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[Intervention Review]

Intravenous heparin during ruptured abdominal aortic aneurysmal repair

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ABSTRACT

Background

There have been enormous advances in the screening, diagnosis, intervention and overall prognosis of abdominal aortic aneurysms (AAAs) in the last decade, but despite these, ruptured AAAs (rAAAs) still cause around 3500 to 6000 deaths in England and Wales each year. Open repair remains standard treatment for rAAA in most centres but increasingly endovascular aneurysm repair (EVAR) is being adopted. This has a 30-day postoperative mortality of 40%. This has remained static despite surgical, anaesthetic and critical care advances.

One significant change to current practice for elective repairs of AAAs, as opposed to emergency repairs of rAAAs, has been the introduction of intravenous heparin. This provides a protective effect against cardiac and thrombotic disease in the postoperative period. This practice has not gained widespread acceptance for emergency repairs of rAAA even though a reduction in mortality and morbidity has been demonstrated in elective repairs.

Objectives

The primary objective was to assess the effect of intravenous heparin on all-cause mortality in ruptured abdominal aortic aneurysm (rAAA) management in people undergoing an emergency repair.

The secondary objectives were to assess the effect of intravenous heparin in rAAA management on the incidence of general arterial disease, for example, cardiovascular, cerebral, pulmonary and renal pathologies, in people undergoing emergency repair.

Search methods

The Cochrane Vascular Information Specialist (CIS) searched the Specialised Register (December 2015). In addition the CIS searched CENTRAL;2015, Issue 11). The CIS searched clinical trials registries for details of ongoing or unpublished studies.

Selection criteria

We sought all published and unpublished randomised controlled trials (RCTs) and controlled clinical trials (CCTs) of intravenous heparin in rAAA repairs (including parallel designs).

Data collection and analysis

Two review authors independently assessed studies identified for potential inclusion in the review. We used standard methodological procedures in accordance with the *Cochrane Handbook for Systematic Review of Interventions*.

Main results

We identified no RCTs or CCTs that satisfied the inclusion criteria.

Authors' conclusions

We identified no RCTs or CCTs of intravenous heparin in rAAA repairs (including parallel designs). Therefore, we were unable to assess the effect of intravenous heparin on all-cause mortality and incidence of general arterial disease, for example, cardiovascular, cerebral, pulmonary and renal pathologies in rAAA management in people undergoing an emergency repair. It is clear that an RCT is needed to address this question in rAAA management as there is no high quality evidence.

PLAIN LANGUAGE SUMMARY

Intravenous heparin during ruptured abdominal aortic aneurysmal repair

Background

An abdominal aortic aneurysm (AAA) is a swelling (aneurysm) of the aorta, the main blood vessel that leads away from the heart down through the abdomen to the rest of the body, and can develop in both men and women. A growing aneurysm can lead to rupture. The rupture of an AAA leads to massive blood loss and is frequently fatal.

There have been enormous advances in managing AAAs in the last decade but ruptured AAAs (rAAAs) still have an unchanged high death rate. Intravenous heparin provides a protective effect against heart and blood clot problems. This practice has not gained widespread acceptance for emergency repairs of rAAA even though a reduction in death and morbidity has been demonstrated in surgical repair that is scheduled in advance because it does not involve a medical emergency (elective repair).

Study characteristics

We searched the medical literature for all randomised controlled trials (RCTs) and controlled clinical trials (CCTs) of intravenous heparin in rAAA repairs (current until December 2015).

Key results

We found no RCTs or CCTs of intravenous heparin in rAAA repairs that satisfied the inclusion criteria.

Quality of the evidence

We found no RCTs or CCTs of intravenous heparin in rAAA repairs (including parallel designs). Therefore, we were unable to assess the effect of intravenous heparin on all-cause mortality and incidence of general arterial disease, for example, cardiovascular, cerebral, pulmonary and renal pathologies in ruptured abdominal aortic aneurysm (rAAA) management in people undergoing an emergency repair. It is clear that an RCT is needed to address this question in rAAA management as there is no high quality evidence.

BACKGROUND

Description of the condition

Abdominal aortic aneurysms (AAAs) were first described in AD 100 by Roman physicians. Its modern description was advanced by the first ligation of the aorta in a patient having an AAA by Rudolf Matas in 1923 (Bhattacharya 2010). An aneurysm is defined as an abnormal, focal dilatation of a vessel resulting in a 50% increase in its diameter. The normal diameter for the abdominal aorta is 2 cm which translates to an aorta measuring 3 cm in width being aneurysmal (Bhattacharya 2010; Goldberg 2005).

There have been enormous advances in the screening, diagnosis, intervention and overall prognosis of AAAs, but ruptured AAAs (rAAAs) still cause around 3500 to 6000 deaths in England and Wales each year (Graham 2012). The biggest advances in elective repair of an AAA have been the development of minimally invasive endovascular aneurysm repair (EVAR) and the introduction of national screening programmes to detect asymptomatic AAAs to permit intervention before rupture might occur. This has contributed to decreasing the AAA mortality by identifying people at potential risk of rupture. They can then undergo an elective repair (mortality is lower than in emergency repair). Despite these advances, open repair remains the normal treatment for rAAA in most centres and the 30-day postoperative mortality (often more than 40%) remains static despite surgical, anaesthetic and critical care advances (Bhattacharya 2010; Chinien 2008; Graham 2012). The extremely high mortality of a rAAA cannot be underestimated as total mortality rates range from 67% to 94% (Reimerink 2013).

