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Vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver diseases (Review)

Martí-Carvajal AJ, Solà I

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TABLE OF CONTENTS

[Intervention Review]

Vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver diseases

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ABSTRACT

Background

Upper gastrointestinal bleeding is one of the most frequent causes of morbidity and mortality in the course of liver cirrhosis. Several treatments are used for upper gastrointestinal bleeding in people with liver diseases. One of them is vitamin K administration, but it is not known whether it benefits or harms people with acute or chronic liver disease and upper gastrointestinal bleeding. This is an update of this Cochrane review.

Objectives

To assess the beneficial and harmful effects of vitamin K for people with acute or chronic liver disease and upper gastrointestinal bleeding.

Search methods

We searched The Cochrane Hepato-Biliary Controlled Trials Register (February 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2 of 12, 2015), MEDLINE (Ovid SP) (1946 to February 2015), EMBASE (Ovid SP) (1974 to February 2015), Science Citation Index EXPANDED (1900 to February 2015), and LILACS (1982 to 25 February 2015). We sought additional randomised trials from two registries of clinical trials: the World Health Organization Clinical Trials Search Portal and the metaRegister of Controlled Trials. We looked through the reference lists of the retrieved publications and review articles.

Selection criteria

Randomised clinical trials irrespective of blinding, language, or publication status for assessment of benefits and harms. We considered observational studies for assessment of harms only.

Data collection and analysis

\We aimed to summarise data from randomised clinical trials using Standard Cochrane methodology and assess them according to the GRADE approach.

Main results

We found no randomised trials on vitamin K for upper gastrointestinal bleeding in people with liver diseases assessing benefits and harms of the intervention. We identified no quasi-randomised studies, historically controlled studies, or observational studies assessing harms.

Authors' conclusions

This updated review found no randomised clinical trials of vitamin K for upper gastrointestinal bleeding in people with liver diseases. The benefits and harms of vitamin K need to be tested in randomised clinical trials. Until randomised clinical trials are conducted to assess the

trade-off between benefits and harms, we cannot recommend or refute the use of vitamin K for upper gastrointestinal bleeding in people with liver diseases.

PLAIN LANGUAGE SUMMARY

Vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver diseases

Review question
We reviewed vitamin K for upper gastrointestinal bleeding in people with acute liver disease (that is, loss of normal liver functions which occurs in days or weeks; most often, people do not have a pre-existing liver disease) or chronic liver disease (that is, progressive destruction of normal liver functions, usually associated with fibrotic regeneration of the liver tissue).

Background
Upper gastrointestinal bleeding (vomiting of blood) is one of the most frequent causes of morbidity and mortality in the course of liver disease. Vitamin K administration is used as a supplementary intervention, but it is unknown whether it benefits or harms people with acute or chronic liver disease and upper gastrointestinal bleeding.

Study characteristics
We searched scientific databases for studies assessing the benefits and harms of vitamin K in people of any age with liver disease. This updated review found no randomised clinical trials (clinical studies where people are randomly put into one of two or more treatment groups) on the benefits or harms of vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver diseases. The evidence is current to February 2015.

Key results
There is no evidence to recommend or refute the use of vitamin K for upper gastrointestinal bleeding in people with liver diseases.

Quality of evidence
We found no randomised clinical trials.

BACKGROUND

Description of the condition

Upper gastrointestinal bleeding is the loss of blood caused by illnesses that affect the alimentary canal from the mouth to the duodenum. According to the volume and speed of blood loss, upper gastrointestinal bleeding can lead to chronic anaemia or acute, life-threatening symptoms. Haematemesis (vomiting of blood) and melena (dark coloured, tarry stools containing digested blood) are the most common symptoms and signs of upper gastrointestinal bleeding (Green 2003). The annual incidence of upper gastrointestinal bleeding in France was 143 people per 100,000 (Czernichow 2000). The annual incidence of acute upper gastrointestinal bleeding in the UK was between 47 and 116 people per 100,000 (Dallal 2001). In the United States, from 1998 to 2006, the number of hospitalisations for upper gastrointestinal bleeding per 100,000 people decreased by 14% (Zhao 2008). Epidemiology and demographics of upper gastrointestinal bleeding (i.e., prevalence, incidence, and mortality) have been reviewed (Sostres 2011).

