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Perioperative antioxidants for adults undergoing elective non-cardiac surgery (Protocol)

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[Intervention Protocol]

Perioperative antioxidants for adults undergoing elective non-cardiac surgery

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the benefits and harms of antioxidant use in the perioperative period in adults who undergo non-cardiac surgery.

BACKGROUND

Description of the condition

Reactive oxygen species (ROS) are molecules containing one or more unpaired electrons, predominantly formed through the reduction of oxygen by the addition of one electron, thus making the molecule highly reactive (Halliwell 2015). Physiological concentrations of ROS serve many useful roles in cell signalling, immunity, differentiation, and cell death (apoptosis) (Scheiber 2014). However, supranormal concentrations can lead to an imbalanced state of oxidative stress. This is a result of excessive production of ROS, causing damage to a wide range of molecules, including nucleic acids, lipids, and protein structures. Lipid peroxidation (oxidative degradation of lipids) is particularly damaging due to its self-perpetuating chain reactivity (Kohen 2002). The delicate balance of maintaining the steady state of ROS is dependent on the scavenging capacity of innate antioxidant systems within the body (Shyur 2005).

Surgery is the treatment of injuries or disorders by incision or manipulation, and it involves the use of instruments. Disruption of tissue by direct handling and cutting leads to localised trauma and inflammatory responses (Desborough 2000). ROS is central to the inflammatory process, playing vital roles in signalling and mediation. During the initial immune response, an oxidative burst is released from white blood cells, combined with the release of cytokines (immune factors), causing disruption to the endothelium (cells lining the internal surface of blood vessels, modulation

clotting, and immune function). This results in a vicious cycle of inflammation, tissue damage, and ultimately organ dysfunction (Valko 2007; Mittal 2014). In particular, surgical tissue injury involving that of manipulation to the abdominal content and ischaemia reperfusion (a process of reduction or cessation of blood flow to a tissue followed by restoration of flow) have been demonstrated to increase oxidative stress (Anup 1999; Bentes de Souza 2003; Mittal 2008; Luo 2011). Several studies and systematic reviews have measured the production of oxidative stress following different surgical techniques. In a systematic review of 14 studies comparing abdominal aortic aneurysm (AAA) repair by an open versus endovascular approach (a less invasive approach), open AAA repair was demonstrated to produce higher levels of oxidative stress (Aivaditi 2011). A systematic review evaluating general surgical procedures compared oxidative stress markers in laparoscopic versus open abdominal surgeries. The conditions evaluated included gallbladder resection (cholecystectomies), gynaecological, upper and lower gastrointestinal surgeries. A wide range of oxidative stress markers were used and not all studies recorded clinical outcomes, which made the results unsuitable for meta-analysis. Despite this, there was a preponderance to lower systemic oxidative stress levels in less invasive procedures found in the laparoscopic group (Arsalani-Zadeh 2011). In orthopaedic surgery, ischaemia reperfusion due to the use of tourniquets has been associated with an increase in local and systemic oxidative stress markers. The presence of increased oxidative stress metabolism has been linked to adverse surgical outcomes (Hafez 2000; Misthos 2006); these include multi-organ complications of myocardial injury, sepsis, pulmonary oedema, acute kidney injury, liver injury, and even cancer recurrence (Cornu-Labat 2000; Mishra 2005; O'Leary 2013). These may be findings of association. The clinical relevance of the use of oxidative stress markers as a potential biomarker for disease outcome and severity is still an area that requires further study.

Lifestyle factors have been linked to generation of oxidative stress, in particular, in the obese, smokers, and in chronic alcohol use; the consequences of this leads to a pro-inflammatory state which leads to comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, and cirrhosis (Aseervatham 2013). It is, therefore, plausible that these lifestyle factors and their associated comorbidities play a role in surgical risk modification at a cellular level through the activation of oxidative stress pathways.