Deaths in the postoperative period are usually due to a combination of exsanguination and the physiological insults of prolonged hypotension resulting in myocardial infarction, cerebral infarction, cerebral haemorrhage, pulmonary infarction (including pulmonary embolism), visceral ischaemia and infarction, limb ischaemia and infarction, acute kidney injury (and acute exacerbations of established chronic kidney disease), respiratory failure, disseminated intravascular coagulation, sepsis, prolonged intensive care unit and overall hospital stay. The latter two expose the patient to an enormous range of hospital-acquired infections which can compound management in the postoperative period (Arya 2015; Bhattacharya 2010) and affect quality of life (Tambyraja 2004; Tambyraja 2005).

One significant change to current practice for elective repairs of AAAs, as opposed to emergency repairs of rAAAs, has been the introduction of heparin. This has demonstrated a clear reduction in morbidity and mortality due to providing a protective effect against cardiac and thrombotic disease in the postoperative period (Graham 2012). This practice has not gained widespread acceptance for emergency repairs of rAAA due to the need to balance these protective effects against exsanguination on the operating table (Wiersema 2013).

Description of the intervention

The use of intravenous heparin in vascular surgery is widespread to prevent thrombosis in arteries distal to the operative site. Its use as an anticoagulant in vascular patients is highly valued as these people often have significant underlying arterial disease predisposing them to thrombotic and embolic phenomena (that is, occlusive disease) (Bhattacharya 2010).

The one risk of using intravenous heparin is uncontrolled bleeding in people paradoxically predisposed to have anticoagulant as well as coagulant pathologies. However, it has been suggested that heparin does not increase blood loss during routine elective AAA repair and if given before aortic cross clamping, it acts as an important prophylactic agent against perioperative myocardial infarction (Thompson 1996). Conversely, more recent evidence suggests that heparin increases operation time, blood loss and blood transfusion requirements (Wiersema 2012) that have their concomitant complications, such as infective complications in blood transfusion (Thompson 1996).

The use of heparin has generated one of the biggest changes in the intraoperative management of elective repairs of AAAs, but the use of heparin in emergency repairs continues to be controversial as the evidence base is far from robust for use in elective repairs (Wiersema 2013).

How the intervention might work

Heparin acts as an anticoagulant to prevent the formation of thromboses or extension of existing thromboses. It binds to the enzyme inhibitor antithrombin, which inactivates the effect of thrombin and other coagulation enzymes involved in blood clotting (IX, X, XI and XII). It can be administered intravenously or by subcutaneous injection (Chuang 2001). People with rAAA are also highly likely to have generalised arterial disease, including cardiac, cerebral and renal pathologies (for example angina, stroke and renal failure) and the use of heparin may serve to offset the deleterious consequences of undetected and untreated thrombosis and emboli. This may have an effect on the relative incidence of non-fatal myocardial infarction, non-fatal cerebral infarction, non-fatal cerebral haemorrhage, non-fatal pulmonary infarction (including pulmonary embolism), visceral ischaemia and infarction, limb ischaemia and infarction, acute kidney injury (and acute exacerbations of established chronic kidney disease), respiratory failure, disseminated intravascular coagulation, sepsis, mean intensive care unit and hospital length of stay.

Why it is important to do this review

It is common practice not to use intravenous heparin intraoperatively in people presenting with a rAAA despite its use in elective AAA repairs, resulting in a clear reduction in mortality and morbidity predominantly from cardiac causes. Up to 80% of vascular surgeons use heparin in elective repairs but less than 50% use heparin for emergency repairs (Graham 2012). If assessed according to region and country, heparin is used in rAAA at a frequency of 53% in the USA, 34% in Europe and 16% in Scotland (Chinien 2008; Milne 1995).

Vascular surgery is one of 10 recognised surgical specialties in the United Kingdom (The Royal College of Surgeons of England 2014), recognising the need for specialist training, courtesy of increasing sub-specialisation in the surgical specialties and a highly particular patient case mix. Subsequently, due to an ever aging population, changing demographic and increasing collaboration across vascular surgical sciences, a Cochrane Review is needed to assess if the benefit of using intravenous heparin intraoperatively in elective repairs is similarly observed in emergency rAAA repairs. By not using heparin we could be inadvertently contributing to mortality and morbidity in patients.

OBJECTIVES

The primary objective was to assess the effect of intravenous heparin on all-cause mortality in ruptured abdominal aortic aneurysm (rAAA) management in people undergoing an emergency repair.

The secondary objectives were to assess the effect of intravenous heparin in rAAA management on the incidence of general arterial disease, for example, cardiovascular, cerebral, pulmonary and renal pathologies, in people undergoing emergency repair.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) of intravenous heparin in rAAA repairs, including parallel designs.

Types of participants

Participants who had a radiological or surgical diagnosis of a rAAA who went on to have an emergency open repair or emergency EVAR.

Types of interventions

Intervention: intraoperative use of 5000 units of intravenous heparin during repair of rAAA. If other doses were given we planned to analyse them in the subgroup analysis.

Comparison: no intravenous heparin intraoperatively, reflecting generally accepted current practice.

Types of outcome measures

Primary outcomes

- All-cause mortality
- 30-day all-cause mortality (and 6-month all-cause mortality)

Secondary outcomes

Incidence of

- Non-fatal myocardial infarction
- Non-fatal cerebral infarction and haemorrhage
- Non-fatal pulmonary infarction and haemorrhage (including pulmonary embolism)
- Non-fatal visceral ischaemia and infarction
- Non-fatal limb ischaemia and infarction, for example thrombectomy, bypass and fasciotomy
- Acute kidney injury (and acute exacerbations of established chronic kidney disease)
- Incidence of re-operation to control a bleeding diathesis
- Incidence of abdominal compartment syndrome
- Mean intensive care unit length of stay (and mean hospital length of stay)
- Intraoperative blood loss (and total transfusion volume)

- Quality of life measures, for example RAND 36-Item Health Survey (RAND36)

Search methods for identification of studies

We did not impose any restriction on language of publication.

