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Preoperative alcohol cessation prior to elective surgery (Review)

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[Intervention Review]

Preoperative alcohol cessation prior to elective surgery

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ABSTRACT

Background

Hazardous drinking has been associated with an increased postoperative complication rate after surgery. Common complications include postoperative infections, cardiopulmonary complications, and bleeding episodes. Preoperative abstinence may to some degree reverse alcohol-induced pathophysiological processes and thus prevent postoperative complications.

Objectives

To assess the effect of preoperative alcohol cessation interventions on the rate of postoperative complications including mortality in hazardous drinkers. To assess the effect of preoperative alcohol cessation interventions for hazardous drinkers on alcohol use in the postoperative period and in the long term.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 9); Ovid MEDLINE (1966 to September 2011); Ovid EMBASE (1966 to September 2011); CINAHL via EBSCOhost (1982 to September 2011). We combined the MEDLINE search strategy with the Cochrane highly sensitive search strategy, as contained in the *Cochrane Handbook for Systematic Reviews of Interventions*, to identify randomized controlled trials (RCTs).

Selection criteria

We included all randomized controlled trials (RCTs) that evaluated the effects of a preoperative alcohol cessation intervention on postoperative complications or postoperative alcohol consumption, or both, in the short and long term in hazardous drinkers . We excluded intraoperative and postoperative alcohol interventions.

Data collection and analysis

Three authors independently assessed studies to determine eligibility and extracted data using a tool based on guidance in the *Cochrane Handbook for Systematic Reviews of Interventions*. Where required, we obtained additional information through collaboration with the original author. We presented the main outcomes as dichotomous variables. Where data were available, we planned to conduct subgroup analyses as well as a sensitivity analysis to explore risk of bias.

Main results

We included two studies which involved 69 patients. Both studies were RCTs evaluating the effect of intensive alcohol cessation interventions including pharmacological strategies for alcohol withdrawal and relapse prophylaxis.

Our primary outcome measure was postoperative complications and in-hospital and 30-day mortality. Meta-analysis showed an effect on the overall complication rates (odds ratio (OR) 0.22; 95% confidence interval (CI) 0.08 to 0.61; P = 0.004). There was no significant reduction of in-hospital and 30-day mortality (OR 0.39; 95% CI 0.06 to 2.83; P = 0.35).

Secondary outcomes included length of stay and postoperative alcohol use. No significant reduction was found.

Authors' conclusions

Based on the finding of two studies, it appears that intensive preoperative alcohol cessation interventions, including pharmacological strategies for relapse prophylaxis and withdrawal symptoms, may significantly reduce postoperative complication rates. No effect was found on mortality rates and length of stay.

The effect of preoperative alcohol cessation intervention should be further explored in an effort to reduce the adverse effect of alcohol use on surgical outcomes. The number needed to screen to identify eligible patients for alcohol intervention studies in surgical settings seems to be extremely high. This may indicate that these studies are difficult to perform. Nevertheless, timing, duration and intensity of alcohol cessation interventions need to be subject to further investigation.

PLAIN LANGUAGE SUMMARY

The effect of alcohol cessation on complications following surgery

Hazardous drinking affects human health in several ways, even in patients without an alcohol-related disease. These include an increased risk of surgical complications. In addition to the well known alcohol-induced disorders of the liver, pancreas, and nervous system; heavy drinking affects cardiac function, immune capacity (the body's ability to defend itself against infections), haemostasis (blood clot formation), and surgical stress responses. Cardiac insufficiency and arrhythmias (a disorder of the heart rate) are common among hazardous drinkers. Both are important risk factors for the development of postoperative complications, such as postoperative infections, cardiopulmonary complications (heart and lung complications), and bleeding episodes. Reduced immune capacity is found in most patients drinking three or more alcohol units (AU) per day.

