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Total intravenous anaesthesia versus inhalational anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic surgery (Review)

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TABLE OF CONTENTS

[Intervention Review]

Total intravenous anaesthesia versus inhalational anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic surgery

Suzanne Forsyth Herling[1], Bjørn Dreijer[1], Gitte Wrist Lam[2], Thordis Thomsen[3], Ann Merete Møller[4]

[1]Department of Anaesthesiology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark. [2]Department of Urology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark. [3]Department of Nursing Research, Rigshospitalet, The Abdominal Centre, Copenhagen, Denmark. [4]The Cochrane Anaesthesia, Critical and Emergency Care Group, Herlev and Gentofte Hospital, University of Copenhagen, Herlev, Denmark

Contact: Suzanne Forsyth Herling, Department of Anaesthesiology, Herlev and Gentofte Hospital, University of Copenhagen, Herlev Ringvej 75, Herlev, 2730, Denmark. Suzanne.forsyth.herling@regionh.dk, Suzanne.herling@gmail.com.

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ABSTRACT

Background

Rapid implementation of robotic transabdominal surgery has resulted in the need for re-evaluation of the most suitable form of anaesthesia. The overall objective of anaesthesia is to minimize perioperative risk and discomfort for patients both during and after surgery. Anaesthesia for patients undergoing robotic assisted surgery is different from anaesthesia for patients undergoing open or laparoscopic surgery; new anaesthetic concerns accompany robotic assisted surgery.

Objectives

To assess outcomes related to the choice of total intravenous anaesthesia (TIVA) or inhalational anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic gynaecological, urological or gastroenterological surgery.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016 Issue 5), Ovid MEDLINE (1946 to May 2016), Embase via OvidSP (1982 to May 2016), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost (1982 to May 2016) and the Institute for Scientific Information (ISI) Web of Science (1956 to May 2016). We also searched the International Standard Randomized Controlled Trial Number (ISRCTN) Registry and Clinical trials gov for ongoing trials (May 2016).

Selection criteria

We searched for randomized controlled trials (RCTs) including adults, aged 18 years and older, of both genders, treated with transabdominal robotic assisted laparoscopic gynaecological, urological or gastroenterological surgery and focusing on outcomes of TIVA or inhalational anaesthesia.

Data collection and analysis

We used standard methodological procedures of Cochrane. Study findings were not suitable for meta-analysis.

Main results

We included three single-centre, two-arm RCTs involving 170 participants. We found one ongoing trial. All included participants were male and were undergoing radical robotic assisted laparoscopic radical prostatectomy (RALRP). The men were between 50 and 75 years of age and met criteria for American Society of Anesthesiologists physical classification scores (ASA) I, II and III.

We found evidence showing no clinically meaningful differences in postoperative pain between the two types of anaesthetics (mean difference (MD) in visual analogue scale (VAS) scores at one to six hours was -2.20 (95% confidence interval (CI) -10.62 to 6.22; P = 0.61) in a sample of 62 participants from one study. Low-quality evidence suggests that propofol reduces postoperative nausea and vomiting (PONV) over the short term (one to six hours after surgery) after RALRP compared with inhalational anaesthesia (sevoflurane, desflurane) (MD -1.70, 95% CI -2.59 to -0.81; P = 0.0002).

We found low-quality evidence suggesting that propofol may prevent an increase in intraocular pressure (IOP) after pneumoperitoneum and steep Trendelenburg positioning compared with sevoflurane (MD -3.90, 95% CI -6.34 to -1.46; P = 0.002) with increased IOP from baseline to 30 minutes in steep Trendelenburg. However, it is unclear whether this surrogate outcome translates directly to clinical avoidance of ocular complications during surgery. No studies addressed the secondary outcomes of adverse effects, all-cause mortality, respiratory or circulatory complications, cognitive dysfunction, length of stay or costs. Overall the quality of evidence was low to very low, as all studies were small, single-centre trials providing unclear descriptions of methods.

Authors' conclusions

It is unclear which anaesthetic technique is superior - TIVA or inhalational - for transabdominal robotic assisted surgery in urology, gynaecology and gastroenterology, as existing evidence is scarce, is of low quality and has been generated from exclusively male patients undergoing robotic radical prostatectomy.

An ongoing trial, which includes participants of both genders with a focus on quality of recovery, might have an impact on future evidence related to this topic.

PLAIN LANGUAGE SUMMARY

Intravenous or inhalational anaesthesia for abdominal surgery assisted by a computerized surgical robot

This review assessed anaesthesia provided for computerized robotic assisted surgery in the abdomen via the veins or by breathing into the lungs (inhalation).

Review question

What are the advantages and disadvantages of using anaesthesia delivered via the veins compared with anaesthesia delivered by the lungs for robotic assisted abdominal surgery with a focus on managing pain, nausea and vomiting, adverse effects and associated costs?

Background

Computerized robotic assisted surgery in the abdomen is associated with reduced bleeding and less surgical trauma because incisions are small. With rapidly increasing use of computerized robotic assisted surgery has come the need to re-evaluate the two main types of anaesthesia administration. Robotic surgery demands different positioning of the patient during the procedure and introduction of carbon dioxide gas into the abdominal cavity to create a better overview. These factors may affect the functioning heart and lungs and may alter pressure in the brain and in the eyes, with accompanying risk of adverse effects.

Study characteristics

The evidence is current to May 2016 and was provided by three small randomized controlled trials involving 170 males who had their prostate removed. These studies took place in hospitals in Korea and Turkey. We looked for differences in pain and postoperative nausea and vomiting (PONV) and changes in pressure inside the eyes between patients receiving anaesthetic via the veins or by inhalation.

Study funding sources

Studies were funded by the institution, or the funding sources were not stated.

Key results

Postoperative pain was no different between the two types of anaesthesia. Anaesthesia delivered through the veins reduced PONV at one to six hours after prostate surgery compared with anaesthesia provided via inhalation. One study showed that anaesthesia delivered through the veins prevented an increase in pressure inside the eyes during surgery compared with inhalational anaesthesia. We cannot conclude whether this means that anaesthesia provided via the veins reduces ocular complications, as no patients in this small study developed these complications.

Quality of the evidence

The quality of the evidence was considered low, as included studies were small and provided an unclear description of methods. All participants in these studies were men who were undergoing robotic assisted laparoscopic removal of the prostate. An ongoing trial includes men and women undergoing abdominal robotic surgery, also with a focus on the quality of recovery. Additional studies are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Inhalational anaesthesia compared with intravenous anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic surgery

Inhalational anaesthesia compared with intravenous anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic surgery

Patient or population: adults undergoing transabdominal robotic assisted laparoscopic surgery
Setting: Training and Research Hospital in Turkey and Univerity Hospital in South Korea
Intervention: inhalational anaesthesia
Comparison: intravenous anaesthesia

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with intravenous anaesthesia	Risk with inhalational anaesthesia				
Pain in the PACU (VAS)	Mean pain in the PACU (VAS) was 42.9	MD 1 lower (9.82 lower to 7.82 higher)	-	62 (1 RCT)	⊕⊕⊖⊖ LOW[a]	VAS 0 to 100, with higher score indicating greater pain
Pain at 1 to 6 hours (VAS)	Mean pain from 1 to 6 hours (VAS) was 42.5	MD 2.2 lower (10.62 lower to 6.22 higher)	-	62 (1 RCT)	⊕⊕⊖⊖ LOW[a]	VAS 0 to 100, with higher score indicating greater pain
Pain at 6 to 24 hours (VAS)	Mean pain from 6 to 24 hours (VAS) was 34.5	MD 1 lower (7.51 lower to 5.51 higher)	-	62 (1 RCT)	⊕⊕⊖⊖ LOW[a]	VAS 0 to 100, with higher score indicating greater pain
Presence of nausea	Study population		RR 0.39 (0.19 to 0.80)	62 (1 RCT)	⊕⊕⊖⊖ LOW[a]	
	581 per 1000	226 per 1000 (110 to 465)				
Nausea intensity (VNRS) in PACU	Mean nausea intensity (VNRS) in PACU was 0.2	MD 0.7 lower (1.35 lower to 0.05 lower)	-	62 (1 RCT)	⊕⊕⊖⊖ LOW[a]	VNRS 0 to 10: 1 to 3 = mild, 4 to 6 = moderate, 7 to 10 = severe, or with retching and vomition
Nausea intensity (VNRS) at 1 to 6 hours	Mean nausea intensity (VNRS) at 1 to 6 hours was 0.4	MD 1.7 lower (2.59 lower to 0.81 lower)	-	62 (1 RCT)	⊕⊕⊖⊖ LOW[a]	VNRS 0 to 10: 1 to 3 = mild, 4 to 6 = moderate, 7 to 10 = severe, or with retching and vomition
Nausea-vomiting rate at 1 hour	Study population		RR 23.00 (1.44 to 366.71)	42 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	

	0 per 1000	0 per 1000 (0 to 0)				
Nausea-vomiting rate at 3 hours	Study population		RR 2.00 (0.20 to 20.41)	42 (1 RCT)	⊕⊝⊝⊝ VERY LOW[a,b,c]	
	48 per 1000	95 per 1000 (10 to 972)				
Adverse effects: increase in IOP during maintenance of anaesthesia	Mean Increase in IOP during maintenance of anaesthesia was 2.1	MD 3.9 lower (6.34 lower to 1.46 lower)	-	66 (1 RCT)	⊕⊕⊝⊝ LOW[a,d]	No participants experienced ocular complications No included study reported other adverse events of interest

*__Risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; IOP: intraocular pressure; MD: mean difference; OR: odds ratio; RR: risk ratio; VAS: visual analogue scale; VNRS: verbal numerical rating scale.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Few participants.
[b]Unclear allocation concealment and blinding.
[c]Power calculation for the study performed on mean difference in pH between groups and minimal relevant difference not stated; primary outcomes: heart rate, mean atrial pressure and values for oxygen and carbon dioxide.
[d]Addresses a restricted version of the review question.

BACKGROUND

Description of the condition

The introduction of robotic assisted transabdominal surgery has resulted in the need for re-evaluation of the most suitable form of anaesthesia. The objective of this approach is to minimize perioperative risk and discomfort for patients both during and after surgery. Anaesthesia for patients undergoing robotic assisted surgery is different from anaesthesia for patients undergoing open or laparoscopic surgery, and new anaesthetic concerns accompany robotic surgery. These concerns include physiological effects of fixed extreme positioning of the patient over a long time, pneumoperitoneum, restricted access to the patient during surgery and the need for carefully monitored relaxation of the patient. Regardless of the method of surgery performed, it is universal that the three anaesthetic qualities - sleep, freedom from pain and muscle relaxation - generally can be attained by two methods.

1. Total intravenous anaesthesia (TIVA), in which the patient receives all anaesthetic drugs through an intravenous line.
2. Inhalational anaesthesia, by which one of the drugs is delivered through the lungs.

This review addresses the advantages and disadvantages of TIVA compared with inhalational anaesthesia in transabdominal robotic assisted surgery.

Anaesthetists advocating for TIVA might highlight the lower risks of postoperative nausea and vomiting (PONV) and of pollution of the operating room and environment compared with anaesthesia gas (Vari 2010). However, those advocating for inhalational anaesthesia might focus on easier monitoring and regulation of delivered anaesthesia, faster emergence from anaesthesia and, although controversial in non-cardiac surgery, the proposed cardioprotective effects of inhalational anaesthesia (Landoni 2009). How these circumstances influence patients in the context of transabdominal robotic assisted surgery must be considered.