Electronic searches

The Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials:

- The Cochrane Vascular Specialised Register (3rd December 2015);
- The Cochrane Central Register of Controlled Trials (CENTRAL (2015, Issue 11)) via The Cochrane Register of Studies Online.

See [Appendix 1](#) for details of the search strategy used to search the CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE, Embase, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the [Specialised Register](#) section of the Cochrane Vascular module in *The Cochrane Library* (www.cochranelibrary.com).

The CIS searched the following trials registries (December 2015) for details of ongoing and unpublished studies using the terms "ruptured and aneurysm and heparin":

- World Health Organization International Clinical Trials Registry who.int/ictpr/en/
- ClinicalTrials.gov clinicaltrials.gov/; and
- ISRCTN database isrctn.com/.

Searching other resources

We searched online abstracts from the following societies.

- The Vascular Society of Great Britain and Ireland (2006-2015)
- The Association of Surgeons of Great Britain and Ireland (2003-2015)
- The Society for Vascular Surgery (2002-2015)
- The British Society for Endovascular Therapy (June 2016)
- The British Society of Interventional Radiology (2014-2015)

Data collection and analysis

Selection of studies

SL and JB identified all randomised controlled trials (RCTs) and controlled clinical trials (CCTs), including parallel design, extracted from the searches, and the relevant references, before evaluating trials for inclusion in the review from the study titles and abstracts. This process consisted of three steps and was conducted in an unblinded fashion: step 1: screen titles, exclude obviously irrelevant titles; step 2: review abstracts, exclude obviously irrelevant articles; step 3: review full articles, exclude articles not meeting the inclusion criteria (see [Figure 1](#)).

Figure 1. Study flow diagram

SL and JB evaluated all selected studies in relation to the characteristics of the study, baseline demographics of the participants by treatment groups, details of intervention and control, proposed primary and secondary outcomes and results for their appropriateness for inclusion.

In case of any disagreement regarding the eligibility of a study, we assessed the full text of the study and, if further disagreement continued, the senior author (JP) acted as arbiter. Ultimately, if we discarded a study, we documented the reasons.

We selected studies according to guidance in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement ([Liberati 2009](#)).

Data extraction and management

SL and JB intended to independently extract and record the following data: the source, including the title, lead author's name, year of publication, country of origin and language of publication; the method, including inclusion and exclusion criteria and study design; the participants, including the number, age, gender and diagnosis (rAAA); the intervention (heparin), including the dose, route of administration and timing and the outcomes, including each primary and secondary outcome; and potential funding conflicts. We planned to extract this data using a proforma designed by Cochrane Vascular; this is a detailed form across more than 5 pages extracting out every single specific of the study being examined, and including risk of bias. We planned to store the extracted information electronically.

In case of any disagreement regarding the data extracted from a study once the full text had been thoroughly examined by both SL and JB, the senior author (JP) would act as arbiter.

Assessment of risk of bias in included studies

SL and JB intended to independently assess the quality of the included studies by using the 'Risk of bias' tool as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

This provides a standard and extremely detailed protocol and recommended list of statements for making judgements regarding random sequence generation (selection bias), allocation methods and concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and any other relevant biases.

We planned to use these six items to evaluate and assess the risk of bias as 'low risk', 'high risk' or 'unclear risk', with 'unclear risk' of bias indicating either a lack of information or uncertainty over the potential for bias. We intended to use funnel plots to assess publication bias ([Sterne 2011](#)).

Measures of treatment effect

We intended to use the odds ratio (OR) and its 95% confidence interval (CI) as a measure of effect for each dichotomous outcome, the mean difference (MD) and its 95% CI between the intervention and control group for each continuous outcome and the hazard ratio (HR) and its 95% CI as a measure of overall survival.

Unit of analysis issues

We planned for each participant (intervention and control group) to be a unit of analysis.

Dealing with missing data

We intended to carry out an intention-to-treat (ITT) analysis and to attempt to ascertain the number of participants having each primary and secondary outcome. The authors (SL and JB) planned to request missing data from the original investigators. If an attempt to extract the missing data was not successful we planned to present the available data, but we might not conduct a meta-analysis, depending on the proportion of missing data.

Assessment of heterogeneity

We intended to assess the clinical heterogeneity of the selected studies by confirming if the baseline demographics of the participants, intervention, primary and secondary outcomes and results were comparable (that is, assessment of quality). If these were comparable across selected studies then we planned to conduct a formal meta-analysis using Review Manager (RevMan) ([RevMan 2014](#)).

We intended to assess the statistical heterogeneity of the selected studies using forest plots, Chi² test and I² statistic ([Deeks 2011](#)). We planned to use the forest plot to enable us to assess the plots of each selected study for each outcome to ensure there was overlap of the CIs of the effect estimate. If no overlap existed it might be inappropriate to conduct a meta-analysis. If we used the Chi² test, a P value less than 0.1 would indicate significant heterogeneity. If we used the I² statistic, a value of 25% to 50% would indicate low heterogeneity, 50% to 75% moderate heterogeneity and greater than 75%, significant heterogeneity. The I² statistic examines the percentage of total variation across the selected studies due to heterogeneity rather than chance ([Higgins 2003](#)).

In the absence of clinical heterogeneity but in the presence of significant statistical heterogeneity (I² > 75%) we planned to use a random-effects model.

Assessment of reporting biases

We intended to use funnel plots to explore reporting biases when ten or more studies were included in the meta-analysis. However, other reasons such as heterogeneity and small study effects may also cause asymmetrical funnel plots.

Data synthesis

We intended to use the OR for direct comparison and planned to use a fixed-effect model to present the analysis unless significant heterogeneity (> 75%) existed, requiring us to use a random-effects model. Our statistical analysis would adhere to the guidelines for statistical analysis outlined in Cochrane Vascular's training module for using [RevMan 2014](#).