The objective of this review was to assess the effect of alcohol interventions on complications following surgery. Interventions included all alcohol interventions aimed at helping patients to either quit drinking or to reduce their alcohol consumption before surgery. We identified two relevant studies involving 69 patients. Both studies involved intensive alcohol interventions aimed at complete alcohol cessation before surgery. The interventions included pharmacological (drug) strategies for alcohol withdrawal and relapse prophylaxis (relapse prevention) and were four to eight weeks in length (these interventions are comparable to the gold standard smoking cessation interventions).

The results showed that intensive interventions aimed at complete alcohol cessation reduced the number of complications. No effect was found on mortality rates (number of deaths) and length of stay.

Due to the small number of included studies, as well as the small size of the included studies, one should be careful about drawing firm conclusions based upon these results. More research is needed to clarify the most beneficial intervention programme. This includes research on the effect of reduced alcohol consumption and the most beneficial period of alcohol intervention programmes. However, as recruitment of patients to this field of research seems challenging, these studies may be difficult to perform.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Preoperative alcohol cessation intervention versus treatment as usual for hazardous drinking

Patient or population: patients with hazardous drinking
Settings: surgical
Intervention: preoperative alcohol cessation intervention versus treatment as usual

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pre-operative alcohol cessation intervention versus treatment as usual				
Postoperative complications number of complications Follow-up: mean 1 months	**Study population**		**OR 0.22** (0.08 to 0.61)	69 (2 studies)	⊕⊕⊕◯ **moderate**[1]	
	618 per 1000	**262 per 1000** (114 to 496)				
	Moderate					
	603 per 1000	**250 per 1000** (108 to 481)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Not blinded intervention

BACKGROUND

Description of the condition

Alcohol abuse with heavy or hazardous drinking is of widespread concern internationally. Sufficient evidence exists to indicate that alcohol is a significant threat to world health (WHO 2001). Worldwide, alcohol is linked to 1.8 million deaths per annum and global alcohol consumption continues to increase (WHO 2008). In the UK, the number of alcohol-attributable admissions for 2005 to 2006 was 909 per 100,000 men and 510.4 per 100,000 women (NICE 2008). In Europe, the prevalence of hazardous drinkers in surgical settings has been reported to range from 7% to 49% for patients undergoing elective surgical procedures, and 14% to 38% for emergency surgical procedures (Kip 2008; Tønnesen 2003; Tønnesen 2009).

Hazardous drinking affects human physiology in several ways, even in the absence of end stage disease. In addition to the well known alcohol-induced disorders of the liver, pancreas, and nervous system, heavy drinking affects cardiac function, immune capacity, haemostasis, and endocrine stress responses (Spies 2001). Subclinical cardiac insufficiency and arrhythmias are common among hazardous drinkers (Tønnesen 1992b), and both are important risk factors for the development of postoperative complications. Reduced immune capacity is found in most patients drinking three or more alcohol units (AU) per day (Tønnesen 2003). This has been explained by suppressed cellular elements of the immune system and suppression of delayed-type hypersensitivity reactions (DHT) (Tønnesen 2009). For surgical patients, the poor DHT response is further suppressed by the surgical trauma per se and the result may be a compromised postoperative immune system (Spies 2004). Prolonged bleeding time and an increased endocrine stress response during surgery are other pathophysiological mechanisms that may contribute to increased complication rates among hazardous drinkers (Tønnesen 1999b). The increased endocrine stress can be measured by increased epinephrine, norepinephrine, and cortisol blood levels (Spies 2004; Tønnesen 1999a).

Preoperative alcohol-induced organ dysfunction adds to the burden of the disease requiring surgery and the stress response from the surgical procedure itself. The result may be a poor surgical outcome. The postoperative complication rate has been reported to be increased by about 50% at an intake of 3 to 4 AU/day when compared to an intake of 0 to 2 AU/day. The complication rate for patients drinking more than 5 AU/day has been reported to be increased by 300% to 500%. Common postoperative complications include postoperative infections, cardiopulmonary complications, and bleeding episodes (Tønnesen 2003). Preoperative abstinence may to some degree reverse alcohol-induced pathophysiological processes, and postoperative complications might be preventable with preoperative alcohol cessation (Tønnesen 1999a; Tønnesen 2003).