Two issues in transabdominal robotic assisted surgery that might influence outcomes of anaesthesia are positioning and pneumoperitoneum. Extreme positioning, for example, steep Trendelenburg (in lower abdominal surgery) or steep anti-Trendelenburg (in upper abdominal surgery), and insufflation of carbon dioxide in the abdominal cavity affect the patient's cardiovascular and respiratory systems, as well as intracerebral pressure. At the same time, the patient's normal compensatory mechanisms are blunted by the anaesthesia. Absorption of carbon dioxide over abdominal tissue membranes, as well as upward pressure on the diaphragm and compromised venous return, is a constant challenge for the patient's respiratory and circulatory systems. These physiological disturbances are tolerated differently by patients according to their age, body mass index (BMI), medications and comorbidity. Furthermore, pneumoperitoneum is shown to be associated with multiple cardiovascular changes during laparoscopy, which may be exacerbated during steep Trendelenburg positioning, as reported in a study from 2007 (Danic 2007). The same study showed 68% decreased pulmonary compliance due to chest binding, steep 45-degree Trendelenburg and high insufflation (Danic 2007).

Intravenous (IV) fluid administration during surgery may also influence the level of PONV (Voldby 2016) and may play a specific role in development of ischaemic optic neuropathy (ION) (Kan 2015).

Restricted access to the patient during often lengthy robotic assisted surgery demands careful preparation of IV lines and monitoring equipment, as well as focus on avoiding nerve damage and ocular injury (Awad 2012; Danic 2007; Kakar 2011; Sullivan 2008).

Refinement of surgical conditions for transabdominal robotic assisted surgery with reduced bleeding and potential advantages of lower rates of surgical trauma due to minor incisions make it possible to consider robotic assisted surgery for a broader patient population. Some of the patients subjected to robotic assisted surgery may be considered inoperable by traditional operating techniques, especially the growing patient population with a very high BMI (Stone 2010). This additional aspect of change in patient selection has to be considered when the type of anaesthesia is selected.

Robotic assisted surgery is used increasingly for treatment of patients with cancer in gynaecology (Mettler 2008), in urology (Sohn 2013) and in gastrointestinal oncology (Mak 2014; Papanikolaou 2014). Anaesthesia for robotic assisted surgery in the treatment of cancer involves another aspect of the choice of anaesthetic, namely, potentially different effects of inhalational agents and TIVA on the immune system, thereby influencing cancer recurrence (Fodale 2014). It is suspected that (particular) inhaled anaesthetics might be potentially genotoxic (Fodale 2014).

Use of robotic assisted surgery is expanding rapidly in the developed world. At present, two manufacturers provide the robotic surgical systems now available on the market (Paranjape 2014). One such system is the Zeus Surgical System (Computer Motion), and the other is the da Vinci Surgical System (Intuitive Surgical). The latter manufacturer claims that since 2000, the da Vinci Surgical System has been used in more than three million minimally invasive procedures performed worldwide (da Vinci 2016). The high cost and increasing volume of robotic assisted surgeries have implications for public health (Barbash 2010), as health services have limited budgets, and limited evidence has been provided by large multi-centre randomized controlled trials (RCTs) to show which patients may benefit from robotic assisted surgery as opposed to conventional surgery (Gurusamy 2012; Liu 2014). Outcomes such as shorter length of stay, less postoperative pain, fewer episodes of PONV, faster recovery and return to habitual functioning after anaesthesia and surgery are of great importance for public health.

This review sought to compare two different anaesthesia techniques for transabdominal robotic assisted surgery with focus on postoperative patient comfort (pain, PONV, cardiovascular and respiratory complications), as well as patient safety.

Description of the intervention

For maintenance of anaesthesia, TIVA or a halogenated inhalational agent may be used in combination with intravenous drugs for a painless operation. Drugs used to keep the patient pain free are mainly opioid-based but might also include a secondary analgesic or a regional anaesthetic administered as a central nervous blockade (Gerges 2006).

This review focused on the applicability of general anaesthesia provided for transabdominal robotic assisted surgery through intravenous infusion of a hypnotic and an analgesic agent compared with a halogenated inhalational agent together with an analgesic. For this review, we did not consider level of relaxation, combination with regional anaesthesia nor local infiltration. Instead, we focused on different aspects of delivery of these two types of anaesthesia regimens and included measures of pain, PONV, cardiovascular and pulmonary impact, effects on cerebral autoregulation, cognitive function, practical aspects, controllability and environmental effects.

How the intervention might work

Differences between the two types of anaesthesia that we have studied can be seen in their physiological properties and in practical delivery of these drugs. Although delivery of anaesthesia gas is easily monitored via the ventilator, pumps and intravenous lines associated with TIVA may be associated with error through accidental disconnection; furthermore, no direct feedback mechanism has been developed to monitor delivery. It is important to consider cardiovascular stability when drugs used for anaesthesia are selected for transabdominal robotic assisted surgery, during which patients are in non-physiological positions such as the steep head-down (Trendelenburg) or the steep head-up (anti-Trendelenburg) position for a long time. Traditionally, anaesthesia gas is considered to have a better safety profile than TIVA-based anaesthesia in patients with cardiovascular morbidity (Landoni 2009) and may have cardioprotective properties during cardiac surgery (Hert 2003), although this might be controversial in cases of non-cardiac surgery (Landoni 2009). For obese patients undergoing surgery such as knee arthroscopy, transurethral resection of the prostate or minor breast or hand surgery, inhalational anaesthetics (desflurane) may have a safer profile than propofol with regards to postoperative pulmonary function. This has been measured by surrogate outcomes such as oxyhaemoglobin saturation and lung function (Zoremba 2011). The combination of extreme positioning and pneumoperitoneum during most transabdominal robotic assisted procedures is known to affect intracerebral pressure (Kalmar 2010). For this reason, it is important that anaesthesia provided for this type of surgery preserves cerebral autoregulatory mechanisms to prevent cerebral events and postoperative cognitive dysfunction. Comparative studies of the use of sevoflurane versus propofol-remifentanil for spinal or maxillofacial surgery have reported that propofol preserves cerebral autoregulation, but this is not the case when sevoflurane is used in higher concentrations (Conti 2006). Cerebral vascular responsiveness to carbon dioxide (CO_2) is impaired during sevoflurane anaesthesia but not during anaesthesia with propofol-remifentanil (Conti 2006).

Why it is important to do this review

Robotic assisted techniques are used increasingly for a wide variety of surgical specialities in the developed world (Barbash 2010). It is imperative that outcomes of anaesthesia for transabdominal robotic assisted surgery are known. Advantages and disadvantages must be clear to both clinicians and patients, so they can choose the most appropriate anaesthesia technique. At present, we know of isolated RCTs conducted to address this clinical question in specialized areas of the field (gynaecology, urology or gastroenterology) (Atallah 2009; Yoo 2012a; Yoo 2014a). We expect that this body of evidence will expand over the next few years, as several ongoing trials have been registered at http://clinicaltrials.gov/. (See Ongoing studies).

OBJECTIVES

To assess outcomes related to the choice of total intravenous anaesthesia (TIVA) or Inhalational anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic gynaecological, urological or gastroenterological surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) conducted in any clinical or research setting in which management of anaesthesia for transabdominal robotic assisted laparoscopic surgery was the intervention.

Types of participants

We included RCTs with adult participants aged 18 years and older, of both genders, undergoing transabdominal robotic assisted gynaecological, urological or gastroenterological surgery.

Types of interventions

We included RCTs that provided the following interventions during transabdominal robotic assisted surgery.

1. TIVA (propofol and opioid-based) versus inhalation-based anaesthesia (isoflurane, desflurane or sevoflurane in combination with an opioid).

Types of outcome measures

Primary outcomes

1. Postoperative pain within 24 hours (as measured by the authors of included studies)
2. PONV within 24 hours (as measured by the authors of included studies)

Secondary outcomes

1. Adverse effects (as measured by the authors of included studies), for example, cerebral oedema, stroke and ocular complications (including changes in intraocular pressure as proxy for ocular complications)
2. All-cause mortality within 90 days
3. Respiratory complications requiring treatment within 48 hours (as measured by the authors of included studies)
4. Circulatory complications requiring treatment within 48 hours (as measured by the authors of included studies)
5. Cognitive dysfunction (as measured by the authors of included studies)
6. Length of stay in the postoperative ward (as measured by the authors of included studies)
7. Costs (as measured by the authors of included studies)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016 Issue 5), Ovid MEDLINE (1946 to 17 May 2016), Embase via OvidSP (1982 to 17 May 2016), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost (1982 to 17 May 2016) and the Institute for Scientific Information (ISI) Web of Science (1956 to 17 May 2016).

We adapted our MEDLINE search strategy (Appendix 2) for searches of other databases. Search terms consisted of a combination of thesaurus-based and free text terms for the interventions.

We imposed no language restrictions or limitations related to publication status.

Searching other resources

We searched the following resources in May 2016.

1. International Standard Randomized Controlled Trial Number (ISRCTN) Registry (http://www.controlled-trials.com/).
2. ClinicalTrials.gov (http://www.clinicaltrials.gov/).

Data collection and analysis

Selection of studies

We have summarized the initial search for literature in the PRISMA study flow diagram (Figure 1).

Figure 1. Study flow diagram.

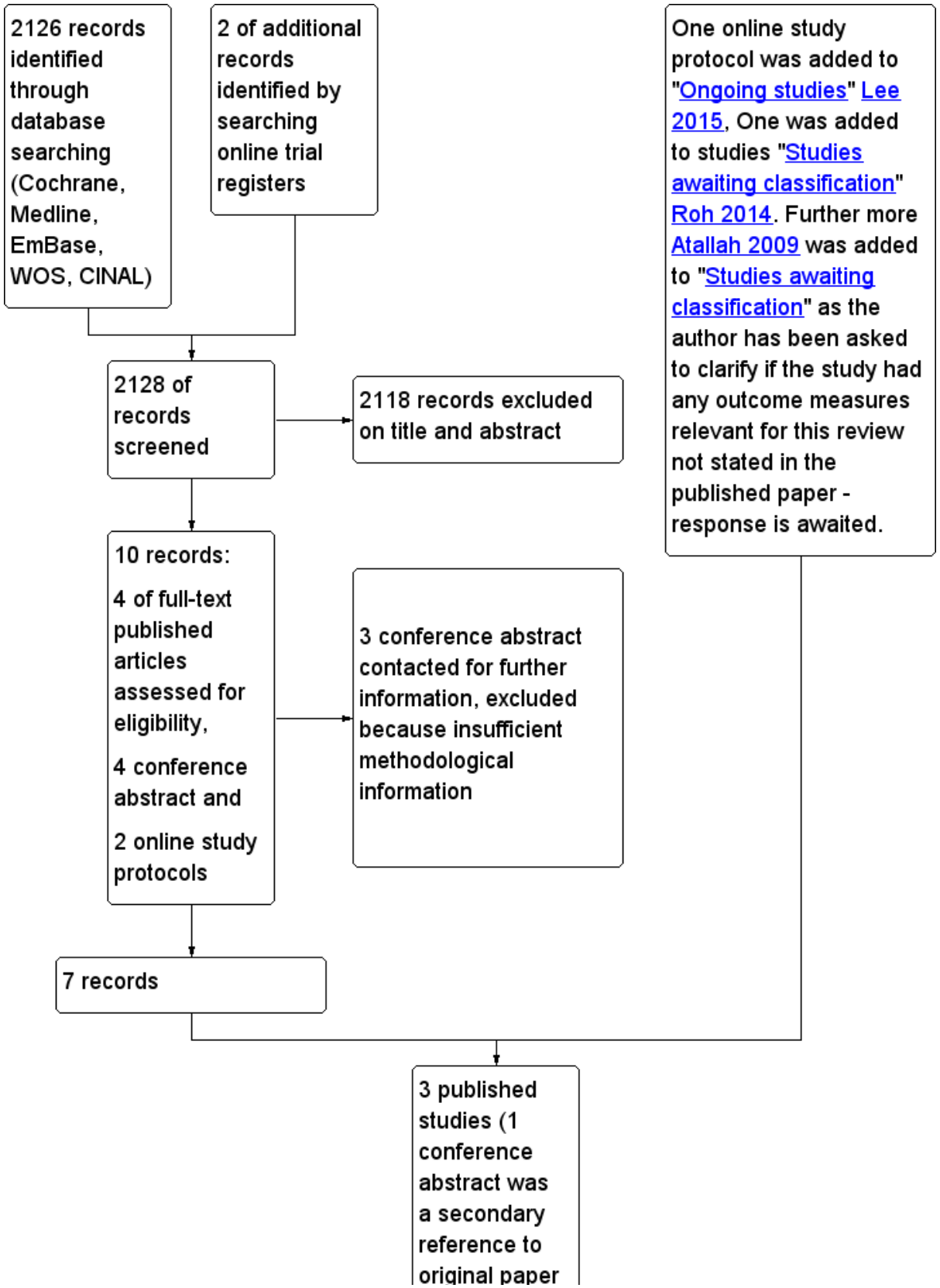
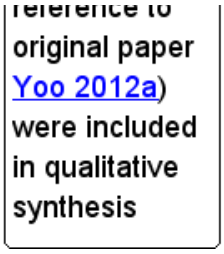