Upper gastrointestinal bleeding is one of the most frequent causes of morbidity and mortality in the course of liver cirrhosis (Protell 1981; Longstreth 1998; del Olmo 2000; Zaltman 2002). In people with advanced cirrhosis, acute upper gastrointestinal bleeding is the most serious and life-threatening complication (Afessa 2000; van Leerdam 2008). The causes of acute upper gastrointestinal bleeding in people with cirrhosis are: 1. rupture of varices in the oesophagus, stomach, or duodenum; 2. reflux oesophagitis; 3. acute lesions in the mucosal lining of the stomach membrane lesion; 4. peptic ulceration; and 5. reduction in blood coagulation factors (Amitrano 2002; Green 2003).

Description of the intervention

Several primary treatments are used for upper gastrointestinal bleeding in people with liver diseases. These are directed against the source of bleeding, for example, vasoactive treatment or endoscopic therapy for bleeding varices (Ioannou 1999; D'Amico 2002). Supplementary interventions are also often used including administration of vitamin K, which participates in the control of the formation of coagulation factors II, VII, IX, and X and anticoagulant proteins C and S by the liver. In liver disease, there is impaired synthesis of these clotting factors, resulting in a prolonged prothrombin time (Blonski 2007; Pluta 2010; Kavanagh 2011; Tripodi 2011; Wicklund 2011). This lack of production of clotting factors is more likely to be associated with impaired hepatocyte function than with a deficiency in vitamin K. One study, designed to research thrombin generation for assessment of the function of blood coagulation in people with cirrhosis, showed that although the prothrombin time is prolonged in people with cirrhosis, this may not correspond to an actual coagulation impairment (Tripodi 2005). The proposed explanation is that, in liver disease, the reduction of procoagulant factors in people with cirrhosis is compensated for by the reduction of anticoagulant factors, thus leaving the coagulation balance unaltered (Tripodi 2005). Therefore, administration of vitamin K to people with liver disease may have only partial or no effect in improving prolonged prothrombin time.

Why it is important to do this review

While vitamin K is used for treating coagulopathies in people with upper gastrointestinal bleeding, there appears to be no specific studies supporting its use (Lucena 2002). Furthermore, vitamin K is associated with anaphylactoid reactions (Pereira 1998; Fiore 2001).

We identified no systematic reviews or meta-analyses on vitamin K administration to people with upper gastrointestinal bleeding, apart from our own Cochrane Hepato-Biliary systematic reviews (Martí-Carvajal 2005; Marti-Carvajal 2008; Martí-Carvajal 2012). The present review presents an update of the most recent review published in 2012 (Martí-Carvajal 2012).

OBJECTIVES

To assess the beneficial and harmful effects of vitamin K for people with acute or chronic liver disease and upper gastrointestinal bleeding.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include randomised clinical trials (parallel group or cross-over trials) irrespective of publication status (trials could be unpublished or published as an article, an abstract, or a letter), language, and blinding. For cross-over trials, we planned to include only data from the first intervention period.

We intended to include quasi-randomised studies, prospective observational studies, and observational studies with a historical control group in order to assess data on harms.

Types of participants

People with liver disease and upper gastrointestinal bleeding, irrespective of aetiology.

Types of interventions

Vitamin K at any dose, route of administration, and duration of treatment versus placebo or no intervention. Since upper gastrointestinal bleeding in people with liver disease requires different medical and endoscopic treatments (i.e., primary intervention), vitamin K is considered a supplementary intervention. Thus, for the purpose of the review, eligible randomised clinical trials had to compare the same primary interventions with and without vitamin K supplementation.

Types of outcome measures

Primary outcomes

- Mortality.
- Early re-bleeding.
- Serious adverse events. We used the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event (ICH-GCP 1997), that is, any untoward medical occurrence that resulted in death, was life threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect. We considered all other adverse events as non-serious.

Secondary outcomes

- Quality of life.
- Non-serious adverse events.
- Number of participants transfused.
- Number of blood transfusions.
- Coagulation factors II, VII, and X.
- Length of hospital stay.
- Length of intensive care unit stay.

We planned to report the first seven of the above primary and secondary outcomes in the 'Summary of findings' table.