In this review, hazardous drinking was defined as an alcohol consumption equivalent to three or more AU/day (with one AU equating to 12 grams of ethanol). This corresponds to the amount of alcohol associated with increased postoperative complication rates in most clinical studies (Tønnesen 2009).

Description of the intervention

Available Cochrane reviews on alcoholism treatment evaluate pharmacological and psychosocial interventions and show some efficacy for benzodiazepine to treat alcohol withdrawal (Amato 2010) and for acamprosate and opioid antagonists to treat alcohol dependence (Rösner 2010a; Rösner 2010b). Anticonvulsants have not been found efficient to treat alcohol withdrawal (Minozzi 2010). Disulfiram has shown some effect on short-term abstinence and days until relapse (Jørgensen 2011).

Brief alcohol interventions include advice and a short intervention but no pharmacological strategies. They are based on a motivational interviewing technique and generally aim for reduced alcohol intake and not for alcohol cessation. Two Cochrane reviews have reported that these interventions are effective in reducing alcohol intake for patients in primary care and for general hospital populations (Kaner 2007; McQueen 2009).

In the surgical setting, preoperative alcohol cessation interventions vary in intensity and timing (Shourie 2006; Tønnesen 1999a). Intensive interventions last from four to eight weeks and include complete alcohol cessation before surgery. They are comparable to the gold standard intervention programmes for smoking cessation. Intensive alcohol cessation interventions include empowerment of the patient, information and recommendation, treatment of alcohol withdrawal, relapse prophylaxis supported by pharmacological strategies, and follow up by expert staff. The potential effect of preoperative alcohol cessation interventions on postoperative complications is related to their effect on reducing alcohol consumption and the timing and intensity of the intervention (Tønnesen 2009).

Since the surgical setting is characterized by a fixed operation date, a relatively short preoperative period, and a minimal length of hospital stay, alcohol cessation intervention programmes in this setting need to be very effective.

How the intervention might work

Preoperative abstinence may to some degree reverse the pathophysiological processes seen among hazardous drinkers (Tønnesen 2003). Preoperative abstinence has been shown to significantly reduce the incidence of arrhythmia in the postoperative period (Tønnesen 1999b). Two weeks of abstinence from alcohol significantly improves DHT, and after eight weeks DHT has been shown to be normalized (Tønnesen 1992a). The prolonged bleeding time seen in the perioperative period is also reversible, and four weeks

of abstinence from alcohol improves the stress response to surgery (Tønnesen 1999a).
The relatively short period of abstinence required to normalize dysfunctioning organ systems among hazardous drinkers may explain the beneficial effects of alcohol cessation interventions on postoperative complication rates.

Why it is important to do this review

Anaesthesiologists include screening for high alcohol intake in their preoperative assessment of patients for surgical risk. Although a large number of patients are screened and found to be at risk, alcohol cessation interventions are not routinely applied.
This review maps out the evidence on alcohol cessation interventions in the surgical setting and describes their effects on postoperative complications. Without a rigorous review of the evidence for, and against, these interventions, there is a danger that they will be adopted without a clear benefit for the patients. On the other hand, if the effectiveness of preoperative alcohol cessation interventions can be established, they may add an effective intervention for reducing postoperative complication rates and should then be routinely applied.
Preoperative screening provides not only the opportunity to identify patients for preventative preoperative interventions but also presents an opportunity to screen large and diverse patient populations for at-risk drinking (Kip 2008). Alcohol screening followed by effective alcohol cessation interventions may play an important role in preventing severe consequences of alcohol use disorder (AUD) and thereby contribute to an improvement in public health (Kip 2008). Although this is not the primary concern of this review, the short- and long-term effects of alcohol interventions on alcohol use were assessed.