Figure 1. (Continued)



We (SH and BD) reviewed titles and abstracts to begin to determine whether studies fulfilled the inclusion criteria. We (SH and BD) assessed the full-text articles of eligible studies to decide if they were relevant for inclusion. We (SH and BD) resolved disagreements by discussion with a third review author (AM). If we found missing information or inconsistencies in the studies, we (SH) contacted the authors of those studies.

Data extraction and management

We (SH and BD) extracted data from published papers and from reports of original researchers. We (SH and BD) used a modified version of the Cochrane Anaesthesia, Emergency and Critical Care Group (ACE) data extraction form (see Appendix 6). This form includes data on participants, risk of bias, methods of randomization, blinding, reporting of outcomes, results and applicability. We recorded this information in the Characteristics of included studies, Characteristics of excluded studies and 'Risk of bias' sections of the review. We (SH and BD) resolved disagreements by discussion with a third review author (AM). We (SH) entered extracted data into Review Manager 5 (RevMan 5.3) for analysis and (BD) checked the accuracy of these data.

Assessment of risk of bias in included studies

We (SH and BD) independently assessed risk of bias in studies to be included using the criteria provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We reported on the following domains.

1. Adequate sequence generation.
2. Allocation concealment.
3. Blinding of outcome assessment.
4. Incomplete outcome data.
5. Selective reporting.
6. Other bias (e.g. baseline imbalances).

We (SH and BD) graded studies as having 'low risk', 'high risk' or 'unclear risk' of bias and resolved disagreements by discussion with a third review author (AM). We (SH and BD) created plots of risk of bias in Review Manager (RevMan 5.3).

We presented results in the 'Risk of bias' summary of review authors' judgements about each risk of bias item presented as percentages across all included studies (Figure 2) and in the 'Risk of bias' summary of review authors' judgements about each risk of bias item for each included study (Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item presented as percentages across all included studies.

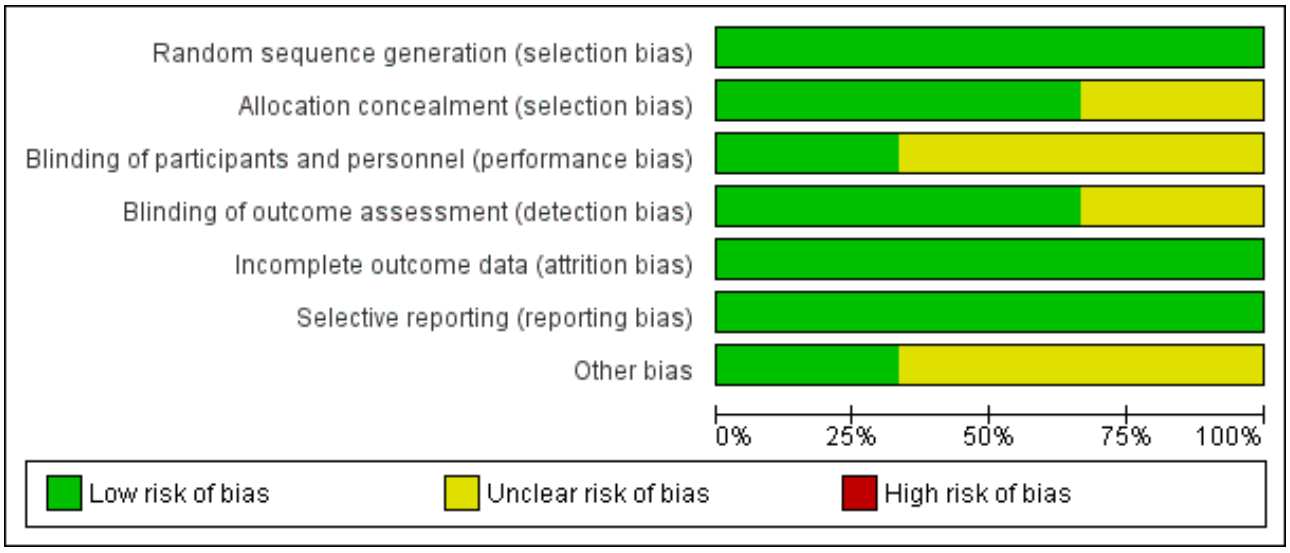
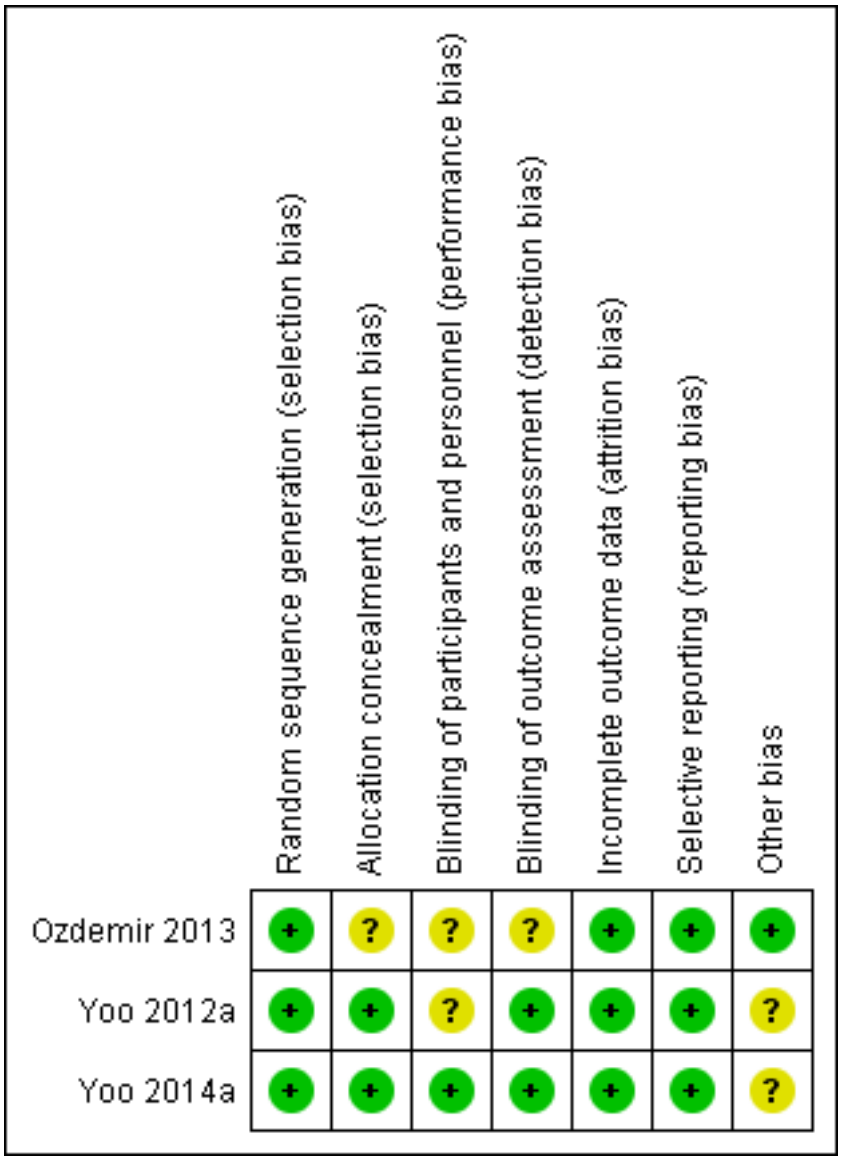


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We reported results in absolute numbers and percentages and as mean values with standard deviations (SDs) (see Differences between protocol and review section).

Unit of analysis issues

The unit of analysis consisted of participants included and randomly assigned. We included no cross-over trials and no cluster-randomized trials (see Differences between protocol and review section).

Dealing with missing data

We noted level of attrition in included studies and encountered no reports of missing data (see Differences between protocol and review section).

Assessment of heterogeneity

We did not assess heterogeneity statistically (see Differences between protocol and review section).

Assessment of reporting biases

When possible, we assessed within study reporting bias by seeking online protocols and comparing them with published studies. As we retrieved fewer than 10 studies, funnel plots were not relevant.

Data synthesis

We planned to use a fixed-effect model if we identified moderate heterogeneity (I^2 value 30% to 60%). If we identified substantial heterogeneity, (I^2 value 50% to 90%), we would use a random-effects model. We would analyse all statistics using Review Manager (RevMan 5.3). Further, we planned that if we identified considerable heterogeneity (I^2 value 75% to 100%), we would not pool the data. We would instead summarize studies, present information in tables

and describe data qualitatively. We would consider evidence of heterogeneity significant if we found P < 0.05 for the Chi^2 test and 95% confidence intervals (CIs) for the I^2 statistic. We did not test for heterogeneity in this review.

Included studies showed clinical diversity (clinical heterogeneity), as they focused on different outcomes and revealed variability in design and risk of bias (methodological diversity). Statistical heterogeneity covers variability in intervention effects (Higgins 2011), which we were not able to measure from data presented in the studies (see Summary of findings for the main comparison).

Differences in how outcomes are defined and measured are expected to lead to differences in observed effects of interventions, and as we have included only three studies, our investigation of heterogeneity is of questionable value (Higgins 2011). (See Differences between protocol and review.)

Subgroup analysis and investigation of heterogeneity

Originally, we planned to perform subgroup analysis, as the following subgroups might have outcomes different from those of the remaining population. Groups included gynaecology patients; urology patients; gastroenterology patients; and patients positioned with head up. However, this was not relevant, as included studies were homogenic in terms of participants - all were men included in the urology group (see Differences between protocol and review).