The quantification and detection of ROS in biological systems is challenging due to their short-lived and highly reactive nature (Ho 2013; Woolley 2013; Griedling 2016). Electron paramagnetic resonance is considered the gold standard for ROS detection and the only technique which offers direct measurement of unpaired electrons. However, signal detection can be challenging. Instead, multiple techniques have been developed as alternative ways to measure metabolic products of ROS-mediated damage. Examples are immunoassays, liquid chromatography, and mass spectroscopy (Griedling 2016). The antioxidant system can also be measured to reflect the oxidative burden. Both enzymatic and non-enzymatic antioxidants can be assayed (Rosenfeldt 2013). Commercial kits and laboratory-based protocols can be used to detect oxidative stress in biological samples obtained from different sites of the body. Due to the challenges of quantifying oxidative stress, these markers are not part of a routine clinical workup, and the prevalence and degree of oxidative stress postsurgery is currently unknown. Point of care testing kits are now available, which may make clinical quantification more accessible and relevant for future practice.

Description of the intervention

Perioperative complications manifest through the dysfunctions of major organ systems. Conventional ways to reduce these complications are through preoperative risk stratification, intraoperative goal-directed fluid therapy, and postoperative management in an environment with advanced physiological monitoring and greater nursing input. Preventive therapeutic strategies to reduce perioperative oxidative stress may have favourable patient outcomes, such as reduction in postoperative complications, a shorter hospital stay, and a better long-term quality of life. One approach is the perioperative administration of exogenous antioxidants.

An antioxidant can be defined as a substance that prevents the transfer of electrons to and from molecular oxygen and organic molecules. It causes ROS stabilisation or terminates the propagation of ROS reactions (Bray 1990; Gutteridge 1995). Exogenous antioxidants are consumed or accessed in the form of dietary intake, food supplements, or administration by a clinician, and they primarily take the form of naturally occurring, non-enzymatic agents. In a perioperative setting, they are typically given by the surgical team or the anaesthetist. Examples include vitamins, bioflavonoids, carotenoids, modified amino acids, and trace elements. These antioxidants may be used in isolation or as a cocktail with variable dosing regimens during the perioperative period.

How the intervention might work

The action of antioxidants can be both systemic and local. They are a heterogeneous group of compounds that do not share a common biological mechanism and include both enzymatic and non-enzymatic pathways (Rahal 2014). In general, common antioxidants used in the perioperative period include vitamin A, C, and E, which act as direct ROS scavengers (Koekkoek 2016). The use of perioperative antioxidants may provide therapeutic benefit, through the reduction in developing postoperative complications. Vitamin C, in particular, has been found to decrease postoperative atrial fibrillation in patients after cardiac surgery and reduction in postoperative pain scores in laparoscopic bowel resection patients (Jeon 2016; Geng 2017). N-acetylcysteine (NAC) has also demonstrated some promising therapeutic benefit. It provides the rate-limiting molecule, cysteine, for glutathione production (Skvarc

2016) and seems to reduce incidence in postoperative atrial fibrillation and acute kidney injury (Ali-Hassan-Sayegh 2016). Other examples include zinc and selenium; these are cofactors used by antioxidant enzymes and have a complex interplay within the antioxidant network (Rizzo 2010; Pisoschi 2015).

Why it is important to do this review

Surgery is the mainstay treatment for many health conditions; the findings of a global study of patient outcomes after elective surgery reports a postoperative complication rate of 16.8% of one or more complications, and an overall mortality of 2.8% (Pearse 2016). To reflect the scale of the issue on public health, with global estimates of 310 million patients undergoing surgery per year (Weiser 2008), with improved access to surgical procedures, the risk of developing postoperative complications will continue to increase (Alkire 2015; Weiser 2015). At an individual level, development of postoperative complications affect long-term patient survival (Khuri 2005) and quality of life, which in turn leads to decreased economic productivity of the entire society (Head 2008; Pearse 2011). Innovative ways are being explored to improve post-surgical outcomes and antioxidants may offer a simple and accessible way of improving such outcomes.

