analysis did not find this to have impact on positive margins, however the use of intraoperative ultrasound may be of use to improve visualisation [21, 22].

Meta-analysis of 6 comparative studies found there was a significantly lower fall in eGFR in patients who had undergone off-clamp PN as opposed to on-clamp PN. Of the

Fig. 6. Meta-analysis of overall complications.

Fig. 7. Meta-analysis of blood transfusion rates.

other 7 comparative studies which were not included in the meta-analysis for change in eGFR, 4 found renal function to be superior in patients who had undergone off-clamp PN (although 1 study had a significantly longer follow-up duration in the on-clamp group). Whilst the other 3 studies failed to find any statistically significant difference between off-clamp and on-clamp PN, these were all small studies (20, 34 and 21 patients in total respectively).

Whilst the results of this meta-analysis suggest that off-clamp PN is associated with superior renal outcome when compared to on-clamp PN, it is worth noting that whilst Thompson et al. [5] concluded that 'each increasing minute of warm ischaemia invites additional risk of renal consequences', George et al. [7] found that the benefit of off-clamp PN disappeared when restricting to patients with WIT of less than 30 min. Thus, methods to

Fig. 8. Meta-analysis of urinary leaks.

Fig. 9. Meta-analysis of positive surgical margins.

reduce the clamp time rather than to completely eliminate it, such as the use of 'on-demand' clamping and/or early unclamping, must also be considered [23, 24]. Other strategies to minimise renal ischaemia such as selective arterial clamping [25–27], clamping the renal artery and not the renal vein, which has been suggested to allow for limited oxygenation via venous backflow [28], and utilising cold ischaemia have also been described (although the latter is challenging during minimal access surgery) [29, 30].

It is also important to interpret the results of this meta-analysis with consideration of its limitations. None of the studies were randomised (although 1 study stated that patients were randomised, how this was enforced was not described). Many studies did not describe how group allocation was performed, and those that did often stated surgeon preference or allocation of smaller or exophytic tumours to the off-clamp group which would lead to significant selection bias, and although tumour size did not differ in a statistically significant manner between the off-

Fig. 10. Meta-analysis of change in eGFR.

Fig. 11. Meta-analysis of tumour size in studies included in meta-analysis of eGFR.

Table 2. Renal outcomes in studies not included in meta-analysis of eGFR

Reference (first author)	Renal outcome	Off-clamp	On-clamp	p
Kobayashi, 2008 [9]	change in [creatinine], mg/dl	-0.03±0.11	-0.03±0.11	0.75
	MAG3 renal scintigraphy, % [†]	42.1	44.9	0.6
Kondo, 2002 [10]	postoperative DMSA uptake, %	34.8±8.9	39.9±7.3	0.15
Koo, 2010 [11]	postoperative [creatinine], mg/dl	1.1	1.1	NS
Kopp, 2012 [12] [‡]	number of patients with eGFR <60	8/64	40/164	0.049
Petrasz, 2012 [15]	change in [creatinine], mg/dl	-0.099	-0.369	<0.05
Thompson, 2010 [19]	number of patients with ARF	10	70	0.041
	number of patients with CKD	hazard ratio 2.3	hazard ratio 2.3	0.028
Wszolek, 2011 [20]	early change in eGFR, %	11.0	16.1	0.08
	late change in eGFR, %	11.8	27.7	0.01

[†] Outcome only measured in 10/23 patients in study. [‡] Follow-up period: off-clamp 24.7 months, on-clamp 53.6 months.

clamp and on-clamp groups, there was a non-statistically significant trend for smaller tumours in the off-clamp group. Insufficient studies provided information on tumour location and depth (or nephrometry scores) for analysis to be performed, which are also key determinants of tumour and hence operative complexity [31]. It has also been recently demonstrated that the percentage of parenchyma spared is a major determinant of postoperative renal function [32]; none of the studies included addressed this issue, which may be of particular importance, if for example, for a given tumour, percentage of parenchyma spared is less in off-clamp procedures due to difficulty in visualisation of tumour margins.

None of the studies made use of intention-to-treat analysis; thus if an operation originally began off-clamp, but was later converted to on-clamp in order to control bleeding, this operation would presumably be included by the study authors in the on-clamp group. Indeed, Petrasz et al. [15] began all 38 cases off-clamp, but only 13/38 were completed off-clamp. Whilst off-clamp PN may be beneficial in cases which are completed off-clamp, when patients are converted to on-clamp surgery, outcomes may be inferior when compared to outcomes if the cases had begun on-clamp.

Another significant limitation of the study is that in two of the largest studies, both open and laparoscopic approaches were used, and there was differing use of these surgical approaches between off-clamp and on-clamp cases. Indeed, Thompson et al. [19] completed 92/96

(96%) off-clamp cases by open surgery, whilst 319/362 (88%) in the on-clamp group had open surgery and the remainder laparoscopically. Smith et al. [17] completed all off-clamp cases laparoscopically, whilst in the on-clamp group, 51/116 (44%) patients had open surgery, 57/116 (49.1%) had laparoscopic surgery and 8/116 (0.9%) had robotic surgery. Most studies failed to state the exact follow-up period when postoperative renal function was measured for each group. Additionally, some of the studies failed to provide means and standard deviations for continuous variables and hence these were in some cases estimated from medians, ranges and interquartile ranges as described in the Methods section.

There is the need for large prospective randomised studies with long-term follow-up which compare off-clamp to on-clamp PN. Measurement of pre- and postoperative renal function by DMSA or MAG3 renal scintigraphy as opposed to just eGFR via serum [creatinine] should be considered as it would allow for better discrimination of renal function.

In conclusion, the present meta-analysis suggests that off-clamp PN may be associated with improved long-term renal outcome when compared to on-clamp PN, but no difference in peri- and postoperative variables, surgical complications and oncological outcomes. However, the meta-analysis was limited by the design of the underlying studies, and hence further work is needed in order to definitively establish whether off-clamp PN confers any advantage over on-clamp PN.

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