Sensitivity analysis

We had planned that if we identified sufficient studies, we would perform a sensitivity analysis by comparing results with both inclusion and exclusion of RCTs classified as having 'low risk of bias', so we could decide whether our conclusions were robust (Higgins 2011). However, we found too few studies to do this (see Differences between protocol and review).

'Summary of findings' table and GRADE

We used the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with the following specific outcomes.

1. Postoperative pain within 24 hours (as measured by the authors of included studies).
2. PONV within 24 hours (as measured by the authors of included studies).
3. Adverse effects (as measured by the authors of included studies) (e.g. cerebral oedema, stroke, ocular complications, including changes in intraocular pressure as proxy for ocular complications).
4. All-cause mortality within 90 days.
5. Respiratory complications requiring treatment within 48 hours (as measured by the authors of included studies).
6. Circulatory complications requiring treatment within 48 hours (as measured by the authors of included studies).
7. Costs (as measured by the authors of included studies).

For our review, we constructed a 'Summary of findings' table using GRADE software. The GRADE approach appraises the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. Assessment of the quality of a body of evidence takes into consideration within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias (Guyatt 2008).

RESULTS

Description of studies

Results of the search

We identified 2126 records through the database search, and we found two relevant ongoing studies in online trial databases. We excluded a total of 2118 records on review of titles and abstracts. During the database search, we found four relevant public conference abstracts (Calza 2011a; Calza 2011b; Choi 2013; Yoo 2012b). One study had been presented at two conferences (Calza 2011a; Calza 2011b); one (Yoo 2012b) was related to an included paper (Yoo 2012a); and one was provided only as a conference abstract (Choi 2013).

We contacted all authors of relevant abstracts (not duplicated in any paper) to request further information on their studies (Calza 2011a; Calza 2011b; Choi 2013) and to assess progress and publication status (Figure 1). We excluded all three of these, as study authors provided insufficient information for assessment of the quality of evidence. We excluded a fourth (Yoo 2012b) because it was already duplicated in the included published paper (Yoo 2012a).

Online, we discovered two ongoing topic-relevant studies and included them in the review (Figure 1) as ongoing studies. We contacted the authors of the two ongoing studies to obtain up-to-date information on progress and publication status (Lee 2015; Roh 2014). We described Roh 2014 in the Studies awaiting classification section, and Lee 2015 in the Ongoing studies section.

Through the search, we identified four eligible studies, and we retrieved these four studies as full text (Figure 1). Atallah 2009 reported outcome measures that were not relevant for inclusion in the present review, as they described haemo-respiratory dynamics, oxygenation and biochemical variables. We contacted study authors to ask it they had measured other outcomes relevant to this review. As we await their response, we have characterized this study as 'Awaiting classification'.

Included studies

We included three studies in this review (Ozdemir 2013; Yoo 2012a; Yoo 2014a) (see Characteristics of included studies). Yoo 2012a was reported in an original paper and as a conference proceeding (Yoo 2012b).

Design

The three included studies were single-centre, two-arm RCTs that were conducted in Korea (Yoo 2012a; Yoo 2014a) and in Turkey (Ozdemir 2013), respectively. They were conducted between 2010 (Yoo 2012a; Yoo 2014a) and 2012 (Ozdemir 2013). All three studies evaluated TIVA versus inhalational anaesthesia in men undergoing robotic assisted laparoscopic radical prostatectomy (RALRP) (Ozdemir 2013; Yoo 2012a; Yoo 2014a).

We found no RCTs in gynaecology or gastroenterology relevant for inclusion in this review.

Funding

Funding sources were the department (Yoo 2014a) or the hospital (Yoo 2012a) or were not stated (Ozdemir 2013).

Participants

The three studies included a total of 170 participants - all men: 42 (Ozdemir 2013), 62 (Yoo 2012a) and 66 (Yoo 2014a), respectively. American Society of Anesthesiologists physical classification scores (ASA) were I to II (Yoo 2012a; Yoo 2014a) and I to III (Ozdemir 2013). Participants' ages ranged from 50 to 70 years (Yoo 2012a; Yoo 2014a), and from 50 to 75 years (Ozdemir 2013). The indication for RALRP was not directly stated, but we assume it was early-stage prostate cancer, as this is the conventional surgery for clinically localized cancer (Sampat 2015).

Exclusion criteria in the included studies varied according to the outcomes of interest. Ozdemir 2013 excluded men with neurological or psychological disease and severe cardiovascular disease, Yoo 2012a excluded participants with a history of motion sickness/PONV, use of antiemetics 24 hours before surgery, regular use of corticosteroids, chemotherapy within the previous four weeks, radiotherapy within the previous eight weeks, hepatic dysfunction, confirmed renal impairment and obesity with BMI > 35 kg/m^2.

One study excluded men with baseline intraocular pressure (IOP) > 30 mmHg, diabetic retinopathy, cataract, uncontrolled hypertension, unstable angina or congestive heart failure; as well as participants having surgery or medication for glaucoma before surgery (Yoo 2014a).

Two studies excluded men with allergy towards the anaesthetic drugs (Ozdemir 2013; Yoo 2014a).

None of the three included studies reported significant differences in baseline measurements (Ozdemir 2013; Yoo 2012a; Yoo 2014a).

However, Ozdemir 2013 compared only age and duration of surgery.

Settings

All three studies were conducted at a university hospital (Ozdemir 2013; Yoo 2012a; Yoo 2014a).

Interventions

Investigators compared TIVA with propofol versus inhalational anaesthesia with sevoflurane in one study (Yoo 2014a), or versus desflurane in two studies (Ozdemir 2013; Yoo 2012a); in all three studies, the anaesthesia was combined with remifentanil in both groups.

Yoo 2012a gave antiemetic prophylaxis to participants in both groups.

One study defined delivery of the interventions according to weight (Ozdemir 2013); two studies defined delivery of the interventions by a target-controlled infusion system and end-tidal concentration of the inhalational anaesthetic (Yoo 2012a; Yoo 2014a).

Outcomes

The most common outcomes in the three included studies consisted of PONV (Ozdemir 2013; Yoo 2012a), circulatory condition (mean arterial pressure (MAP)) (Ozdemir 2013; Yoo 2014a) and respiratory condition (end-tidal CO_2 ($ETCO_2$)) (Ozdemir 2013; Yoo 2014a) measured perioperatively. Other stated outcomes were intensity of pain and use of analgesics (Yoo 2012a), use of antiemetics (Yoo 2012a), change in intraocular pressure (Yoo 2014a), intraoperative blood gas values (Yoo 2014a), heart rate (HR) (Ozdemir 2013), central venous pressure (CVP) (Yoo 2014a), oxygen saturation (SpO_2) (Ozdemir 2013), respiratory rate (Yoo 2014a), hydrogen ion concentration (pH) (Ozdemir 2013), Bispectral Index Score (Yoo 2014a), Aldrete Recovery Score (Ozdemir 2013) and patient satisfaction (Ozdemir 2013). Included studies reported only outcomes 1, 2 and 3 of interest in this review (as discussed in the Effects of interventions section). None of the included studies addressed outcomes 4 through 7 (see Summary of findings for the main comparison).

See Characteristics of included studies for details.

Excluded studies

We excluded three studies described only as conference abstracts (Calza 2011a; Calza 2011b; Choi 2013).

See Characteristics of excluded studies for details.

Ongoing studies

At http://clinicaltrials.gov/., we discovered one ongoing study (Lee 2015) conducted in Korea to test desflurane versus propofol for laparoscopic and robotic assisted laparoscopic gastrectomy; however, this study is not yet recruiting. The primary outcome is quality of recovery (Lee 2015). We contacted the principal investigator of this study but have not received a response.

See Characteristics of ongoing studies for details.

Awaiting classification

Two studies are awaiting classification (Atallah 2009; Roh 2014).

Roh 2014 is a completed study conducted in Korea to compare effects of propofol and desflurane on RALRP. We found this study on http://clinicaltrials.gov/, and the primary outcome was reported as change in malondialdehyde, interleukin-1β, interleukin-6 tumour necrotic factor and nitric oxide during operation. The study was completed in February 2015. We contacted the principal investigator to request further information without success.

Atallah 2009 is a completed small single-centre, two-arm RCT conducted in Egypt. This study compared anaesthesia with isoflurane (n = 8) versus ketamine-midazolam-fentanyl - TIVA (n = 7) for patients (both genders) undergoing robotic assisted laparoscopic radical cystectomy and open surgery. Outcome measures included system organ function (primary), operative conditions (secondary) and recovery profiles (secondary). None of the reported outcomes comply with those required in the present review. We contacted study authors to request further information on additional outcomes and await their response.

See Characteristics of studies awaiting classification for details.

Risk of bias in included studies

Overall we assessed the three included studies as having low risk of bias, but two studies had several ambiguities (Ozdemir 2013; Yoo 2012a). Yoo 2012a included a third arm in the online study protocol, and Ozdemir 2013 based power calculations on a secondary outcome; bias assessment for these studies was difficult owing to limited reporting of study methods. Figure 2 and Figure 3 summarize risk of bias.

Allocation

All three included studies were RCTs that adequately described the method of randomization. Two studies used sealed envelopes (Ozdemir 2013; Yoo 2014a), and one used computer-generated random numbers (Yoo 2012a). We considered all three included studies to have low risk of selection bias. One study did not state allocation concealment (Ozdemir 2013).

Blinding

None of the three studies described blinding of participants (Ozdemir 2013; Yoo 2012a; Yoo 2014a) nor blinding of the anaesthetist. Two studies reported blinding of outcome assessors (Yoo 2012a; Yoo 2014a). Ozdemir 2013 did not describe blinding of outcome assessors.

Incomplete outcome data

None of the three included studies reported missing data among the relatively small samples of participants (Ozdemir 2013; Yoo 2012a; Yoo 2014a).

Selective reporting

All three included studies reported outcomes as stated in the Methods section (Ozdemir 2013; Yoo 2012a; Yoo 2014a), and two of the three studies were in agreement with available online study protocols (Yoo 2012a; Yoo 2014a).

Other potential sources of bias

Included studies had several other potential sources of bias. One study included a third arm in the online protocol that was not included in the published study (Bai 2011). The third comparison involved TIVA without antiemetic prophylaxis.

The power calculation in Ozdemir 2013 was based on a secondary outcome - mean difference in pH between groups - but investigators did not state whether the minimal clinically relevant difference was known. The primary outcome in this study was perioperative vital signs (HR, MAP, SpO_2 and $ETCO_2$). Furthermore, investigators reported only two baseline characteristics for the two groups: comorbidity and length of time in Trendenburg (Ozdemir 2013).

One study asked participants to rate their worst episode of nausea within a maximum of 24 hours after surgery (Yoo 2012a). This outcome may be at risk of recall bias, as noted by the study authors (Yoo 2012a).

Effects of interventions

See: **Summary of findings for the main comparison** Inhalational anaesthesia compared with intravenous anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic surgery

Primary outcomes

1. Postoperative pain within 24 hours (as measured by the authors of included studies)

Only one study assessed postoperative pain within 24 hours (n = 62) as a secondary outcome (Yoo 2012a). Researchers measured pain on a visual analogue scale (VAS) (0 = no pain and 100 = intolerable pain) during stay in the post-anaesthesia care unit (PACU) at one to six hours, six to 24 hours and 24 to 48 hours postoperatively (Yoo 2012a). The mean difference (MD) in VAS at one to six hours was -2.20 (95% CI -10.62 to 6.22; P = 0.61) (see Table 1). Study authors concluded that they observed no difference in pain intensity or number of participants requiring rescue analgesics between the two groups at any time point (Yoo 2012a). Owing to the small series, we concluded that the quality of evidence must be considered low.