Many experimental models have demonstrated improved outcomes for degenerative diseases using antioxidants, as well as showing promising results in patients undergoing cardiac surgery. However, the therapeutic benefits of antioxidants in other clinical studies have generated conflicting results (Bjelakovic 2012; Egea 2017). To the best of our knowledge, meta-analysis of perioperative antioxidant use has only been conducted in cardiac surgery. The efficacy of perioperative antioxidants in the setting of non-cardiac surgery remains uncertain and meta-analysis and systematic review of current data are lacking. Due to the wide variety of antioxidants available and heterogeneous use in clinical practice, the need for a systematic review of the literature should be fulfilled. This may shed light into potential management options and future research directions in reducing oxidative stress during the perioperative period.

OBJECTIVES

To assess the benefits and harms of antioxidant use in the perioperative period in adults who undergo non-cardiac surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials that are available as published and ahead-of-print papers. We will also consider quasi-randomised studies, controlled clinical studies, and other observational studies for data on harms if retrieved with our searches for randomised clinical trials. This is because adverse events are rarely reported in randomised clinical trials (Storebø 2018). Moreover, such observational studies may provide information on rare or late-occurring adverse events (Storebø 2018). We are aware that the decision not to search for all observational studies may bias our review towards assessment of benefits and may overlook certain harms, such as late or rare harms. We will also include any relevant conference abstracts. We will apply no language restrictions.

Types of participants

We will include adults of 18 years and older admitted as inpatients who undergo non-cardiac surgery in an operating theatre.

Types of interventions

Intervention group

- Perioperative antioxidants: the administration of the first dose of antioxidants must occur within a 48-hour perioperative period (i.e. at a time no earlier than 24 hours before the start of surgery and no later than 24 hours after the end of the surgery).
- Antioxidants continued to be given after the 24-hour period, where the first dose was given during the first 48-hour perioperative period.
- Antioxidants stopped within the 48-hour period.

Control group

- Perioperative placebo or no treatment.

Co-interventions will be allowed provided that they are applied equally among the groups.

We will not include trial participants if their administration of antioxidants started outside the 48-hour perioperative period.

Types of outcome measures

Primary outcomes

- Long-term mortality (maximal follow-up).
- Serious complications within 30 days after surgery (Clavien-Dindo classification Grade III or IV) (Dindo 2004).
- Serious adverse drug reactions or events secondary to the intervention 90 days after surgery. Serious adverse events are defined as any event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability or incapacity (ICH-GCP 1997).

- Health-related quality of life as defined in the included trials using a validated scale such as EQ-5D or 36-item Short Form (SF-36) (Ware 2014; EuroQol 2017). We will consider health-related quality of life at one year follow-up as the most important time point since we anticipate that this follow-up period is likely to capture the outcomes related to a perioperative intervention.

Secondary outcomes

- Non-serious complications within 30 days after surgery (Clavien-Dindo classification Grade I or II) (Dindo 2004).
- Non-serious adverse drug reactions or events secondary to the intervention 90 days after surgery. Non-serious adverse events are any events which do not fulfil the criteria for serious adverse events and which are considered generally minor in nature, such as rash, myalgia, and hair loss (CIOMS 2005).
- Duration of intensive care unit (ICU) stay.
- Duration of hospital stay.

Exploratory outcomes

- Laboratory oxidative stress markers and antioxidant capacity.

These outcome measures are sometimes reported in randomised clinical trials using antioxidants as additional indications of treatment benefit (Ali-Hassan-Sayegh 2016; Geng 2017). They are of particular interest to clinicians; aside from laboratory oxidative stress markers, they provide information on the rate of recovery for the patient and indicate the health care costs for the institution. The interest in the use of laboratory oxidative stress markers has also been growing, as a potential biomarker for prognostication and disease severity; we have therefore included these measures in our study protocol (Rosenfeldt 2013; Frijjhoff 2015; Mizuno 2016).