Subgroup analysis and investigation of heterogeneity

We intended to carry out subgroup analysis if the number of participants was deemed large enough (a power calculation). We planned to stratify participants according to their preoperative rAAA Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) ([Smith 2014](#)) Score (riskprediction.org.uk/vasc-index.php) ([Smith 2014](#)). See

Table 1 and Table 2. If this had not been computed then we planned to stratify participants according to age (> 61 years), and pre-existing coronary and respiratory disease.

The proposed subgroup analysis included median age (and range), sex ratio (male:female) and established preoperative chronic renal disease, ischaemic heart disease, hypertension, diabetes, respiratory disease and smoking status, previous stroke, abdominal aortic aneurysmal repair, concomitant anticoagulation and statin medication regime. Of importance was to categorise emergency repairs of ruptured abdominal aortic aneurysms into surgical procedural types, for example emergency EVAR and emergency open repair subgroups, and when heparin was administered, for example, preaortic and postaortic cross clamp subgroups.

Sensitivity analysis

We planned to assess outcomes before and after the selective exclusion of poor-quality studies.

'Summary of findings' table

We planned to create a 'Summary of findings' table. We planned to use a GRADE approach to interpret the findings (Schünemann 2011). We planned to develop a 'Summary of findings' table for the primary outcomes of this review as described in detail in Primary outcomes using the GRADE Profiler software (GRADEpro GDT 2015)). We planned to assess the quality of the body of evidence by considering the overall risk of bias of the included studies, the directness of the evidence, inconsistency of the results, precision of the estimates, and the risk of publication bias (Atkins 2004).

RESULTS

Description of studies

Results of the search

See Figure 1.

The searches for this systematic review retrieved 139 reports. Of these five contained titles that required examination of the abstract. Subsequent examination demonstrated that none met the inclusion criteria once the abstracts had been examined (see Figure 1).

Included studies

No studies met the inclusion criteria.

Excluded studies

Of the five abstracts examined not a single study addressed the review question and subsequently did not meet the inclusion criteria (see Characteristics of excluded studies).

Risk of bias in included studies

No studies met the inclusion criteria.

Effects of interventions

We identified no RCTs or CCTs of intravenous heparin in rAAA repairs (including parallel designs). Therefore, we were unable to assess the effect of intravenous heparin on all-cause mortality and

incidence of general arterial disease, for example, cardiovascular, cerebral, pulmonary and renal pathologies in rAAA management in people undergoing an emergency repair.

DISCUSSION

Summary of main results

We identified no RCTs or CCTs of intravenous heparin in rAAA repairs (including parallel designs). Therefore, we were unable to assess the effect of intravenous heparin on all-cause mortality and incidence of general arterial disease, for example cardiovascular, cerebral, pulmonary and renal pathologies in rAAA management in people undergoing an emergency repair.

Overall completeness and applicability of evidence

The lack of any trials that fitted our inclusion criteria highlights a real need for a randomised controlled trial (RCT) to address the review question. The paucity of current trials is perhaps a reflection of controversies existing around the evidence base for use of heparin in elective AAA (eAAA) repairs (Wiersema 2013), even though 80% of vascular surgeons use heparin in elective cases (Graham 2012). This highlights a reluctance for some surgeons to use heparin during rAAA repairs perhaps because of a lack of such RCT data, or perhaps due to a clinical concern of potentially exacerbating bleeding tendencies in an often coagulopathic patient.

Quality of the evidence

We identified no RCTs or CCTs of intravenous heparin in rAAA repairs (including parallel designs). Therefore, we were unable to assess the quality of the evidence.

Potential biases in the review process

We identified no RCTs or CCTs relevant for inclusion in this review. The CIS of Cochrane Vascular performed a comprehensive search of the literature and we selected studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We resolved any disagreements by discussion.

Agreements and disagreements with other studies or reviews

The original Joint Vascular Research Study Group (Thompson 1996) investigated heparinisation in eAAA repairs and only acquired discernible differences in mortality and morbidity between the heparin and non-heparinised groups using outcome factors outside of their original study design, for example, fatal and non-fatal myocardial infarction (MI). No significant differences existed regarding blood transfusion rates, blood loss and distal thrombosis between the two groups whilst investigating the relationship between intraoperative intravenous heparinisation and thrombotic complications in eAAA repairs in 284 participants.

Despite this study being a prospective multi-centre randomised controlled trial (RCT) it possessed multiple biases: randomisation was through a sealed envelope (selection bias: potentially compromising trial integrity), heparin was administered in a non-blinded fashion (allocation bias: as peri-operative critical care could potentially independently improve if heparin is given due to blood loss concerns) and outcomes could not be judged against statistical analysis of preoperative vascular risk factors

because these had not been collated (missing data: a retrospective extraction of these factors was not undertaken).

The final point in regard to missing data is important because if statistical analysis of preoperative risk factors for vascular disease could not be undertaken then the internal (and external) validity of the recorded differences in fatal MI (1.4% of heparinised and 5.7% of non-heparinised participants) and non-fatal MI (2% of heparinised and 8.5% of non-heparinised participants) between the two groups would be weakened. Preoperative risk factors for vascular disease, for example myocardial infarction, pulmonary embolism, hypertension, diabetes mellitus and hypercholesterolaemia should be recorded for fair comparison of any trial of vascular intervention: the missing data weakens the conclusions.

[Thompson 1996](#) is a landmark trial but if published against contemporary practice it encounters obstacles according to the Consolidated Standards of Reporting Trials ([CONSORT 2010](#)), for example, a power calculation was not conducted (items 7a and 7b), randomisation sequence generation did not exist (items 8a and 8b), allocation concealment mechanism was not robust (item 9), implementation lacked trial integrity (item 10), blinding did not occur, (item 11a) and statistical analysis was not thorough as data did not exist (items 12a and 12b). Overall analysis was restricted to the lesional event and postoperative lesional characteristics. This renders this RCT at Level 2b according to the Oxford Centre for Evidence Based Medicine ([OCEBM](#)) 2009 classification.