2. PONV within 24 hours (as measured by the authors of included studies)

Two included studies (n = 104) used PONV as an outcome measure - primary outcome measure in one (Yoo 2012a) and secondary outcome measure in the other (Ozdemir 2013) - but measured PONV in different ways (number of participants with PONV or intensity and severity of PONV or rated by the Apfel score (Apfel 1999)). One study (n = 42) measured the number of participants experiencing nausea or vomiting at one, two and three hours after surgery (Ozdemir 2013). This study showed that the risk ratio (RR) at one hour was 23.00 (95% CI 1.44 to 366.71; P = 0.03) (highest rates in the sevoflurane group) for nausea or vomiting, or both, and after three hours was 2.00 (95% CI 0.20 to 20.41; P = 0.56) (Ozdemir 2013). This study had several unclear risks of bias such as selection bias, performance bias, detection bias and attrition bias and pooled frequencies for both nausea and vomiting (Figure 3). Owing to the small series and unclear allocation concealment and blinding, we concluded that the quality of evidence should be considered very low.

Yoo 2012a (n = 62) measured intensity and severity of PONV at one to six hours and six to 48 hours after surgery. Investigators scored participants before surgery by using the Apfel score, which is known to predict PONV (Apfel 1999). Baseline risk for PONV was assumed to be the same for both groups (mean 1.7, standard deviation (SD) 0.4 to 0.5) (Yoo 2012a). Researchers measured the intensity of nausea using an 11-point verbal numerical rating scale (VNRS: 0 = no nausea and 10 = worst intolerable nausea) (Yoo 2012a). They defined nausea as VNRS ≥ 1, and PONV as the presence of nausea, retching or vomiting. They defined severity of PONV as mild: 1 to 3; moderate: 4 to 6; and severe: 7 to 10, or with retching or vomiting (Yoo 2012a). The RR for the presence of nausea was 0.39 (95% CI 0.19 to 0.80; P = 0.01) (highest in the desflurane group). The MD for intensity of nausea in the PACU was - 0.70 (95% CI -1.35 to -0.05; P = 0.03) (highest in the desflurane group). At between one and six hours, the MD for intensity of nausea was -1.70 (95% CI -2.59 to -0.81; P = 0.0002) (highest in the desflurane group). Study authors concluded that participants receiving TIVA with propofol had a lower incidence and severity of PONV up to six hours after surgery compared with participants receiving desflurane as an anaesthetic (Yoo 2012a). After six hours, results showed no significant difference (Yoo 2012a). This study was at unclear risk of performance bias specifically (Figure 3). Again, owing to the small series, we considered the quality of evidence to be low. Both studies found, through a limited time effect (one hour and up to six hours), that TIVA - propofol based - was more effective than

inhalation-based anaesthesia in reducing PONV (Ozdemir 2013; Yoo 2012a).

Secondary outcomes

3. Adverse effects (as measured by the authors of included studies) (e.g. cerebral oedema, stroke, ocular complications)

Intraocular pressure

None of the three included studies addressed "adverse effects". However, we chose to include a study that examined changes in IOP as the primary outcome because changes in IOP could lead to ocular complications. Cases of permanent ocular damage occurring in previously healthy patients after RALRP with prolonged operative time have been reported. Extreme patient positioning may be a risk factor for ischaemic optic neuropathy (ION) after RALRP (Weber 2007). An increase in IOP may jeopardize retinal perfusion and may cause retinal ischaemia, especially among older patients with arteriosclerotic involvement in retinal perfusion (Yoo 2014a). Increased IOP is known to be a time-dependent phenomenon that is worsened when combined with a steep Trendelenburg position (Awad 2009). Yoo 2014a measured changes in IOP during anaesthesia for robotic surgery as a primary outcome (n = 66). A blinded ophthalmologist measured IOP using a handheld tonometer (Yoo 2014a). This study showed similar IOP at baseline in participants receiving sevoflurane and those receiving propofol as well as a decline in IOP after induction of anaesthesia (Yoo 2014a) and increased IOP with pneumoperitoneum and Trendelenburg positioning (Yoo 2014a). During maintenance of anaesthesia, the level of IOP was higher in the sevoflurane group than in the propofol group (MD -3.90, 95% CI -6.34 to -1.46; P = 0.002) (Yoo 2014a). None of the participants in either group experienced ocular complications (Yoo 2014a). We judged this study to be at low risk of bias (Figure 3). However, owing to the small sample size and the restricted version of the review question, we concluded that the quality of evidence must be considered low. In conclusion, investigators found that propofol was better in attenuating the rise in IOP during RALRP with the steep Trendelenburg position when compared with sevoflurane (Yoo 2014a).

4. All-cause mortality within 90 days

No study reported this outcome.

5. Respiratory complications requiring treatment within 48 hours (as measured by authors of included studies)

No study reported this outcome.

6. Circulatory complications requiring treatment within 48 hours (as measured by authors of included studies)

No study reported this outcome.

7.Costs (as measured by authors of included studies)

No study reported this outcome.

DISCUSSION

Summary of main results

We found three studies including men undergoing robotic assisted laparoscopic radical prostatectomy (RALRP). These studies showed that propofol may reduce postoperative nausea and vomiting (PONV) over the short term (one to six hours after surgery) after RALRP compared with inhalational anaesthesia (sevoflurane, desflurane). Propofol may prevent an increase in intraocular pressure (IOP) after pneumoperitoneum and steep Trendelburg positioning compared with sevoflurane. However, it is unclear whether this surrogate outcome translates directly to clinical avoidance of ocular complications during surgery. We found evidence of no clinically meaningful effect on postoperative pain.

Few studies (Ozdemir 2013; Yoo 2012a; Yoo 2014a) have addressed the question of which type of anaesthesia - inhalational or intravenous - is preferable for different kinds of robotic assisted laparoscopic surgery. This is surprising given that the robotic technique is applied so widely in the developed world today. Several aspects of the anaesthesia technique are relevant for patient outcome and satisfaction, including cardiorespiratory and cerebral complications, as well as postoperative pain, nausea and vomiting.

None of the included studies reported adverse effects.

Owing to the number and quality of included studies, we did not pool data across studies and we did not test for publication bias.

Overall completeness and applicability of evidence

Evidence related to the superiority of inhalational or total intravenous anaesthesia (TIVA) for patients undergoing robotic assisted transabdominal laparoscopic surgery is incomplete, and, to our knowledge, only a few studies have been carried out; findings are applicable to a limited population: male patients undergoing radical robotic prostatectomy. It is unclear if findings of this review apply to women and to robotic surgery in gynaecology and gastroenterology. We have included limited data from three studies (Ozdemir 2013; Yoo 2012a; Yoo 2014a).

Quality of the evidence

The total body of evidence does not permit a robust conclusion on whether TIVA or inhalational anaesthesia provides better outcomes for adults undergoing transabdominal robotic assisted laparoscopic gynaecological, urological or gastroenterological surgery. The quality of evidence is generally considered low to very low owing to risk of bias and very small samples. The three studies included a total of 170 patients- all were men undergoing RALRP - and all were small single-centre randomized controlled trials (RCTs). The methodological quality of the included studies was difficult to assess, as details are reported poorly, so the predominant classification of bias was unclear. For Ozdemir 2013, it is unknown how allocations were concealed; blinding of staff, participants and outcome assessors was not described; and we could not consult an online protocol to assess for reporting bias. Thus it was not possible to assess risk of selection bias, performance bias, detection and attrition bias, and for baseline comparison, only data on age and operation time were presented (Ozdemir 2013). Data on comorbidity (diseases or symptoms related to nausea/vomiting) and time in Trendelenburg would have been relevant to report. The power calculation was performed on differences in pH between groups (Ozdemir 2013). The minimal clinically important difference was not stated, and it is surprising that the primary outcome was vital signs (heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO_2) and end-tidal carbon dioxide ($ETCO_2$)). We considered the quality of evidence from this study as very low, as it was a small study and

allocation concealment and blinding were unclear. Yoo 2012a compared desflurane/remifentanil with propofol/remifentanil; all participants had ramosetron (antiemetic) administered at completion of surgery (Yoo 2012a), and the primary outcome was the incidence of nausea. It was unclear whether participants were blinded; therefore, we considered the study to be at unclear risk of performance bias. This study had an unknown source or potential source of bias, as the online protocol (Bai 2011) revealed a third arm in the original trial (including n = 93). The published paper did not mention the third arm described in the original study protocol (Yoo 2012a) (n = 62). Participants in this third arm received TIVA but without antiemetic prophylaxis (Bai 2011). The significance of this discrepancy between protocol and published paper is unknown. We considered the quality of evidence from this study as low owing to a small sample size (n = 62).

Finally, the later Yoo study (Yoo 2014a) applied improved methods and was at low risk of bias in all categories, but study authors found no association between changes in IOP and ocular complications, as no participants in the study developed such complications. IOP is considered a questionable surrogate outcome. We considered the quality of evidence derived from this study as low, as the sample was small (n = 66) and evidence showed indirectness because the paper addressed a restricted version of the review question.

Potential biases in the review process

We conducted a thorough process to identify relevant studies, and we believe this review is comprehensive in identifying all eligible studies. We repeated the search several times during preparation of the review.

Publication bias is a possible cause of a small study effect - a tendency for estimates of the intervention effect to be more beneficial in smaller studies (Higgins 2011) - and this review suffers from including only small studies.

After identifying the studies, we decided against testing for heterogeneity, as none of these studies included similar outcomes measured in the same way.

We consider our inclusion criteria very broad so as not to exclude any studies that might carry some evidence related to the review question. We included a study (Yoo 2014a) with the surrogate outcome for ocular complications as changes in IOP.

We found that the literature supported the relevance of ocular complications, as a cohort study evaluating 1500 RALRPs reported that the most common anaesthesia-related complication was corneal abrasion (Danic 2007): Corneal abrasion was seen in 3% of cases despite the use of eye tape. However, none of the participants developed long-term sequelae (Danic 2007). A large register study including nearly one million participants undergoing hysterectomy and prostatectomy found a 6.5-fold increased risk of corneal abrasion in patients undergoing robotic assisted surgery compared with those undergoing open surgery (Sampat 2015). However, none of the included studies in this review reported corneal abrasion.

Another potential source of bias is lack of response from study investigators or sponsors whom we have tried to reach for clarification of methods and additional study results.

This review may have a location bias (Higgins 2011), as all included studies were conducted in Korea (Yoo 2012a; Yoo 2014a) or in Turkey (Ozdemir 2013).

Agreements and disagreements with other studies or reviews

In light of the limited number of included studies, small sample sizes and inclusion of exclusively male participants undergoing robotic assisted laparoscopic surgery within urology, the superiority of TIVA or inhalational anaesthesia for transabdominal robotic surgery remains unclear to the review authors, but differences between inhalation anaesthetics and TIVA have previously been reported for other types of non-robotic assisted surgery.