Search methods for identification of studies

Electronic searches

We will search the Cochrane Hepato-Biliary Group Controlled Trials Register (Cochrane Hepato-Biliary Group Module), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Bireme), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index - Science (Web of Science) (Royle 2003). Appendix 1 gives the preliminary search strategies with the expected time spans of the searches.
To identify further ongoing or completed trials, we will search the World Health Organization International Clinical Trials Registry Platform Search Portal (apps.who.int/trialsearch/), which searches various trial registers, including ISRCTN and www.clinicaltrials.gov. We will also search European Medicines Agency (EMA) (www.ema.europa.eu/ema/), the Food and Drug Administration (FDA) (www.fda.gov), other regulatory authorities, as well as pharmaceutical company sources for ongoing or unpublished trials. We will not apply any language restrictions; we will review studies published in a foreign language on a case-by-case basis and, if necessary, we will obtain translations.
We will also endeavour to identify randomised clinical trials referenced in non-English databases, using our personal contacts, local access, or asking Sarah Louise Klingenberg, the CHBG Information Specialist, to contact Cochrane collaborators from around the world, with the same intent.

Searching other resources

We will perform a manual search of the reference list of identified manuscripts, as well as the reference collections of expert review authors and colleagues.
We will also perform a search using Google Scholar to identify any suitable studies.

Data collection and analysis

We will perform the review following the recommendations of Cochrane (Higgins 2011) and the Cochrane Hepato-Biliary Group Module. We will perform the analysis with Review Manager 5 (Review Manager 2014).

Selection of studies

Two independent authors will identify titles and abstracts of potentially eligible studies. We will resolve any disagreement by discussion and by advice from the senior authors, in the event of lack of agreement. We will obtain the full texts of potentially eligible studies and extract the study characteristics using a pre-designed pro forma (Appendix 2).

Data extraction and management

Two authors (JLS and JVS) will independently extract data. If the two abstractors disagree, we will attempt to reach a consensus by resolving any disparity in data collection through discussion. If this is not the case, we will involve a third person to arbitrate. In the absence of appropriate published data, we will make up to three attempts to contact authors of eligible studies to obtain any required data.

Assessment of risk of bias in included studies

We will perform the 'Risk of bias' assessment according to the Cochrane 'Risk of bias' tool (Higgins 2011) and described in the

Cochrane Hepato-Biliary Group Module to assess the risk of bias in included studies. Specifically, we will assess the risk of bias in included trials for the following domains, using the methods below (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Savović 2012a; Savović 2012b; Lundh 2017; Savović 2018).

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We will only include such studies for assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque or sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: if it is likely that the investigators who assigned the participants knew the allocation sequence or the participants are aware of the treatment assignment, then high risk of bias exists. We will only include such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias: either of the following: insufficient information to permit judgment of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: either of the following: no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinded outcome assessment

- Low risk of bias: blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
- Unclear risk of bias: either of the following: insufficient information to permit judgment of 'low risk' or 'high risk'; or the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values or the study used sufficient methods, such as multiple imputation, to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: all predefined, or clinically relevant and reasonably expected, outcomes are reported on. If the original study protocol is available, the outcomes should be those called for in that protocol. (Note: if the study protocol is obtained from a study registry (e.g. www.clinicaltrials.gov), the outcomes to be sought are those enumerated in the original protocol if the study protocol was registered before or at the time that the study was begun; if the study protocol was registered after the study was begun, those outcomes will not be considered to be reliable in representing the outcomes initially being sought.) If the study protocol is not available (or if the protocol was registered after the study was begun), then we will assess all-cause mortality and serious adverse events as we deem these to be the most clinically relevant and reasonably expected outcomes.
- Unclear risk: the study authors do not report all predefined outcomes fully, or it is unclear whether the study authors recorded data on these outcomes or not.
- High risk: the study authors do not report one or more predefined outcomes.

For-profit bias

- Low risk of bias: the study appeared free of industry sponsorship or other type of for-profit support that could manipulate the study design, conductance, or study results (industry-sponsored studies overestimate the efficacy by about 25%) (Lundh 2017).
- Unclear risk of bias: the trial may or may not be free of for-profit bias as the trial does not provide any information on clinical trial support or sponsorship.
- High risk of bias: the trial is sponsored by industry or received other type of for-profit support (Lundh 2017).