OBJECTIVES

- To assess the effect of preoperative alcohol cessation interventions on the rate of postoperative complications including mortality in hazardous drinkers.

- To assess the effect of preoperative alcohol cessation interventions for hazardous drinkers on alcohol use in the postoperative period and longer term.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) that evaluated the effects of pharmacological and psychosocial preoperative alcohol cessation interventions on postoperative complications or postoperative alcohol consumption, or both, in the short and long term.

Types of participants

We included studies involving hazardous drinkers undergoing all types of surgical procedures under general anaesthesia, regional anaesthesia, or sedation who were given a preoperative alcohol cessation or control intervention. We included studies of inpatients as well as studies in a day or ambulatory care facility. We excluded studies of non-surgical patients.

Types of interventions

Our interventions of interest were all pharmacological and psychosocial preoperative alcohol cessation interventions, given in relation to a surgical procedure, that aimed to stop or reduce alcohol consumption preoperatively. We considered both brief and intensive interventions, including interventions with pharmacological strategies for alcohol withdrawal and relapse prophylaxis. The control groups included surgical patients receiving treatment as usual (TAU) and an assessment of their alcohol history.
We excluded trials of intraoperative and postoperative alcohol interventions.

Types of outcome measures

Primary outcomes

1. Any type of postoperative complication (e.g. wound-related complications, secondary surgery, cardiopulmonary complications, and admission to intensive care)
2. In-hospital and 30-day mortality

Postoperative complications were a composite outcome and were defined by the need for treatment.

Secondary outcomes

1. Length of stay (LOS)
2. Prevalence of non-hazardous drinkers in the postoperative period (three, six, nine, and 12-month follow up)
3. Prevalence of non-alcohol use disorder (non-AUD) patients in the postoperative period (three, six, nine, and 12-month follow up)
4. Postoperative alcohol consumption (grams of alcohol/week) (three, six, nine, and 12-month follow up)

We reported length of stay in number of days from admission to discharge.

We defined hazardous drinking as an alcohol consumption equivalent to three or more alcohol units (AU) per day (with one AU equating to 12 grams of ethanol).
AUD was defined by validated questionnaires such as the Alcohol Use Disorder Identification Test (AUDIT) (Babor 2001; Bradley 1998); Michigan Alcoholism Screening Test (MAST) (Selzer 1971); and CAGE (Cut down; Annoyed; Guilty; Eye-opener) (O'Brien 2008).
Postoperative alcohol consumption was self reported with or without biochemical validation. Self reported alcohol consumption is often underestimated (but never overestimated). Biochemical validation might include false positive and negative results (Neumann 2008). We planned to perform a sensitivity analysis including biochemically validated studies.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 9) (Appendix 1*);* Ovid MEDLINE (1966 to September 2011) (Appendix 2); Ovid EMBASE (1966 to September 2011) (Appendix 3); CINAHL via EBSCOhost (1982 to September 2011) (Appendix 4).
We combined the MEDLINE search strategy with the Cochrane highly sensitive search strategy for identifying RCTs as contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Searching other resources

We searched for trials by manually searching abstracts of appropriate conference proceedings.
We checked the reference lists of relevant articles. We contacted relevant trial authors to identify any additional or ongoing studies.
We also searched for trials on specific sites:

1. http://www.controlled-trials.com;
2. http://clinicaltrials.gov;
3. http://www.centerwatch.com.

We did not apply any language or publication date restrictions.

Data collection and analysis

Selection of studies

Two authors (KO and HT) independently scanned the titles and abstracts of reports identified by the search strategies.
We retrieved and evaluated potentially relevant studies, chosen by at least one author, using full-text versions.
Two authors (KO and HT) independently assessed the congruence of trials with the review's inclusion criteria (Appendix 5). We resolved disagreements by discussion with a third author (AM).
Studies formally considered and excluded are listed and reasons for exclusion given in the Characteristics of excluded studies.