PONV

Gupta 2004 conducted a systematic review that focused on ambulatory anaesthesia in relation to mixed, gynaecological, orthopaedic, dental and eye surgery. Gupta 2004 included 16 papers and found that propofol induced less nausea and vomiting and reduced the need for antiemetics, and that early recovery after surgery was seen in patients receiving inhalation anaesthesia (Gupta 2004). Kumar 2014 conducted a systematic review and meta-analysis of 18 RCTs testing propofol versus desflurane or sevoflurane in ambulatory surgery. The evidence was judged to be of low quality overall, but after analysing data from 1621 randomly assigned participants, review authors concluded that the occurrence of PONV was less in the propofol group (Kumar 2014). Data revealed no differences in post discharge nausea, vomiting and postoperative pain (Kumar 2014).

Pain (among other outcomes)

An RCT of participants undergoing elective laparoscopic cholecystectomy for benign gallbladder disease (n = 60) found that TIVA with propofol and alfentanil was associated with a significantly reduced rate of PONV and analgesic consumption, shortened recovery time and duration of hospitalization, accelerated onset of bowel movements and increased patient satisfaction compared with desflurane and alfentanil (Akkurt 2009). Pokkinen and colleagues conducted an RCT including 148 women who were randomized to propofol or sevoflurane anaesthesia during laparoscopic hysterectomy, and found no effect on the requirement of oxycodone nor on intensity of pain after surgery (Pokkinen 2014). Similarly, an RCT of participants (n = 80) undergoing laparoscopic cholecystectomy identified no differences in pain four hours after surgery among patients anaesthetized by propofol compared with those anaesthetized by isoflurane, desflurane or sevoflurane (Ortiz 2014). However, another RCT (n = 90) reported that propofol anaesthesia was associated with significantly less pain one-half hour and one hour after surgery among participants undergoing gynaecological laparoscopy with planned opioid-free postoperative analgesia (Li 2012).

Cognitive dysfunction

An RCT (n = 50) with participants undergoing cholecystolithotomy, colectomy or sigmoidectomy showed that sevoflurane-based anaesthesia reduced the incidence of postoperative delirium compared with propofol-based anaesthesia for laparoscopic

surgery of long duration performed in elderly patients (Nishikawa 2004).

Other factors that might be influential

None of the three included studies (Ozdemir 2013; Yoo 2012a; Yoo 2014a) reported use of "air seal" for gas insufflation for pneumoperitoneum, but had it been utilized, the cardiorespiratory condition of patients during surgery might have been influenced. Previous findings in urology suggest that patients undergoing laparoscopic renal surgery using these valveless trocars (Airseal) had significantly less carbon dioxide (CO_2) elimination and thus significantly lower CO_2 absorption intraoperatively when compared with patients undergoing surgery with a standard trocar (Herati 2011). An increase in CO_2 absorption can have several important clinical implications, including higher risk of respiratory acidosis and increased risk of formation of a gas embolism (Herati 2011).

Theoretically, IOP may change during robotic assisted laparoscopic surgery (Awad 2009; Hoshikawa 2014). IOP is known to increase with longer duration of steep head-down positioning (Awad 2009; Hoshikawa 2014), and physicians are recommended to vigilantly observe ocular complications in patients who are positioned steep down for a long period. In a non-systematic review of the pathophysiology and prevention of ocular complications in relation to RALRP, review authors recommended prevention of corneal abrasion by using occlusive dressings and prevention of the rarer ION by limiting time spent in the Trendelenburg position and by providing more judicious administration of IV fluids (Kan 2015). If patients have a history of severe ocular disease, an ophthalmologist should be consulted before robotic surgery is performed (Kan 2015). A study of laparoscopic surgery concluded that the impact of anaesthetics on IOP may change, depending on the surgical position. For laparoscopic surgery performed in the head-down position, propofol may be helpful in preventing ocular hypertension (Hwang 2013).

AUTHORS' CONCLUSIONS

Implications for practice

It is unclear whether TIVA is a superior anaesthetic compared with inhalational anaesthesia for transabdominal robotic assisted laparoscopic surgery in urology, gynaecology and gastroenterology, as existing evidence is scarce and of low quality and has been generated exclusively for male patients undergoing robotic radical prostatectomy. As robotic surgery becomes more and more routine, the duration of surgery is expected to diminish (Watt 2015), thereby reducing strain on patients caused by non-physiological positioning. However, restricted access to patients remains an issue that compromises the anaesthesiologist's access for observing and treating patients during robotic assisted surgery. This may challenge the safety dimension of the choice of anaesthetics. As evidence and experience with transabdominal robotic assisted surgery for older and obese patients continue to be acquired, we expect that future trends will include a broader case mix of patients eligible for robotic assisted surgery. This scenario raises considerations for the anaesthesia provided during surgery, and patient outcomes must be followed closely in the future.

Implications for research

Evidence is in the pipeline, and one online protocol (Lee 2015) describes an RCT planned to test desflurane and propofol in robotic assisted or laparoscopic gastrectomy for 84 patients of both sexes using the QoR-40 score (obtained from a questionnaire) to measure the quality of recovery. Although it involves only a single centre and is a small series, results of this study will be of interest at the time of its planned completion in July 2016. Another online protocol (Roh 2014) documents an RCT including 50 participants (completed but not published) conducted to assess males undergoing RALRP with desflurane versus propofol and to test oxidative stress and nitric oxide.

We found no protocols for multi-centre large RCTs in different specialities utilizing robotic assisted surgery. Additional RCTs are needed to determine the effects of TIVA versus inhalation anaesthesia on postoperative pain, PONV, adverse events, all-cause mortality, respiratory and circulatory complications, cognitive dysfunction, length of post-anaesthesia care unit (PACU) stay and costs.

In research within anesthesiology, it is tempting to choose surrogate outcomes, for example, "intraocular pressure" instead of "ocular complications", or "change in MAP" instead of "circulatory complications", as these measurements are easier to obtain. However, the correlation between surrogate and clinical outcomes might not be strong. Changes in intraocular pressure or MAP might have no clinical consequences for the patient. Surrogate endpoints can be easier to complete while not answering the essential question and do not closely reflect the target of treatment (Møller 2006). If a surrogate outcome should be used, the correlation between surrogate and actual outcomes must be strong, and the correlation must go both ways (Møller 2006). When surrogate measures are used, trials should be considered preliminary or hypothesis-generating, and conclusions must be drawn with extreme care (Møller 2006). It would be best if future researchers would choose outcome measures that are clinically relevant and that measure how a patient feels, functions or survives (Møller 2006).

As adverse events are rare (or underreported), multi-centre studies with greater power should prove significant.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ozdemir 2013

Methods	Single-centre, 2-arm RCT **Setting:** training and research hospital in Istanbul **Country:** Turkey **Groups:** propofol and remifentanil vs sevoflurane and remifentanil **Period:** before 2012 - not stated in paper
Participants	**Sample size:** 42 **Surgery:** robotic assisted laparoscopic radical prostatectomy - urology **Included:** males scheduled for RALRP with ASA I to III status, 50 to 75 years. **Excluded:** neurological or psychological disease, allergy to propofol, hypersensitivity or intolerance to opioids or to sevoflurane, severe pulmonary or cardiovascular system disease
Interventions	Propofol and remifentanil (n = 21) vs sevoflurane and remifentanil (n = 21) **Procedure:** robotic assisted radical prostatectomy
Outcomes	**HR:** reported **MAP:** reported **SpO_2:** reported **$ETCO_2$:** reported **pH:** reported **Aldrete Recovery Score** (circulation, conscience, O_2-sat, respiration, activity): reported **Nausea-vomiting score:** reported **Patient satisfaction:** reported
Notes	No imbalances stated at baseline; only age and operation time reported. No data on comorbidity (known disease or symptoms related to nausea or vomiting) nor on Trendelenburg time Time from anaesthesia to measurement of Aldrete score unclear

Ozdemir 2013 *(Continued)*

Power calculation performed on mean difference in pH between groups; however, minimal relevant difference not stated; primary outcome measures: HR, MAP, SpO_2 and $ETCO_2$

Conclusion: TIVA provides early (1 and 2 hours) and better quality recovery and fewer side effects (nausea and vomiting) in robotic prostatectomy cases. Prolonged steep Trendelenburg position and CO_2 pneumoperitoneum were well tolerated by both groups

Funding: not stated

Conflict of Interest: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers in sealed envelopes
Allocation concealment (selection bias)	Unclear risk	Unknown how allocations were concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated whether participants or personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data stated
Selective reporting (reporting bias)	Low risk	All planned (as stated in paper) outcomes reported. No online protocol can be found for comparison
Other bias	Low risk	Same surgeon and anaesthetist for all procedures - significance unknown

Yoo 2012a

Methods	Single-centre, 2-arm RCT **Setting:** University College of Medicine (Hospital) **Country:** Korea **Groups**: TIVA with propofol vs desflurane **Period:** November 2010- May 2011
Participants	**Number:** 62 **Surgery:** robotic-assisted laparoscopic radical prostatectomy - urology **Included:** male between 50 and 70 years of age with ASA I or II

Yoo 2012a *(Continued)*

	Excluded: history of motion sickness/PONV, use of antiemetics 24 hours before surgery, regular use of corticosteroids, chemotherapy within 4 weeks, radiotherapy within 8 weeks, hepatic dysfunction, confirmed renal impairment or obesity (BMI > 35 kg/m^2)
Interventions	TIVA with propofol and remifentanil and antiemetic prophylaxis (n = 31) vs desflurane and remifentanil and antiemetic prophylaxis (n = 31) **Procedure:** robotic assisted laparoscopic radical prostatectomy
Outcomes	**Incidence of nausea:** reported **Incidence of retching:** reported **Incidence of vomiting:** reported **Use of antiemetics:** reported **Severity of PONV:** reported **Intensity of pain - VAS:** reported **Use of rescue analgesics:** reported
Notes	A third arm with patients treated with TIVA without antiemetic prophylaxis not reported in the paper but reported in the online protocol (Bai 2011) **Conclusion:** TIVA with propofol reduced incidence and severity of PONV compared with desflurane in patients with low risk of PONV after RALRP until 6 hours after surgery Letter asking for further information on this study sent 2015 September 16. No reply **Funding:** faculty research grant of Yonsei University College of Medicine for 2007 (6-2007-0190) **Conflict of Interest:** none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	A physician outside the trial performed randomization and assignment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants presumed blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout of participants
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported

Yoo 2012a *(Continued)*

Other bias	Unclear risk	A third arm with patients treated with TIVA without antiemetic prophylaxis not reported in the paper but reported in the online protocol

Yoo 2014a

Methods	Single-centre, 2-arm RCT **Setting:** University Collage of Medicine (Hospital) **Country:** Korea **Groups:** TIVA with propofol vs inhalation anaesthesia with sevoflurane **Period:** May 2011-March 2012
Participants	**Sample size:** 66 **Surgery:** robotic assisted laparoscopic radical prostatectomy **Included:** men > 50 years, ASA I and II **Excluded:** baseline IOP > 30 mmHg, diabetic retinopathy, cataract, known allergies to anaesthetic drugs, uncontrolled hypertension, unstable angina or congestive heart failure. Surgery or medication for glaucoma before RALRP
Interventions	TIVA with propofol (n = 33) vs inhalation anaesthesia with sevoflurane (n = 33) **Procedure:** robotic assisted radical prostatectomy
Outcomes	**Changes in IOP from baseline to 30 minutes after positioning in Trendelenburg with CO_2 pneumoperitoneum:** reported **Number of men with IOP ≥ 24 at any time point:** reported **Ocular perfusion pressure:** reported **Arterial blood gas:** reported **MAP at all time points:** reported **CVP at all time points:** reported **Respiratory rate at all time points:** reported **$ETCO_2$ at all time points:** reported **Bispectral Index Score at all time points:** reported
Notes	Online protocol (Yoo 2014b) had additional exclusion criteria: illiteracy and retinal detachment Study finds a significant change in IOP in the sevoflurane group indicating that propofol is a more effective anaesthetic in attenuating the rise in IOP, thereby decreasing the risk for ocular hypoperfusion during steep Trendelenburg with pneumoperitoneum, which is used in transabdominal robotic assisted surgery. However, the study cannot show an association with ocular complications, as no participants in the study developed such a complication Administration of habitual medication and fasting before surgery not described **Conclusion:** Propofol is found to be better in attenuating the rise in IOP during RALRP with steep Trendelenburg position