Other bias

Dosing bias

- Low risk of bias: reasonable dosage and intervals used in the intervention arm.
- Unclear risk of bias: the trial may or may not have been free of dosing bias that could put it at risk of bias.
- High risk of bias: intervention bias in dosing of treatment and deviation from set dosing schedule .

Baseline imbalance
- Low risk of bias: if there was no baseline imbalance in important characteristics.
- Unclear risk of bias: if the baseline characteristics were not reported.
- High risk of bias: if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Overall risk of bias

We will assess overall risk of bias in the trials as:
- Low risk of bias: if all the bias domains described in the above paragraphs are classified as low risk of bias.
- High risk of bias: if one or more of the bias domains described in the above paragraphs are classified as 'unclear' or 'high risk of bias'.

We will solve disagreements by discussion and, if this is not resolved, we will consult a third author (DSM). There will be two assessors and one adjudicator.

Measures of treatment effect

We will calculate risk ratios (RRs) with 95% confidence intervals (CI) for dichotomous data and mean differences (MDs) with 95% CI for continuous data. We will also calculate Trial Sequential Analysis-adjusted confidence Intervals if the cumulative Z-curve does not cross the trial sequential monitoring boundaries (see below). We will calculate standardised mean differences (SMDs) and 95% CIs when combining results from studies using different ways of measuring a continuous outcome. Where possible, we will use follow-up scores in preference to change scores.

For continuous outcomes, we plan to impute the standard deviation from P values according to guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If the data are likely to be normally distributed, we plan to use the median for meta-analysis when the mean is not available. If it is not possible to calculate the standard deviation from the P value or the confidence intervals, we plan to impute the standard deviation using the largest standard deviation in other trials for that outcome. This form of imputation may decrease the weight of the study for calculation of mean differences and may bias the effect estimate to no effect for calculation of standardised mean differences (Higgins 2011).

Unit of analysis issues

The unit of randomisation in the included trials is likely to be individual participants undergoing surgery as originally assigned to the trial groups of the trials. If we find cluster-randomised clinical trials, we will include these provided that the effect estimate has been adjusted for cluster correlation and is available.

Dealing with missing data

We will perform an intention-to-treat analysis, whenever possible. Otherwise, we will use the data that are available to us (e.g. a trial may have reported only per-protocol analysis results). As 'per-protocol' analyses may be biased, we plan to conduct best-worst case scenario analyses (good outcome in intervention group and bad outcome in control group) and worst-best case scenario analyses (bad outcome in intervention group and good outcome in control group) as sensitivity analyses, whenever possible.

Assessment of heterogeneity

We will assess the clinical and methodological heterogeneity by assessing the various potential effect modifiers listed in the Subgroup analysis and investigation of heterogeneity section. If there is significant clinical or methodological heterogeneity between the trials, we will perform meta-analysis in a homogenous subset of trials if two or more trials are available in each homogenous subset of trials; otherwise, we will perform a narrative synthesis. If we do not perform a meta-analysis, we will use Fisher's exact test to compare the two interventions. We will consider a P value of less than 0.05 to be statistically significant.

We will evaluate assessment of heterogeneity between comparable trials visually using forest plots, and the Chi^2 and I^2 statistics, with the level of significance for the Chi^2 test being set at P = 0.1 (Deeks 2010). Thus, a P value for Chi^2 of < 0.1 will be considered to indicate statistically significant heterogeneity among studies. The degree of heterogeneity observed in the results will be quantified using the I^2 statistic, which can be interpreted as the percentage of variation observed between the trials attributable to between-trial differences rather than sampling error (chance).