Search methods for identification of studies

We searched The Cochrane Hepato-Biliary Controlled Trials Register (Gluud 2015), the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid SP), EMBASE (Ovid SP), Science Citation Index EXPANDED, and LILACS (Royle 2003) to February 2015. Appendix 1 shows the search strategies with the time spans of the searches.

We looked through the reference lists of the retrieved publications and review articles.

We also searched the following trial databases for ongoing and unpublished trials:

- World Health Organization Clinical Trials Search Portal (apps.who.int/trialsearch/);
- metaRegister of controlled trials (www.controlled-trials.com/mrct/search.html).

In future updates, we will also search for study reports at regulatory agencies (US Food and Drug Administration and European Medicines Agency) and trials at www.clinicaltrials.gov.

Data collection and analysis

We planned to summarise data using standard Cochrane methodology (Higgins 2011a).

Selection of studies

AMC and IS screened the search results for potentially relevant trials and independently assessed them for inclusion or exclusion using a pre-designed eligibility form based on the inclusion criteria. We resolved disagreements through discussion until consensus was reached.

Data extraction and management

Due to the lack of randomised clinical trials, we could not follow what is described below. However, if we identify trials in the future, we will follow our protocol as described (Marti-Carvajal 2004). We will use a form to extract data from each relevant trial (Zavala 2006). Both review authors will independently extract data from the papers and will contact the authors if data are missing. AMC will enter the data into Review Manager 5 (RevMan 2014) and IS will check the data. We will extract information on study design and participant characteristics (age, sex, and disease severity as measured by the Child-Pugh score).

Assessment of risk of bias in included studies

If we identify randomised clinical trials fulfilling the inclusion criteria of our review, we will independently assess the risk of bias of each included trial according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), The Cochrane Hepato-Biliary Module (Gluud 2015), and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Lundh 2012; Savović 2012a; Savović 2012b). We will use the following definitions in the assessment of risk of bias.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent adjudicator.
- Unclear risk of bias: the trial was described as randomised, but the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not, or may not have been, random. Quasi-randomised studies, those using dates, names, or admittance numbers in order to allocate participants, were inadequate and were excluded for the assessment of benefits but included for assessing harms.

Allocation concealment

- Low risk of bias: allocation was controlled by a central and independent randomisation unit, sequentially numbered, opaque and sealed envelopes or similar, so that intervention allocations could not have been foreseen in advance of, or during, enrolment.
- Unclear risk of bias: the trial was described as randomised, but the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was known to the investigators who assigned participants, or the study was quasi-randomised.

Blinding of participants and personnel

- Low risk of bias: it was mentioned that both participants and personnel providing the interventions were blinded, and the method of blinding was described, so that knowledge of allocation was prevented during the trial.
- Unclear risk of bias: it was not mentioned if the trial was blinded, or the trial was described as blinded, but the method or extent of blinding was not described, so that knowledge of allocation was possible during the trial.
- High risk of bias: the trial was not blinded, so that the allocation was known during the trial.

Blinded outcome assessment

- Low risk of bias: outcome assessment was carried out blinded for all relevant outcomes, and the method of blinding was described, so that knowledge of allocation was prevented.
- Unclear risk of bias: blinding of outcome assessment was not described, or the outcome assessment was described as blinded, but the method of blinding was not described, so that knowledge of allocation was possible.

- High risk of bias: outcome assessment was not blinded, so that the allocation was known to outcome assessors.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed 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: the trial reported the following pre-defined outcomes: mortality, early re-bleeding, and serious adverse events. If the original trial protocol was available, the outcomes should be those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g., www.clinicaltrials.gov), the outcomes sought should be those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, those outcomes were not considered to be reliable.
- Unclear risk of bias: not all pre-defined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more pre-defined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other bias domains that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other domains that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias.

We will judge trials at low risk of bias if assessed with low risk of bias in all above domains. We will judge trials at high risk of bias if assessed with unclear risk of bias or high risk of bias in one or more of the above domains.

We will generate a 'Risk of bias' graph and a 'Risk of bias' summary to show a summary of this assessment.