Yoo 2014a *(Continued)*

Funding: departmental sources

Conflict of interest: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Table of random numbers in sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators but the anaesthesiologist blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Ophthalmologist and other outcome assessors blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Other bias	Unclear risk	Not known

ASA: American Society of Anesthesiologists physical classification score; BMI: body mass index; CO_2: carbon dioxide; CVP: central venous pressure; $ETCO_2$: end-tidal CO_2; HR: heart rate; IOP: intraocular pressure; MAP: mean arterial pressure; mmHg: millimetres of mercury; pH: hydrogen ion concentration; PONV: postoperative nausea and vomiting; RALRP: robotic assisted laparoscopic radical prostatectomy; RCT: randomized controlled trial; SpO_2: oxygen saturation; TIVA: total intravenous anaesthesia; VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Calza 2011a	Insufficient information to assess study
Calza 2011b	Insufficient information to assess study
Choi 2013	Insufficient information to assess study

Characteristics of studies awaiting assessment *[ordered by study ID]*

Atallah 2009

Methods	Single-centre, 2-arm RCT with computer-generated randomization

Atallah 2009 *(Continued)*

Participants	Patients (mixed gender) undergoing robotic assisted laparoscopic radical cystectomy and open surgery n = 15
Interventions	Anaesthesia with isoflurane (n = 8) for one group and with ketamine-midazolam-fentanyl - TIVA (n = 7) for the other
Outcomes	System organ function (primary), operative conditions (secondary) (blood loss) and recovery profiles (secondary) Study reported heart rate, mean blood pressure, mean air way pressure, lung compliance, pH, arterial carbon dioxide tension, serum bicarbonate, growth hormone, cortisol, albumin, prothrombin and fibrinogen, bilirubin, aspartate aminotransferase and alanine aminotransferase levels
Notes	**Conclusion:** TIVA was considered an advantage in shortening the duration of pneumoperitoneum without an increase in prothrombin and fibrinogen concentrations **Funding:** not stated **Conflict of interest:** not stated None of the reported outcomes comply with those required in the present review. Study authors were contacted in June 2016 as they may have measured other outcomes - response awaited

Roh 2014

Methods	Single-centre, 2-arm RCT, blinding (participant, caregiver, investigator, outcome assessor)
Participants	Males between 20 and 70 years undergoing robotic assisted laparoscopic radical prostatectomy under general anaesthesia **Excluded:** chronic renal failure; allergy to propofol, nuts or diuretics; vitamin C or E within 5 days before surgery; BMI > 30 kg/m^2; inability to read consent form **Estimated enrolment:** 50 participants
Interventions	Anaesthesia with desflurane as primary anaesthetics guided by Bispectral Index Score (BIS) vs propofol infusion with target-controlled infusion (TCI) device guided by BIS
Outcomes	Changes in serum malondialdehyde, interleukin-1β, interleukin-6, tumour necrotic factor, nitric oxide during operation (100 minutes after pneumoperitoneum, 10 minutes after decompression) Kidney function after anaesthesia (1 day after surgery) - creatine measure
Notes	**Funding:** not stated **Conflict of interest:** not stated

BIS: Bispectral Index Score; BMI: body mass index; RCT: randomized controlled trial; TCI: target-controlled infusion; TIVA: total intravenous anaesthesia.

Characteristics of ongoing studies *[ordered by study ID]*

Lee 2015

Trial name or title	Comparison of desflurane and propofol on quality of recovery in patients undergoing robotic assisted or laparoscopic gastrectomy
Methods	RCT, single-centre, 2-arm, double-blind (participant and outcome assessor)
Participants	Both genders, > 20 years old, scheduled for laparoscopic or robotic gastrectomy, ASA I or II **Estimated enrolment:** 84 participants
Interventions	Anaesthesia with desflurane vs propofol during surgery
Outcomes	Quality of recovery within 24 hours of surgery measured with QoR-40 score
Starting date	August 2015
Contact information	Yonsei University, Korea. KI-Young Lee, jjollong@yuhs.as
Notes	**Expected completion:** July 2016 Letter asking for further information sent 16 September 2015. No reply

ASA: American Society of Anesthesiologists physical classification score; QoR: quality of recovery; RCT: randomized controlled trial.

ADDITIONAL TABLES

Table 1. Effect estimates for single studies

Outcome	Study/Participant	Statistical method	Effect estimate [95% CI]	P value
Pain in the PACU (VAS)	1/n = 62	MD	-1.00 [-9.82 to 7.82]	0.82
Pain at 1 to 6 hours (VAS)	1/n = 62	MD	-2.20 [-10.62 to 6.22]	0.61
Pain at 6 to 24 hours (VAS)	1/n = 62	MD	-1.00 [-7.51 to 5.51]	0.76
Presence of nausea	1/n = 62	RR	0.39 [0.19 to 0.80]	0.01
Nausea intensity in PACU (VNRS)	1/n = 62	MD	-0.70 [-1.35 to -0.05]	0.03
Nausea intensity at 1 to 6 hours (VNRS)	1/n = 62	MD	-1.70 [-2.59 to -0.81]	0.0002
Nausea-vomiting rate at 1 hour	1/n = 42	RR	23.00 [1.44 to 366.71]	0.03
Nausea-vomiting rate at 3 hours	1/n = 42	RR	2.00 [0.20 to 20.41]	0.56
Adverse events: increase in IOP during maintenance of anaesthesia	1/n = 66	MD	-3.90 [-6.34 to -1.46]	0.002

CI: confidence interval; IOP: intraocular pressure; MD: mean difference; PACU: post-anaesthesia care unit; RR: risk ratio; VAS: visual analogue scale; VNRS: verbal numerical rating scale.

APPENDICES

Appendix 1. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Anesthesia] explode all trees
#2 MeSH descriptor: [Anesthesia, General] explode all trees
#3 MeSH descriptor: [Neuromuscular Blockade] explode all trees
#4 MeSH descriptor: [Anesthesia, Local] explode all trees
#5 MeSH descriptor: [Anesthetics, Local] explode all trees
#6 MeSH descriptor: [Anesthesia, Epidural] explode all trees
#7 MeSH descriptor: [Anesthesia, Inhalation] explode all trees
#8 MeSH descriptor: [Anesthesia, Intravenous] explode all trees
#9 MeSH descriptor: [Anesthetics, Intravenous] explode all trees
#10 MeSH descriptor: [Nerve Block] explode all trees
#11 MeSH descriptor: [Analgesia, Epidural] explode all trees
#12 MeSH descriptor: [Analgesia, Patient-Controlled] explode all trees
#13 MeSH descriptor: [Anesthesia and Analgesia] explode all trees
#14 MeSH descriptor: [Pain, Postoperative] explode all trees
#15 MeSH descriptor: [Balanced Anesthesia] explode all trees
#16 (an?esth* or analg*) or ((abdominis plane or neuromuscular) near/3 block*)
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or (#13 and #14) or #15 or #16
#18 MeSH descriptor: [Robotics] explode all trees
#19 MeSH descriptor: [Laparoscopy] explode all trees
#20 MeSH descriptor: [Prostatectomy] explode all trees
#21 MeSH descriptor: [General Surgery] explode all trees
#22 MeSH descriptor: [Hysterectomy] explode all trees
#23 MeSH descriptor: [Nephrectomy] explode all trees
#24 MeSH descriptor: [Cholecystectomy] explode all trees
#25 MeSH descriptor: [Cholecystectomy, Laparoscopic] explode all trees
#26 MeSH descriptor: [Cystectomy] explode all trees
#27 robotic* or (robot* near (surg* or operat* or prostatectomy or assist* or hysterectomy or nephrectomy or laparoscop* or cholecystectomy or cystectomy))
#28 (#18 and (#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)) or #27
#29 #17 and #28

Appendix 2. MEDLINE (OvidSP) search strategy

1. (exp Robotics/ and (exp Laparoscopy/ or exp Prostatectomy/ or exp General Surgery/ or exp Hysterectomy/ or exp Nephrectomy/ or exp Cholecystectomy/ or exp Cholecystectomy, Laparoscopic/ or exp Cystectomy/)) or robotic*.af. or (robot* adj5 (surg* or operat* or prostatectomy or assist* or hysterectomy or nephrectomy or laparoscop* or cholecystectomy or cystectomy or colectomy or colorectal or bariatric or gastro?intestinal or gastric* or cardia*)).mp.
2. exp Anesthesia/ or exp Anesthesia, General/ or exp Neuromuscular Blockade/ or exp Anesthesia, Local/ or Anesthetics, Local/ or Anesthesia, Epidural/ or exp Anesthesia, Inhalation/ or exp Anesthesia, Intravenous/ or exp Anesthetics, Intravenous/ or Nerve Block/ or exp Analgesia, Epidural/ or Analgesia, Patient-Controlled/ or (exp Analgesia/ and exp Pain, Postoperative/) or exp Balanced Anesthesia/ or (an?esth* or analg*).mp. or ((abdominis plane or neuromuscular) adj3 block*).mp.
3. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
4. 1 and 2 and 3

Appendix 3. Embase (OvidSP) search strategy

1. exp anesthesia/ or exp general anesthesia/ or exp neuromuscular blocking/ or exp local anesthesia/ or local anesthetic agent/ or epidural anesthesia/ or exp inhalation anesthesia/ or exp intravenous anesthesia/ or exp intravenous anesthetic agent/ or nerve block/ or exp patient controlled analgesia/ or (exp analgesia/ and exp postoperative pain/) or exp balanced anesthesia/ or (an?esth* or analg*).mp. or ((abdominis plane or neuromuscular) adj3 block*).mp.
2. (exp robotics/ and (exp Laparoscopy/ or exp Prostatectomy/ or exp General Surgery/ or exp Hysterectomy/ or exp nephrectomy/ or exp cholecystectomy/ or exp cystectomy/)) or robotic*.af. or (robot* adj3 (surg* or operat* or prostatectomy or assist* or hysterectomy or nephrectomy or laparoscop* or cholecystectomy or cystectomy)).mp.
3. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.
4. 1 and 2 and 3

Appendix 4. ISI Web of Science search strategy

#1 TS=((analges* or an?esthe*) SAME (general or local or epidural or inhalation or intravenous or patient?controlled or balanced)) or TS=((nerve* or neuro*) SAME block*) or TS=(analgesia SAME pain SAME postoperative) or TI=(an?esth* or analg*) or TS=((abdominis plane or neuromuscular) SAME block*)
#2 TS=(robot* SAME (surg* or operat* or prostatectomy or assist* or hysterectomy or nephrectomy or laparoscop* or cholecystectomy or cystectomy))
#3 TS=(random* or ((clinical or controlled) SAME trial*) or placebo* or multicenter* or prospective) or TS=((blind* or mask*) and (single or double or triple or treble))
#4 #1 and #2 and #3