Furthermore the differences in fatal and non-fatal MI could simply be due to over-representation of people at higher risk of cardiac ischaemia in the non-heparinised group ([Wiersema 2013](#)). These discrepancies highlight the controversy of using intravenous heparin for eAAA repair let alone rAAA repair ([Wiersema 2013](#)).

Consequently, it is difficult to extrapolate results from eAAA repair to rAAA repair. Extrapolation to assume a theoretical benefit on postoperative mortality and morbidity in rAAA repair cannot be clinically justified if robust trial data does not exist for eAAA repairs. eAAA repairs are by definition conducted in controlled, elective settings with significant pre-operative planning in a stable patient. Conversely rAAA repairs are conducted in emergency settings in unstable patients: the physiological insult inflicted on the latter may be much greater (in particular with activation of the coagulation cascade) and other homeostatic mechanisms (see below). This might result in two distinct patient groups (and peri-operative physiological demands) in respect to heparin.

The complexity of such an intervention is highlighted due to recent changes in management options for rAAA, for example, endovascular (EVAR) and permissive hypotension (> 70 mmHg) ([The Vascular Society 2015](#)), that have been shown to decrease mortality from 40% to 20%. This further compounds any extrapolation of benefit of intravenous heparin in eAAA repair to that predicted in rAAA repair.

A singular prospective non-randomised, non-blinded case-control study attempted to investigate intravenous heparin in rAAA repairs ([Chinien 2008](#)). This involved 131 participants but it did not meet our strict inclusion criteria, that is, it was not an RCT nor a CCT and did not report according to our primary and secondary objectives. Even though it stratified preoperative risk factors for vascular disease in the heparinised and non-heparinised groups it did have multiple biases, such as diagnostic bias (rAAA was confirmed at two

different time points, immediate (radiological) and delayed (intra-operative), which could impact on patient outcome), selection bias (heparin was used at the lead surgeon's discretion being exposed to conflicting interests (blood loss and haemodynamic instability)), cross over (a structured randomisation process did not exist) and lack of surgical equipoise (non-heparinised participants were more likely to be operated on by a senior surgical registrar instead of a consultant due to haemodynamic instability and a more urgent need to operate due to profound hypotension).

Even though the presence of a consultant was not a significant factor in outcome ($P = 0.125$) the mortality rates were 24%, 40% and 86% among the two experienced consultants, junior consultants and senior registrars, respectively, therefore their claim of a lower operative mortality of 16% in heparinised compared to 43% in non-heparinised participants (RR 0.37; 95% CI 0.16 to 0.85) as justification for heparin being a positive predictive factor for survival ($P = 0.036$) does not stand up to scrutiny if assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology ([STROBE 2007](#)) for case-control studies. Non-heparinised participants were more profoundly hypotensive (< 100 mmHg), although this did not reach statistical significance ($P = 0.075$), and they were operated on by relatively inexperienced surgeons, for example, senior surgical registrars ($P = 0.125$). The lack of statistical difference in the outcome may be due to insufficient statistical power. Further interrogation of study design reveals that 26.7% of participants crossed over between the two groups regarding heparinisation. The cross over was high as the decision making for heparinisation was based solely on the lead surgeon's preference.

In light of these biases this study ([Chinien 2008](#)) fell short of recently published guidelines for studies and trials ([CONSORT 2010](#)). This renders the subsequent systematic review ([Graham 2012](#)) of this case-control study at Level 3a: its conclusions therefore need careful interpretation according to [OCEBM](#) 2009 classification.

However, one consideration from this study is the acknowledgement that a reduction in postoperative mortality of a rAAA can be achieved if a repair is conducted by a highly experienced surgeon in a dedicated vascular unit. Contemporary practice dictates that the surgeon should be a consultant vascular surgeon, further suggesting the need for a RCT that has surgical equipoise.

Despite little clinical evidence existing for heparin use in rAAA management there is a speculative physiological basis for it. Studies have demonstrated a strong procoagulant state in AAA patients, for example, thrombin and prothrombin fragment generation increases, inhibition of systemic fibrinolysis occurs due to elevation of tissue plasminogen activator (t-PA) antigen (this reduces t-PA activity) and elevated plasminogen activator inhibitor (PAI) activity occurs ([Adam 1999](#)). These suggest a physiological role for heparin use, especially since heparin decreases D-dimer and prothrombin fragment levels following its administration in eAAA repair ([Jelenska 2004](#)).

Further physiological studies suggest a negative correlation between t-PA activity and Troponin I levels and a positive correlation between PAI activity and Troponin I levels in rAAA ([Haggart 2001](#)). The conclusion is that heparin might offset the procoagulant state of rAAA which predisposes people to develop myocardial cell necrosis and a subsequent negative postoperative

recovery ([Adam 2004](#)). This, once again, makes physiological sense, if studies reveal a higher fibrinolytic activity in those rAAA that especially present in hypovolaemic shock ([Skagius 2008](#)). It is clear that the physiological, clinical and statistical evidence base for heparin in both eAAA and rAAA need addressing through an RCT.

AUTHORS' CONCLUSIONS

Implications for practice

We identified no RCTs or CCTs of intravenous heparin in rAAA repairs (including parallel designs). Therefore, we were unable to assess the effect of intravenous heparin on all-cause mortality and incidence of general arterial disease, for example, cardiovascular, cerebral, pulmonary and renal pathologies in rAAA management in people undergoing an emergency repair. Of note is the increasing use of EVAR for rAAA: lack of extensive surgery and surgical anastomoses make coagulopathy less of an issue, and use of intra-procedural heparin is given to prevent thrombosis induced by endovascular wires and catheters. The primary and secondary outcomes remain to be determined in these groups of patients and could provide valuable insights before an RCT is proposed for using heparin in open rAAA repairs.