Measures of treatment effect

For binary outcomes, such as mortality, early re-bleeding and safety, we planned to calculate the risk ratio (RR) with 95% confidence interval (CI). For continuous outcomes, such as number of people transfused and number of blood transfusions, we planned to calculate the mean difference (MD) with 95% CI.

Dealing with missing data

In the case of missing data on participants or missing statistics (such as standard deviations), we intended to contact the trial authors. If unsuccessful, we planned to base our main analysis on participants who had completed the trial, but we planned to perform sensitivity analysis for worse-case and best-case scenarios according to the *Cochrane Handbook for Systematic Reviews of Interventions* Section 16.1 (Higgins 2011b).

Assessment of heterogeneity

We planned to quantify the impact of statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). If the identified trials were comparable enough, we intended to summarise their findings using a random-effects model. In the case of substantial heterogeneity (I^2 > 50%), we planned to do further research to identify possible causes of heterogeneity by exploring the impact of participants' characteristics.

Assessment of reporting biases

We intended to assess whether the review was subjected to publication bias by using a funnel plot that is usually used to illustrate variability between trials in a graphical way. We needed at least 10 trials in order to be able to make judgements about asymmetry, and if asymmetry was present, we planned to attempt to explore other causes for it (Sterne 2011).

Data synthesis

We intended to carry out statistical analysis using Review Manager 5 software (RevMan 2014). If the eligible trials were sufficiently comparable in their clinical characteristics, we planned to summarise their findings using the fixed-effect model and the random-effects model according to the *Cochrane Handbook for Systematic Reviews of Interventions* Section 9.4 (Deeks 2011). In the case of statistically significant differences between the two models, we intended to report both. Otherwise, we planned to report the results of the model having the most conservative findings (Jakobsen 2014).

Trial sequential analysis

A meta-analysis of cumulative data may run the risk of random errors ('play of chance') due to sparse data and repetitive analyses of the same data (Brok 2008; Wetterslev 2008; Brok 2009; Wetterslev 2009; Thorlund 2010; Thorlund 2011). In order to assess the risks of random errors in cumulative meta-analyses, we planned to conduct diversity-adjusted trial sequential analyses (Thorlund 2011; TSA 2011) based on a required information size calculated from the proportion of people with the outcome in the control group; an a priori set relative risk reduction of 20%, an alpha of 5%, a beta of 20%, and the diversity in the meta-analysis (Thorlund 2009; Thorlund 2011; TSA 2011). We planned to conduct sensitivity analyses of the trial sequential analysis to estimate the potential need for further trials.

Subgroup analysis and investigation of heterogeneity

We anticipated clinical heterogeneity in the effects of the intervention, and we planned to conduct the following subgroup analyses when data become available:

- trials with low risk of bias (or with lower risk of bias) compared to trials with high risk of bias;
- participants with cirrhosis compared to participants without cirrhosis;
- Child-Pugh classification A compared to classification B and compared to classification C.

Sensitivity analysis

We planned to conduct sensitivity analyses including only randomised trials with low risk of bias, and perform best-case and worst-case scenario analyses if there are missing participants.

We intended to seek data on the number of participants randomised to the intervention and control groups, irrespective of compliance and whether or not the participant was later thought to be ineligible or was otherwise excluded from the treatment group or follow-up. If we were unable to do so, we planned to record whether the results of each trial were based on an intention-to-treat analysis or on available participant analysis.