Appendix 5. CINAHL (EBSCOhost) search strategy

S1 ((MH "Anesthesia+") OR (MM "Anesthesia Induction") OR (MH "Anesthesia, General+") OR (MM "Anesthesia, Inhalation") OR (MM "Anesthesia, Intravenous") OR (MM "Anesthesia, Local") OR (MM "Analgesia, Epidural") OR (MH "Analgesics+") OR (MH "Anesthetics, General +") OR (MH "Anesthetics, Inhalation+") OR (MH "Anesthetics, Intravenous+") OR (MH "Anesthetics, Local+")) OR TI (an?esth* or analg*) OR TX (((abdominis plane or neuromuscular) N3 block*))
S2 (((MM "Robotics") and ((MM "Laparoscopy") OR (MH "Prostatectomy+") OR (MH "Hysterectomy+") OR (MM "Nephrectomy") OR (MH "Cholecystectomy+") OR (MM "Cystectomy")))) OR AB robotic* OR TX ((robot* N3 (surg* or operat* or prostatectomy or assist* or hysterectomy or nephrectomy or laparoscop* or cholecystectomy or cystectomy)))
S3 TX random* or ((clinical or controlled) N3 trial*) or placebo* or multicenter* or prospective or ((blind* or mask*) and (single or double or triple or treble))
S4 S1 and S2 and S3

Appendix 6. Data extraction form

Data collection form

Review title or ID
Study ID *(surname of first study author and year first full report of study was published, e.g. Smith 2001)*
Report IDs of other reports of this study *(e.g. duplicate publications, follow-up studies)*
Notes:

1. General information

Date form completed *(dd/mm/yyyy)*
Name/ID of person extracting data
Report title *(title of paper/abstract/report from which data are extracted)*
Report ID *(ID for this paper/abstract/report)*
Reference details
Report author contact details
Publication type *(e.g. full report, abstract, letter)*
Study funding sources *(including role of funders)*
Possible conflicts of interest *(for study authors)*
Notes:

2. Study eligibility

Study characteristics	**Eligibility criteria** *(Insert eligibility criteria for each characteristic as defined in the Protocol)*	Yes	No	Unclear	**Location in text** *(pg & ¶/fig/table)*
Type of study	Randomized controlled trial				
Participants: adults +18 years for transabdominal robotic assisted surgery in gynaecology, urology or gastroenterology					
Types of interventions: TIVA vs inhalational anaesthesia					
Types of outcome measures: **Primary outcomes:** 1. Postoperative pain within 24 hours (as measured by included studies)					

(Continued)

2. PONV within 24 hours (as measured by included studies)

Secondary outcomes:

1. Adverse effects (as measured by included studies) (e.g. cerebral oedema, stroke, ocular complications)
2. All-cause mortality within 90 days
3. Respiratory complications requiring treatment within 48 hours (as measured by included studies)
4. Circulatory complications requiring treatment within 48 hours (as measured by included studies)
5. Cognitive dysfunction (as measured by included studies)
6. Length of stay in the postoperative ward (as measured by included studies)
7. Costs (as measured by included studies)

INCLUDE	**EXCLUDE**
Reason for exclusion	
Notes:	

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description *(Include comparative information for each group (i.e. intervention and controls) if available)*	**Location in text** *(pg & ¶/fig/table)*
Population description *(from which study participants were drawn)*		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained	Yes/No/Unclear	
Notes: Clinical.gov. checked		

4. Methods

	Descriptions as stated in report/paper	Location in text (pg & ¶/fig/table)
Aim of study		
Unit of allocation (by individuals, clusters/groups)		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study	Yes/No/Unclear	
Notes:		

5. Risk of bias assessment

See Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (page 198)

Domain	Risk of bias				Support for judgement	Location in text (pg & ¶/fig/table)
	Low risk	High risk	Unclear risk	Non-applicable		
Random sequence generation (selection bias)						
Allocation concealment (selection bias)						
Blinding of participants and personnel (performance bias)						
(if required)						
Blinding of outcome assessment (detection bias)						
(if required)						
Incomplete outcome data						

(Continued)

(attrition bias)	
Selective outcome reporting *(reporting bias)*	OBS: check if there is a protocol in Clinical.trial.gov
Other bias	
Notes:	

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomized *(or total pop. at start of study for NRCTs)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Comorbidities		
Other treatment received *(additional to study intervention)*		
Subgroups measured		
Subgroups reported		
Notes:		

7. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention group 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomized to group *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity, etc., if relevant)*		
Co-interventions		
Economic variables *(i.e. intervention cost, changes in other costs as result of intervention)*		
Notes:		

8. Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		
Unit of measurement *(if relevant)*		

(Continued)

Scales: upper and lower limits *(indicate whether high or low score is good)*	
Is outcome/tool validated?	Yes/No/Unclear
Imputation of missing data *(e.g. assumptions made for ITT analysis)*	
Assumed risk estimate (*e.g. baseline or population risk noted in Background)*	
Power	
Notes:	

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcomes

	Description as stated in report/paper				**Location in text** *(pg & ¶/fig/ table)*
Comparison					
Outcome					
Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results	**Intervention**		**Comparison**		
	No. events	No. participants	No. events	No. participants	
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					

(Continued)

Unit of analysis *(by individuals, clusters/groups or body parts)*	
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*	
Reanalysis required? *(specify)*	Yes/No/Unclear
Reanalysis possible?	Yes/No/Unclear
Reanalysed results	
Notes:	

Continuous outcomes

	Description as stated in report/paper						Location in text (pg & ¶/fig/table)
Comparison							
Outcome							
Subgroup							
Time point *(specify whether from start or end of intervention)*							
Post intervention or change from baseline?							
Results	**Intervention**			**Comparison**			
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants	
No. missing participants and reasons							
No. participants moved from other group and reasons							
Any other results reported							
Unit of analysis *(individuals, clusters/groups or body parts)*							
Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*							
Reanalysis required? *(specify)*	Yes/No/Unclear						
Reanalysis possible?	Yes/No/Unclear						

(Continued)

Reanalysed results	
Notes:	

Other outcomes

	Description as stated in report/paper				Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Time point *(specify whether from start or end of intervention)*					
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis *(by individuals, clusters/groups or body parts)*					
Statistical methods used and appropriateness of these methods					
Reanalysis required? *(specify)*	Yes/No/Unclear				
Reanalysis possible?	Yes/No/Unclear				
Reanalysed results					
Notes:					

10. Applicability

Have important populations been excluded from the study? *(consider disadvantaged populations and possible differences in intervention effects)*	Yes/No/Unclear
Is the intervention likely to be aimed at disadvantaged groups? *(e.g. lower socioeconomic groups)*	Yes/No/Unclear
Does the study directly address the review question? *(any issues of partial or indirect applicability)*	Yes/No/Unclear
Notes:	

11. Other information

	Description as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

CONTRIBUTIONS OF AUTHORS

Suzanne F Herling (SH), Bjørn Dreijer (BD), Gitte Wrist Lam (GL) Thordis Thomsen (TT), Ann Merete Møller (AM).

Conceiving of the review: SH, BD, TT and AM.

Co-ordinating the review: SH.

Undertaking manual searches: SH and BD/Karen Hovhannisyan/Torben Jørgensen.

Screening search results: SH and BD.

Organizing retrieval of papers: SH.

Screening retrieved papers against inclusion criteria: SH and BD.

Appraising the quality of papers: SH, BD and AM.

Abstracting data from papers: SH and BD.

Writing to authors of papers for additional information: SH and BD.

Providing additional data about papers: SH and BD.

Obtaining and screening data on unpublished studies: SH and BD.

Managing data for the review: SH.

Entering data into Review Manager (RevMan 5.3): SH.

Analysing RevMan statistical data: SH.

Performing other statistical analysis not using RevMan: N/A.

Interpreting data: SH, BD, TT, GL and AM.

Making statistical inferences: N/A.

Writing the review: SH, BD, TT, GL and AM.

Securing funding for the review: AM.

Performing previous work that was the foundation of the present study: none of the authors of this review.

Serving as guarantor for the review (one author): AM.

Taking responsibility for reading and checking the review before submission: SH, BD, TT, GL and AM.

DECLARATIONS OF INTEREST

Suzanne F Herling: none known.

Bjørn Dreijer: none known.

Thordis Thomsen: none known.

Gitte W Lam: none known.

Ann Merete Møller: none known.

SOURCES OF SUPPORT

Internal sources

- Department of Anaesthesiology, Copenhagen University Hospital, Herlev, Denmark.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol (Herling 2014).

1. Gitte W Lam is an additional author for this review.
2. "For adults" was added to the title to clarify study participants.
3. We planned to report event rates with 95% confidence intervals (CIs) and risk ratios (RRs) for adverse events, mortality and complications; however, the included studies did not produce data other than absolute numbers with standard deviations and percentages.
4. The unit of analysis consisted of participants included and randomly assigned; this was not stated in the protocol.
5. *We planned to conduct intention-to-treat (ITT) analysis for all outcomes, as far as possible. For studies with more dropouts than estimated, we planned to contact trialists to request additional data on participants lost to follow-up. We planned to perform a sensitivity analysis of best case versus worst case scenarios. However, we did not encounter reports of missing data and so noted the level of attrition in included studies.*
6. *We planned to assess heterogeneity between studies by visually inspecting forest plots. We planned to assess statistical heterogeneity of effect sizes by using the I^2 statistic and the Chi^2 test. The I^2 statistic describes the percentage of variability in effect estimates that is due to heterogeneity rather than to sampling error (*Higgins 2011*). We planned to conduct a meta-analysis if we visually (forest plot), statistically (I^2 statistic) and clinically found heterogeneity acceptable (low enough). We planned to proceed with a meta-analysis if populations, interventions, comparisons, measurements, time frames and settings were reasonably similar; if we identified three or more studies; and if the direction of effect of an intervention was consistent. All review authors will discuss and agree about when to conduct a meta-analysis (*Higgins 2011*). We were not able to calculate effect size from the data needed to perform tests for statistical heterogeneity (see*Summary of findings for the main comparison*). As we have included only three studies, the investigation of heterogeneity is of questionable value (*Higgins 2011*).*
7. Subgroup analysis were not relevant, as the included studies were rather heterogenic in terms of participants - all were male and were from urology.

8. "Change in intraocular pressure" has been added to the outcome post hoc: Adverse effects such as changes in intraocular pressure could lead to ocular complications.
9. As we found an insufficient number of studies, we were unable to perform a sensitivity analysis by comparing results with inclusion and with exclusion of RCTs classified to have 'low risk of bias' to decide whether our conclusions are robust (Higgins 2011).
10. As other bias, we added "baseline imbalances", as we noted these in one study.

INDEX TERMS

Medical Subject Headings (MeSH)

*Anesthesia, Inhalation [adverse effects]; *Anesthesia, Intravenous [adverse effects]; Anesthetics, Inhalation [adverse effects]; Anesthetics, Intravenous; Intraocular Pressure [drug effects]; Laparoscopy [*methods]; Pain Measurement; Pain, Postoperative [diagnosis] [epidemiology]; Postoperative Nausea and Vomiting [epidemiology] [prevention & control]; Propofol; Prostatectomy [*methods]; Randomized Controlled Trials as Topic; Robotic Surgical Procedures [*methods]

MeSH check words

Aged; Humans; Male; Middle Aged