Implications for research

Our review highlights the real need for a robust randomised controlled trial (RCT) according to updated guidelines ([CONSORT 2010](#)) to address the effectiveness of heparin in ruptured abdominal aortic aneurysm (rAAA) management in patients undergoing an emergency repair. Such an RCT would require a multi-centric approach using a hospital, that is, a centre, and not an individual patient as the unit of randomisation in a parallel cross-over design

due to the clinical, biochemical, radiological, surgical, ethical and statistical complexity of such an intervention and potential variability in practice inside and outside centres of expertise, that is, surgical equipoise would need to be achieved.

Such an RCT would require the co-operation of national and international vascular, surgical, endovascular therapy and interventional radiology societies and associations. It would need to address our primary and secondary outcomes and others that might need to be factored in to account for local and national frameworks, for example, in the hub and spoke model of care that exists in vascular surgery in the United Kingdom, elsewhere in Europe and worldwide.

Currently, the Consensus on Arterial PeriProcedural Anticoagulation (CAPPA) group in the Netherlands is working towards conducting trials to address the clinical and statistical efficacy of prophylactic antithrombotics across arterial pathologies including rAAA and eAAA ([Wiersema 2013](#)). To date no trial exists. Consequently an RCT on heparin use during eAAA repairs would also be warranted due to the lack of high quality evidence ([Thompson 1996](#)) as demonstrated in the Discussion.

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REFERENCES

References to studies excluded from this review

Aliev 2004 {published data only}

Aliev MA, Dzhakupov VA, Seidalin AO, Mierbekov EM, Kalyshev RS. The use of low-molecular heparins in reconstructive surgery of ascending aortic aneurysms. *Angiologiya i Sosudistaya Khirurgiya/Angiology and Vascular Surgery* 2004;**10**(3):25-7.

Chinien 2008 {published data only}

Chinien G, Waltham M, Abisi S, Smith A, Taylor P, Burnand KG. Systemic administration of heparin intraoperatively in patients undergoing open repair of leaking abdominal aortic aneurysm may be beneficial and does not cause problems. *Vascular* 2008;**16**(4):189-93.

Grzela 2008 {published data only}

Grzela T, Brawura-Biskupski-Samaha R, Jelenska MM, Szmidt J. Low molecular weight heparin treatment decreases MMP-9 plasma activity in patients with abdominal aortic aneurysm. *European Journal of Vascular and Endovascular Surgery* 2008;**35**(2):159-61.

Lindblad 1994 {published data only}

Lindblad B, Bergqvist D, Wakefield TW, Stanley JC. Time-related anticoagulation after regional and systemic administration of heparin in patients undergoing aortoiliac surgery. *European Journal of Vascular Surgery* 1994;**8**(5):574-7.

Thompson 1996 {published data only}

Thompson JF, Mullee MA, Bell PR, Campbell WB, Chant AD, Darke SG, et al. Intraoperative heparinisation, blood loss and myocardial infarction during aortic aneurysm surgery: a Joint Vascular Research Group study. *European Journal of Vascular and Endovascular Surgery* 1996;**12**(1):86-90.

Additional references

Adam 1999

Adam DJ, Ludlam CA, Ruckley CV, Bradbury AW. Coagulation and fibrinolysis in patients undergoing operation for ruptured and nonruptured infrarenal abdominal aortic aneurysms. *Journal of Vascular Surgery* 1999;**30**(4):641-50.

Adam 2004

Adam DJ, Haggart PC, Ludlam CA, Bradbury AW. Coagulopathy and hyperfibrinolysis in ruptured abdominal aortic aneurysm repair. *Annals of Vascular Surgery* 2004;**18**(5):572-7.

Arya 2015

Arya S, Kim SI, Duwayri Y, Brewster LP, Veeraswamy R, Salam A, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic aneurysm repair independent of age and comorbidities. *Journal of Vascular Surgery* 2015; Vol. 61, issue 2:324-31. [PUBMED: 25312534]

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490-4.

Bhattacharya 2010

Bhattacharya V, Stansby G. Postgraduate Vascular Surgery: The Candidate's Guide to the FRCS. Cambridge University Press, 2010. [978-0-521-13352-4]

Chuang 2001

Chuang YJ, Swanson R, Raja SM, Olson ST. Heparin enhances the specificity of antithrombin for thrombin and factor Xa independent of the reactive center loop sequence: evidence for an exosite determinant of factor Xa specificity in heparin-activated antithrombin. *Journal of Biological Chemistry* 2001;**276**(18):14961-71. [PUBMED: 11278930]

CONSORT 2010

Consolidated Standards of Reporting Trials. CONSORT 2010 Checklist. CONSORT 2010 Key Documents 2010 (Available from consort-statement.org) (accessed December 2015).

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Goldberg 2005

Goldberg A, Stansby G. Surgical Talk. London: Imperial College Press, 2005. [978-186094-494-9]

GRADEpro GDT 2015 [Computer program]

GRADE working Group, McMaster University. GRADEpro GDT. Hamilton (ON): GRADE working Group, McMaster University, 2015.