'Summary of findings' tables

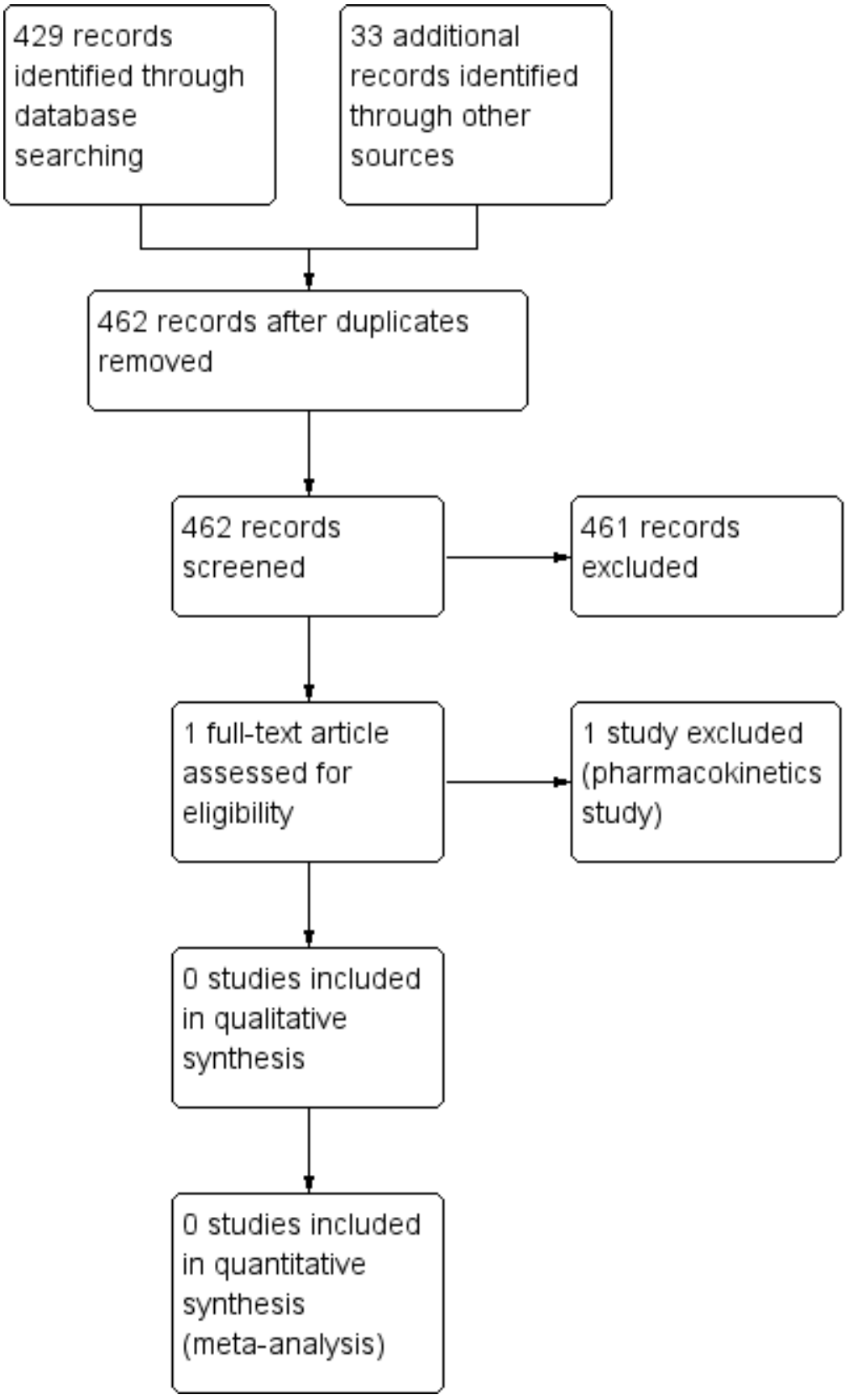
We intended to use the principles of the GRADE system (Guyatt 2011a) in order to assess the quality of the body of evidence associated with specific outcomes (mortality, failure to control bleeding, number of participants receiving a blood transfusion, number of blood transfusions, and adverse events) in our review and construct a 'Summary of findings' table using the GRADEPro software (ims.cochrane.org/revman/other-resources/gradepro). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias, the indirectness of the evidence, heterogeneity of the data, imprecision of effect estimates, and risk of publication bias (Balshem 2011; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2011i; Guyatt 2013a; Guyatt 2013b). We planned to assess the imprecision according to Jakobsen 2014.

RESULTS

Description of studies

The initial bibliographic search identified 462 studies. After manually checking the titles and abstracts, we identified one study to be evaluated further. We excluded the study by Pereira 2005 as it assessed the pharmacokinetics of vitamin K in people with liver diseases. We determined that none of the studies attempted to answer the research questions of this systematic review. See Figure 1.

Figure 1. Study flow diagram (25 February 2015).



Risk of bias in included studies

We included no studies.

Effects of interventions

The searches did not identify any randomised clinical trials eligible for inclusion in this systematic review. We identified no ongoing trials.