Assessment of reporting biases

We will be vigilant for duplicate publications of the same studies. If there was any doubt whether trials shared the same participants, completely or partially (by identifying common authors and centres), we planned to contact the trial authors to clarify whether the trial report was duplicated. We will use funnel plots to assess reporting bias when there are 10 or more trials in a comparison. In the presence of heterogeneity that could be explained by subgroup analysis, we will produce a funnel plot for each subgroup in the presence of the adequate number of trials. We will use the linear regression approach described by (Egger 1997) to determine the funnel plot asymmetry.

Data synthesis

Meta-analysis

We will perform the meta-analyses using Review Manager 5.3 (Review Manager 2014) and according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) as well as those of the Cochrane Hepato-Biliary Group Editrial Team (hbg.cochrane.org). We will present the results of dichotomous outcomes of individual trials as relative risks (RR) with 95% CI and the results of the continuous outcomes as mean difference (MD) with 95% CI. We will apply both the fixed-effect model (DeMets 1987) and the random-effects model (DerSimonian 1986) meta-analyses. If there are statistically significant discrepancies in the results (e.g. one giving a significant intervention effect and the other no significant intervention effect), we will report the more conservative point estimate of the two (Jakobsen 2014). The more conservative point estimate is the estimate closest to the zero effect. If the two point estimates are equal, we will use the estimate with the widest CI as our main result of the two analyses. We will consider a P value of 0.02 or less, two-tailed, as statistically significant if the required information size was reached due to our four primary and four secondary outcomes (Jakobsen 2014). We will use the eight-step procedure to assess if the thresholds for significance are crossed (Jakobsen 2014). We will present heterogeneity using the I^2 statistic (Higgins 2011). We will present the results of the individual trials and meta-analyses in the form of forest plots. If data is insufficient or unsuitable for meta-analysis, a summary of results will be collated to summarise the findings in a narrative way.

Trial Sequential Analysis

We will examine apparently significant beneficial and harmful intervention effects and neutral effects with Trial Sequential Analyses in order to evaluate if these apparent effects could be caused by random error (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010; Thorlund 2011; TSA 2011; Wetterslev 2017).

We will use Trial Sequential Analysis as cumulative meta-analyses are at risk of producing random errors due to sparse data and repetitive testing of the accumulating data (Wetterslev 2008). To minimise random errors, we will calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Wetterslev 2008). The required information size calculation should also account for the diversity present in the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017).

In our meta-analysis, the diversity-adjusted required information size for primary and secondary dichotomous outcomes will be based on the event proportion in the control group; assumption of a priori risk ratio reduction of 20% or the RR reduction observed in the included trials at low risk of bias; a risk of type I error of 2% due to four primary and four secondary outcomes (Jakobsen 2014); a risk of type II error of 10%; and the observed diversity of the included trials in the meta-analysis. We will also calculate and report the Trial Sequential Analysis-adjusted CI (Thorlund 2011). The underlying assumption of Trial Sequential Analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We will add the trials according to the year of publication, and if more than one trial has been published in a year, we will add trials alphabetically according to the last name of the first author.

On the basis of the diversity-adjusted required information size, trial sequential monitoring boundaries will be constructed (Thorlund 2011). These boundaries will determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size. If the cumulative Z-curve crosses the trial sequential monitoring boundary for benefit or harm before the diversity-adjusted required information size is reached, firm evidence may perhaps be established and further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect. That can be determined by assessing if the cumulative Z-curve crosses the trial sequential monitoring boundaries for futility. The diversity-adjusted required information size for primary and secondary continuous outcomes will be based on the assumption of an a priori standardised mean difference of 0.20 and the median variance in the trials; a risk of type I error of 2%; a risk of type II error of 10%, and the observed diversity of the included trials in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses according to risk of bias, intervention characteristics, and treatment characteristics as follows.

Risk of bias assessment

- Trials at low risk of bias compared to trials at high risk of bias.

Surgery

- Severity of surgery: minor, moderate, major, complex major.

Type of antioxidant use in the perioperative period

- Vitamins.
- Micronutrients.
- Amino acids.
- Hormones.
- Enzymes complexes.
- Use of co-interventions, e.g. beta blockers.