Graham 2012

Graham AP, O'Connor EF, Hinchliffe RJ, Loftus IM, Thompson MM, Black SA. The use of heparin in patients with ruptured abdominal aortic aneurysms. *Vascular* 2012;**20**(2):61-4. [PUBMED: 22454548]

Haggart 2001

Haggart PC, Adam DJ, Ludman PF, Ludman CA, Bradbury AW. Myocardial injury and systemic fibrinolysis in patients undergoing repair of ruptured abdominal aortic aneurysm: a preliminary report. *European Journal of Vascular and Endovascular Surgery* 2001;**21**(6):529-34.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green

S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Jelenska 2004

Jelenska MM, Szmidt J, Bojakowski K, Grzela T, Palester-Chlebowczyk M. Compensated activation of coagulation in patients with abdominal aortic aneurysm: effects of heparin treatment prior to elective surgery. *Thrombosis and Haemostasis* 2004;**92**(5):997-1002.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**:e1000100.

Milne 1995

Milne AA, Murphy WG. Current blood transfusion practice in aortic aneurysm surgery in Scotland. The Scottish Vascular Audit Group. *Journal of the Royal College of Surgeons of Edinburgh* 1995;**40**(2):104-8.

OCEBM

OCEBM. Oxford Centre for Evidence Based Medicine. OCEBM Levels of Evidence 2009 Classifications. Available from oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (accessed December 2015).

Reimerink 2013

Reimerink JJ, Van der Laan MJ, Koelemay MJ, Balm R, Legemate A. Systematic review and meta-analysis of population-based mortality from ruptured abdominal aortic aneurysm. *British Journal of Surgery* 2013;**100**(11):1405-13. [PUBMED: 24037558]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Skagius 2008

Skagius E, Siegbahn A, Bergqvist D, Henriksson A. Activated coagulation in patients with shock due to ruptured abdominal

aortic aneurysm. *European Journal of Vascular and Endovascular Surgery* 2008;**35**(1):37-40.

Smith 2014

Smith JJ, Tekkis PP. Vascular-POSSUM Scoring. Risk prediction in surgery 2014; Vol. Available from riskprediction.org.uk/vasc-index.php (accessed December 2015).

Sterne 2011

Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

STROBE 2007

STROBE. Strengthening the reporting of observational studies in epidemiology. STROBE 2007 Checklist. STROBE Case Control Studies (Available from stroke-statement.org/index.php?id=available-checklists) 2007 (accessed December 2015).

Tambyraja 2004

Tambyraja AL, Fraser SC, Murie JA, Chalmers RT. Quality of life after repair of ruptured abdominal aortic aneurysm. *European Journal of Vascular and Endovascular Surgery* 2004;**28**(3):229-33. [PUBMED: 15288624]

Tambyraja 2005

Tambyraja AL, Fraser SC, Murie JA, Chalmers RT. Functional outcome after open repair of ruptured abdominal aortic aneurysm. *Journal of Vascular Surgery* 2005;**41**(5):758-61. [PUBMED: 15886656]

The Royal College of Surgeons of England 2014

The Royal College of Surgeons of England. The surgical specialties. Media background briefings and statistics (Available from rcseng.ac.uk/media/media-background-briefings-and-statistics/the-surgical-specialties-10-vascular-surgery) 2014 (accessed December 2015).

The Vascular Society 2015

The Vascular Society of Great Britain and Ireland. Best practice guidelines for the management and transfer of patients with a diagnosis of ruptured abdominal aortic aneurysm to a specialist vascular centre. Available from vascularsociety.org.uk/guidelines-for-raaa/ 2015 (accessed December 2015).

Wiersema 2012

Wiersema AM, Jongkind V, Bruijninx CMA, Reijnen MMPJ, Vos JA, Van Delden OM, et al. Prophylactic perioperative anti-thrombotics in open and endovascular abdominal aortic aneurysm (AAA) surgery: a systematic review. *European Journal of Vascular and Endovascular Surgery* 2012;**44**(4):359-67. [PUBMED: 22831869]

Wiersema 2013

Wiersema AM, Reijnen MMPJ, Bruijninx CMA, CAPPA Study Group. The use of heparin in patients with ruptured abdominal aortic aneurysms. *Vascular* 2013;**21**(2):119. [PUBMED: 23479776]

References to other published versions of this review

Cochrane Database of Systematic Reviews 2015, Issue 1. [DOI: [10.1002/14651858.CD011486](https://doi.org/10.1002/14651858.CD011486)]

Lammy 2015

Lammy S, Blackmur JP, Perkins JMT. Intravenous heparin during ruptured abdominal aortic aneurysmal repair.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aliev 2004	Study did not address the review question: it was a case series in 30 patients evaluating LMWH use in reconstructive surgery of ascending aortic aneurysms
Chinien 2008	Study attempted to answer the review question but failed: it was a case-control study in 131 participants and contained multiple investigative biases (see Discussion)
Grzela 2008	Study did not address the review question: it was a case-control study of 26 participants investigating LMWH impacting on MMP-2 and MMP-9 levels in pre-eAAA repair
Lindblad 1994	Study did not address the review question: it was a case series in 26 participants correlating anti-coagulant activity and route of heparin delivery
Thompson 1996	Study did not address the review question: it was an RCT in 284 participants investigating heparin use in eAAA and not rAAA repairs

LMWH: low molecular weight heparin

MMP: matrix metalloproteinase

ADDITIONAL TABLES

Table 1. Vascular POSSUM score

Physiological parameters	
Age	< 61 yrs old
	61-70 yrs old
	> 70 yrs old
Cardiac	No cardiac failure
	Diuretic, digoxin, Rx for angina or hypertension
	Peripheral oedema, warfarin, borderline cardiomyopathy
	Raised JVP, cardiomegaly
Respiratory	No dyspnoea
	Dyspnoea on exertion, mild COAD
	Limiting dyspnoea, moderate COAD
	Dyspnoea at rest, pulmonary fibrosis/consolidation on CXR