We found no quasi-randomised studies, historically controlled studies, or cohort studies that we could use to assess harms from vitamin K.

DISCUSSION

Summary of main results

We were unable to identify evidence from randomised clinical trials supporting or refuting the use of vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver disease associated with acquired coagulation disorders.

Overall completeness and applicability of evidence

In one multicentre hospital study on prescribing patterns for prophylaxis and treatment of complications on cirrhosis, Lucena et al. showed that at discharge, vitamin K was utilised in 24% (range 4% to 53%) of the trial participants (Lucena 2002). Lucena et al. also observed that there was a wide variability in prescribing practices across centres, and that the use of non-evidence based treatments such as vitamin K was higher than expected (Lucena 2002). In contrast to these observed practices, other studies have shown that there is a risk of anaphylactoid reactions associated with the use of vitamin K (Pereira 1998; ADRAC 2000; Fiore 2001).

It is widely known that clinicians make practical decisions, often on the basis of inadequate information. Decisions on treatment should be taken based on the results of randomised clinical trials (Alderson 2004; Chalmers 2004).

The basis for the rational use of vitamin K in people with liver disease with upper gastrointestinal bleeding remains unknown. Randomised clinical trials to answer the research question of this systematic review have not yet been carried out. It is possible that some studies have been carried out, but due to their negative results, they remained unpublished (Easterbrook 1991; Gluud 1998). This causes publication bias, reducing the possibilities to develop valid systematic reviews in certain areas. The existence of high-quality data sufficient to make strong recommendations for an intervention varies considerably across specialities (Diringer 2003). This is influenced by a number of factors, from the prevalence of the conditions to the resources available to do research. Keeping clinical uncertainty does not benefit people and may increase health-service costs (Alderson 2000). However, admitting clinical uncertainty helps clarify treatment options and encourages further research (Alderson 2000; Diringer 2003). The paucity of data on vitamin K for people with upper gastrointestinal bleeding in liver disease should stimulate the development of well-planned randomised clinical trials to try to give a response to this widespread practice for upper gastrointestinal bleeding in people with liver disease.

Quality of the evidence

We were unable to identify evidence from randomised clinical trials supporting the use of vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver disease associated with acquired coagulation disorders.

Potential biases in the review process

In the process of performing this systematic review, we also planned to look for 'significance-chasing biases' (Ioannidis 2010), which include, among others, publication bias, selective outcome reporting bias, selective analysis reporting bias, and fabrication bias. Publication bias represents a major threat to the validity of systematic reviews, particularly in reviews that include small trials. However, this Cochrane review contains no trials and as such, we did not evaluate risk of bias. Trials with 'negative' results may have remained unpublished as suppression of information on specific outcomes may have occurred (Ioannidis 2010). We were unable to identify evidence from randomised clinical trials supporting the use of vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver disease associated with acquired coagulation disorders.

Agreements and disagreements with other studies or reviews

We were unable to identify evidence from randomised clinical trials supporting or refuting the use of vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver disease associated with acquired coagulation disorders.

AUTHORS' CONCLUSIONS

Implications for practice

We found no randomised clinical trials of vitamin K for upper gastrointestinal bleeding for inclusion in this review. Therefore, it was not possible to determine whether vitamin K is beneficial or harmful for upper gastrointestinal bleeding in people with liver diseases. Accordingly, we cannot recommend or refute vitamin K for upper gastrointestinal bleeding in people with acute and chronic liver disease.

Implications for research

This systematic review has identified the need for well-designed, adequately powered randomised clinical trials to assess the benefits and harms of vitamin K as a way of improving the survival and decreasing mortality from upper gastrointestinal bleeding in people with liver diseases. Potential trials should be planned according to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Chan 2013a; Chan 2013b). The trials should be reported according to the CONSORT (CONsolidated Standards Of Reporting Trials) statement (Moher 2010), which helps in improving the quality of reporting of benefits and harms in clinical research (Ioannidis 2004; Moher 2010). Trials should include participant-centred outcomes such as mortality, re-bleeding, and serious and non-serious adverse events as recommended by the Patient-Centered Outcomes Research Institute (P-CORI) statement (Selby 2013; Frank 2014; Selby 2014).