Sensitivity analysis

We will perform sensitivity analyses to address the impact of:

- the inclusion or exclusion of missing data, including 'worst-best case' and 'best-worst case' scenario analyses;
- the choice of a fixed-effect or random-effects model.

Also, where possible, we will perform analyses to investigate the effects of various aspects of trial and review methodology, including the inclusion of trials at high risk of bias, small versus large sample size data, and single compared to multicentre studies.
We plan to compare our GRADE and TSA assessments of our Primary outcomes (Castellini 2018) in a sensitivity analysis (Jakobsen 2014).

'Summary of findings' tables

We will assess confidence in the evidence using GRADE criteria (Atkins 2004) and the GRADEpro software (GRADEPro). We will construct a summary of findings table in which we will present assessment of all our four review Primary outcomes and the first three of our Secondary outcomes, using five factors referring to limitations in the study design and implementation of included studies that suggest the quality of the evidence: risk of bias; indirectness of evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of results; and a high probability of publication bias. We will define the levels of evidence as 'high', 'moderate', 'low', or 'very low'. We will follow the recommendations of Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). These grades are defined as follows.

- High certainty: this research provides a very good indication of the likely effect; the likelihood that the effect will be substantially different is low.
- Moderate certainty: this research provides a good indication of the likely effect; the likelihood that the effect will be substantially different is moderate.
- Low certainty: this research provides some indication of the likely effect; however, the likelihood that it will be substantially different is high.
- Very low certainty: this research does not provide a reliable indication of the likely effect; the likelihood that the effect will be substantially different is very high.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage	antioxid* AND (surg* or operat*)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Antioxidants] explode all trees #2 MeSH descriptor: [Ascorbic Acid] explode all trees #4 MeSH descriptor: [Carotenoids] explode all trees #8 MeSH descriptor: [Melatonin] explode all trees #9 MeSH descriptor: [Quercetin] explode all trees #10 MeSH descriptor: [Selenium Compounds] explode all trees #11 MeSH descriptor: [Vitamin E] explode all trees #15 MeSH descriptor: [Acetylcysteine] explode all trees #16 MeSH descriptor: [Allopurinol] explode all trees #18 MeSH descriptor: [Superoxide Dismutase] explode all trees #19 MeSH descriptor: [Ubiquinone] explode all trees #20 MeSH descriptor: [Glutathione] explode all trees

(*Continued*)

		#21 MeSH descriptor: [Curcumin] explode all trees #22 MeSH descriptor: [Flavonoids] explode all trees #23 antioxid*:ti,ab,kw (Word variations have been searched) #24 surg* or operat*:ti,ab,kw (Word variations have been searched) #25 MeSH descriptor: [Preoperative Care] explode all trees #26 MeSH descriptor: [Perioperative Care] explode all trees #27 MeSH descriptor: [Specialties, Surgical] explode all trees #28 #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 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 #29 #24 or #25 or #26 or #27 #30 #28 and #29
MEDLINE Ovid	1946 to date of search	1. exp Antioxidants/ exp Free Radical Scavengers/ 2. exp Superoxide Dismutase/ exp Ubiquinone/ exp Phenol/ exp Glutathione/ exp Glutathione Peroxidase/ exp Curcumin/ exp Flavonoids/ 3. reactive Oxygen Species/ai [Antagonists & Inhibitors] 4. antioxid*.mp. 5. free radical scavengers.mp. 6. exp Specialties, Surgical/ 7. (surg* or operat*).mp. 8. exp Intraoperative Care/ exp postoperative care/ exp preoperative care/ 9. peri?operativ*.mp. 10. post?operativ*.mp. 11. intra?operativ*.mp. 12. randomized controlled trial.pt. 13. controlled clinical trial.pt. 14. randomized.ab. 15. placebo.ab. 16. clinical trial as topic.sh. 17. randomly.ab. 18. trial.ti. 19. exp animals/ not humans.sh. (alternative exp animals/ not (humans and animals).sh) 20. 1 or 2 or 3 or 4 or 5 21. 6 or 7 or 8 or 9 or 10 or 11 22. 12 or 13 or 14 or 15 or 16 or 17 or 18 23. 22 not 19 24. 20 and 21 and 22 and 23