Table 1. Vascular POSSUM score *(Continued)*

ECG	ECG normal
	ECG AF (rate 60-90 bpm)
	ECG any other abnormal rhythm (> 4/min ectopics, Q-waves, ST/T-wave changes)
Systolic BP	110-130 mmHg
	100-109 or 131-170 mmHg
	> 170 or 90-99 mmHg, < 90 mmHg
Pulse Rate	50-80 bpm
	40-49 or 81-100 bpm
	101-120 bpm
	< 40 or > 120 bpm
Haemoglobin	13-16 g/dL
	11.5-12.9 or 16.1-17 g/dL
	10-11.4 g/dL or 17.1-18 g/dL
	< 10 or > 18 g/dL
WBC	4-10 x 10 ⁹
	10.1-20 or 3.1-4 x 10 ⁹
	> 20 or < 3 x 10 ⁹
Urea	< 7.6 mmol/L
	7.6-10 mmol/L
	10.1-15 mmol/L
	> 15 mmol/L
Sodium	> 135 mmol/L
	131-135 mmol/L
	126-130 mmol/L
	< 126 mmol/L
Potassium	3.5-5 mmol/L
	3.2-3.4 or 5.1-5.3 mmol/L
	2.9-3.1 or 5.4-5.9 mmol/L
	< 2.9 or > 5.9 mmol/L
GCS	15
	12-14
	9-11

Table 1. Vascular POSSUM score (Continued)
< 9

Choosing each category estimates a patient's mortality risk based on the following models: V-POSSUM, V(P)-POSSUM (using physiology score only), rAAA-POSSUM, rAAA(P)-POSSUM (using physiology score only).

AF: atrial fibrillation

bpm: beats per minute

COAD: chronic obstructive airways disease

CXR: chest X-ray

ECG: electrocardiograph

g/dL: grams per decilitre

GCS: Glasgow Coma Scale

JVP: jugular venous pulse

mmol/L: millimols per litre

POSSUM score: Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity score

rAAA: ruptured abdominal aortic aneurysm

Rx: treatment

V-POSSUM score: vascular POSSUM score

WBC: white blood cells

Table 2. Operative parameters

Operative parameters	
Operation type	Minor operation
	Moderate operation
	Major operation
	Complex major operation
Number of procedures	One
	Two
	More than two
Operative blood loss	< 100 mLs
	101-500 mLs
	501-999 mLs
	> 1000 mLs
Peritoneal contamination	No soiling
	Minor soiling
	Local pus
	Free bowel content, pus or blood
Malignancy status	Not malignant
	Primary malignancy only
	Malignancy + nodal mets
	Malignancy + distant mets

Table 2. Operative parameters (Continued)

CEPOD	Elective
	Urgent
	Emergency (< 2 hrs)

In the case of a rAAA it is a major operation, conducted once, can incur > 1000 mLs blood loss and peritoneal contamination exists due to blood being lost from the aneurysmal sac, malignancy may or may not be present and the CEPOD classification is emergency (ASAP).

CEPOD: confidential enquiry into perioperative deaths

mets: metastasis

APPENDICES

Appendix 1. CENTRAL Search Strategy

Search run on Thu Dec 3 2015		
#1	MESH DESCRIPTOR Aneurysm, Ruptured EXPLODE ALL TREES	139
#2	MESH DESCRIPTOR Aneurysm, Dissecting	55
#3	#1 or #2	190
#4	aort*:TI,AB,KY	6126
#5	(juxta renal):TI,AB,KY	0
#6	juxtarenal:TI,AB,KY	2
#7	(pararenal or para renal):TI,AB,KY	3
#8	(suprarenal or supra renal):TI,AB,KY	23
#9	(short neck* or shortneck*):TI,AB,KY	9
#10	(visceral aortic segment):TI,AB,KY	0
#11	abdominal:TI,AB,KY	18229
#12	aneur?sm*:TI,AB,KY	2374
#13	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	24590
#14	(ruptur* or tear or bleed* or trauma or leak*):TI,AB,KY	31809
#15	#13 AND #14	2587
#16	RAA:TI,AB,KY	44
#17	#3 OR #15 OR #16	2669

(Continued)

#18	MESH DESCRIPTOR Heparin EXPLODE ALL TREES	3653
#19	heparin*:TI,AB,KY	8313
#20	(LMWH or UH or UFH):TI,AB,KY	1053
#21	(Clexane or klexane or lovenox or fragmin):TI,AB,KY	214
#22	(normiflo or innohep or clivarin* or danaproid or danaparoid or anti-tixarin):TI,AB,KY	70
#23	(Zibor or cy 222 or emborex or monoemborex):TI,AB,KY	38
#24	(lomoparan or orgaran):TI,AB,KY	28
#25	(fluxum or lohepa or lowhepa):TI,AB,KY	11
#26	(AVE5026 or M118 or RO-14):TI,AB,KY	8
#27	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	8650
#28	#17 AND #27	149

CONTRIBUTIONS OF AUTHORS

The original review question was generated by SL. The protocol and review was written by SL and JB. JP provided editorial supervision. SL is the guarantor of the review.

DECLARATIONS OF INTEREST

SL: I was a National Institute for Health Research (NIHR) Academic Clinical Fellow (ACF) in Vascular Surgery at the University of Oxford and Oxford University Hospitals NHS Trust (2013-2014).

JB: None known

JP: None known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added plans for a 'Summary of findings' table according to GRADE ([Atkins 2004](#)) to the methods section. For completeness, we added further details to the planned secondary outcome 'non-fatal limb ischaemia' and added the additional secondary outcome 'incidence of abdominal compartment syndrome'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Emergency Treatment; Anticoagulants [*administration & dosage]; Aortic Aneurysm, Abdominal [*surgery]; Aortic Rupture [*surgery]; Emergencies; Heparin [*administration & dosage]; Injections, Intravenous; Intraoperative Period

MeSH check words

Humans