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Contact editors: Brian Davidson, UK; Christian Gluud, Denmark.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Pereira 2005	A pharmacokinetics randomised trial on vitamin K in people with liver diseases.

APPENDICES

Appendix 1. Search strategies

Name of database	Time span of search	Search strategy
The Cochrane Hepato-Biliary Controlled Trials Register	February 2015.	(vitamin k OR phylloquinon* OR menaquinon* OR menadion*) AND liver disease*
Cochrane Central Register of Controlled Trials (CENTRAL)	Issue 2 of 12, 2015.	#1 MeSH descriptor: [Vitamin K] explode all trees #2 (vitamin* next K) or phylloquinon* or menaquinon* or menadion* #3 #1 or #2 #4 MeSH descriptor: [Gastrointestinal Hemorrhage] explode all trees #5 bleed* or h*emorrhage* #6 #4 or #5 #7 MeSH descriptor: [Liver Diseases] explode all trees #8 liver disease* #9 #7 or #8 #10 #3 and #6 and #9
MEDLINE (Ovid SP)	1946 to February 2015.	1. exp Vitamin K/ 2. ('vitamin K' or phylloquinon* or menaquinon* or menadion*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 3. 1 or 2 4. exp Gastrointestinal Hemorrhage/ 5. (bleed* or h*emorrhage*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 6. 4 or 5 7. exp Liver Diseases/ 8. liver disease*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 9. 7 or 8

(Continued)

		10. 3 and 6 and 9 11. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 12. 10 and 11
EMBASE (Ovid SP)	1974 to February 2015.	1. exp vitamin K group/ 2. ('vitamin K' or phylloquinon* or menaquinon* or menadion*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. 1 or 2 4. exp gastrointestinal hemorrhage/ 5. (bleed* or h*emorrhage*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 6. 4 or 5 7. exp liver disease/ 8. liver disease*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 9. 7 or 8 10. 3 and 6 and 9 11. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 12. 10 and 11
Science Citation Index EXPANDED	1900 to February 2015.	#6 #5 AND #4 #5 TS=(random* or blind* or placebo* or meta-analys*) #4 #3 AND #2 AND #1 #3 TS="liver disease*" #2 TS=(bleed* or h*emorrhage*) #1 TS=("vitamin K" or phylloquinon* or menaquinon* or menadion*)
LILACS	1982 to February 2015.	(1) Vitamin K (2) liver diseases (3) 1+2 (4) ((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS))

(Continued)

		(5) 3 + 4
World Health Organization Clinical Trials Search Portal	25 February 2015.	Upper gastrointestinal bleeding AND liver disease AND vitamin K
metaRegister of Controlled Trials (mRCT)	25 February 2015.	liver disease AND vitamin K

WHAT'S NEW

Date	Event	Description
17 March 2015	New citation required but conclusions have not changed	No change in conclusion. Randomised clinical trials are still lacking.
25 February 2015	New search has been performed	Searches performed in February 2015; however, there were still no trials on the subject of our review.

CONTRIBUTIONS OF AUTHORS

AMC took the lead on writing up the protocol based on the draft versions, with comments from IS (Marti-Carvajal 2004).

Further contribution to the review:

- searching: The Cochrane Hepato-Biliary Controlled Trials Register;
- selection of trials for inclusion: AMC, IS;
- methodological assessment and extraction of data: AMC, IS;
- data entry and management: AMC;
- data analysis: AMC and IS;
- preparation of the review: AMC, IS.

AMC is guarantor for the review.

Both authors approved the final review manuscript for publication.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Centro Cochrane Iberoamericano, Spain.

  Academic.
- Cochrane Hepato Biliary, Denmark.

  Academic.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We re-arranged the outcomes in terms of what the most relevant outcomes are for the people with liver disease.
- We planned 'Summary of findings' tables and the outcomes reported within them and will apply these when we identify trials for inclusion.
- We planned trial sequential analysis and will apply this when we identify trials for inclusion.

NOTES

This review will not be updated until relevant for the review randomised clinical trials are published.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Antifibrinolytic Agents [*therapeutic use]; Chronic Disease; Gastrointestinal Hemorrhage [*drug therapy] [etiology]; Liver Diseases [*complications]; Vitamin K [*therapeutic use]

MeSH check words

Humans