(*Continued*)

Embase Ovid	1974 to date of search	1. exp antioxidant activity/ or exp antioxidant/ or exp scavenger/ or exp carotenoid/ or exp retinol/ / or exp essential fatty acid/ or exp flavonoid / or exp selenium derivative/ or exp selenium/ or exp tocopherol/ or exp oxidoreductase/ or exp acetylcysteine/ or exp allopurinol/ or exp superoxide dismutase/ or exp ubiquinone/ or exp glutathione/ or exp glutathione peroxidase/ or exp glutathione reductase/ or exp curcumin/ 2. antioxid*.mp. 3. free radical scavengers.mp. 4. exp surgery/ or exp abdominal surgery/ or exp bariatric surgery/ or plastic surgery/ or exp vascular surgery 5. surgery/ or surgery.mp. 6. operat*.mp. 7. exp perioperative period/ 8. exp preoperative period/ or exp preoperative care/ 9. exp postoperative complication/ 10. randomized control trial.pt. 11. placebo.ab. 12. controlled clinical trial.pt. 13. randomized.ab. 14. randomly.ab. 15. clinical trials as topic.sh. 16. trial.ti. 17. exp animals/ not humans.sh. (alternative exp animals/ not (humans and animals).sh) 18. 1 or 2 or 3 19. 4 or 5 or 6 or 7 or 8 or 9 20. 10 or 11 or 12 or 13 or 14 or 15 or 16 21. 20 not 17 22. 18 and 19 and 20 and 21
LILACS (Bireme)	1982 to date of search	antioxid$ [Words] and (surg$ or operat$) [Words]
Science Citation Index Expanded (Web of Science)	1900 to date of search	#1 TS=antioxid* #2 TS=(surg* or operat*) #3 #2 AND #1 #4 TS=(random* or blind* OR placebo* OR meta-analys*) #5 #4 AND #3 #6 TS=Animal* #7 #5 NOT #6
Conference Proceedings Citation Index - Science (Web of Science)	1990 to date of search	#1 TS=antioxid* #2 TS=(surg* or operat*) #3 #2 AND #1 #4 TS=(random* or blind* OR placebo* OR meta-

(*Continued*)

		analys*) #5 #4 AND #3 #6 TS=Animal* #7 #5 NOT #6

Appendix 2. Data collection form

Trial identification			
Author and year			
Publication type			
Study eligibility			
RCT	Yes	No	Unclear
Relevant participants	Yes	No	Unclear
Relevant intervention	Yes	No	Unclear
Relevant outcomes	Yes	No	Unclear
DO NOT PROCEED IF ANY OF THE ABOVE ANSWERS NO			
Include			
Exclude reason			
Participants			
Eligibility and how was this defined			
Age (mean, median, range etc)			
Sex of participants (numbers/ %)			
Disease status/type			
Type of surgery			

(*Continued*)

Additional notes			
Interventions			
Experimental interventions (name of antioxidant, dose, timing of administration)			
Control intervention (placebo or no treatment)			
Co-interventions used			
Other trial information			
Aim of trial			
Country/countries			
Trial design (parallel/cross-over, single/multicentre)			
Trial duration			
Withdrawals			
Study funding source			
Possible conflicts of interest			
Notes			

RCT: randomised control trial

CONTRIBUTIONS OF AUTHORS

Draft the protocol: Stevens JL, McKenna H, Van Schoor J, Gurusamy K, Grocott MP, Jell G, Martin DS

Develop a search strategy: Stevens JL, McKenna H, Martin DS

All authors read and approved the final protocol.

DECLARATIONS OF INTEREST

JLS: nothing to declare

HM: nothing to declare

KSG: nothing to declare

JVS: nothing to declare

MPG: nothing to declare

GJ: nothing to declare

DSM: nothing to declare

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