Data extraction and management

Three authors (KO, BP, and HT) independently extracted data using a tool based on guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (Appendix 6; Appendix 7; Appendix 8). We resolved disagreements by discussion with a fourth author (AM). Where required, additional information was obtained through collaboration with the original author.

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each trial. To avoid potential bias, HT and KO independently evaluated the included studies. In case of disagreement, a third author would have been contacted. However, there were no disagreements.
To draw conclusions about the overall risk of bias for an outcome, we evaluated domains such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting as well as recruitment, follow-up rates, and other sources of bias. Any assessment of the overall risk of bias involved consideration of the relative importance of the different domains (Higgins 2011).
Even the most realistic assessment of the validity of a study may involve subjectivity since it is impossible to know the extent of bias (or even the true risk of bias) in a given study. Some domains affect the risk of bias across outcomes in a study, for example random sequence generation and allocation concealment, while others such as blinding and incomplete outcome data may have different risks of bias for different outcomes within a study. Thus, the risk of bias is not the same for all outcomes in a study. When examining blinding as a component of the risk of bias, we planned to perform separate sensitivity analyses for patient-reported outcomes (subjective outcomes) and for mortality (Higgins 2011).
We defined the trials as having low risk of bias only if they adequately fulfilled the criteria listed in the Cochrane Handbook. We performed summary assessments of the risk of bias for each important outcome (across domains) within and across studies, and applied a 'Risk of bias' graph and a 'Risk of bias summary' figure (Higgins 2011).

Random sequence generation

Low risk of bias: the method used generated random sequences, e.g. random number generation or toss of coin.
Unclear: no available information on random sequence generation.
High risk of bias: alternate medical record numbers or other non-random sequence generation.

Allocation concealment

Low risk of bias: allocation method prevented investigators and participants from knowing the next allocation, e.g. central allocation; sealed opaque envelopes; serially-numbered or sequentially-numbered but otherwise identical vehicles, including their contents; or other descriptions of convincing concealment of allocation.
Unclear: no information on allocation method were available or the description did not allow a clear distinction.
High risk of bias: allocation method allowed the investigators or participants, or both, to know the next allocation, e.g. alternate medical record numbers; reference to case record numbers or date of birth; and open allocation sequence, such as unsealed envelopes.

Blinding

Low risk of bias: patients and outcome assessors were kept unaware of intervention allocations after inclusion of participants into the study.
Unclear: blinding was not described.
High risk of bias: no blinding of patients and outcome assessors; categorized as an open-label study; or without use of placebo.

Follow up

Low risk of bias: the numbers and reasons for dropouts and withdrawals in the intervention groups were described, or it was specified that there were no dropouts or withdrawals.
Unclear: the report gave the impression that there were no dropouts or withdrawals but this was not specifically stated.
High risk of bias: the numbers or reasons for dropouts and withdrawals were not described.

Measures of treatment effect

Postoperative complications were a composite outcome and included any type of complication that required intervention, for example wound-related complications, postoperative bleeding, secondary surgery, cardiopulmonary complications, and admission to intensive care. Treatment effects were reported by odds ratio (OR). We reported in-hospital and 30-day mortality if this was reported in included trials (mean difference). We reported the length of stay in number of days from admission to discharge.
We reported postoperative hazardous drinking based on the number of AU consumed per day (OR). We defined hazardous drinking by an alcohol consumption equivalent to three or more AU/day; this is equivalent to 36 grams of alcohol or more (12 g x 3 AU). We measured treatment effect on alcohol consumption by self reported intake and validated questionnaires such as the Alcohol Use Disorder Identification Test (AUDIT) (Babor 2001); Michigan Alcoholism Screening Test (MAST) (Selzer 1971); CAGE (Cut down; Annoyed; Guilty; Eye-opener) (O'Brien 2008) with or without biochemical validation (OR and mean difference). We reported postoperative alcohol consumption as grams of alcohol consumed per week (mean difference). We reported treatment effects regarding postoperative alcohol use for three, six, nine, and 12 months when data were available.

Dealing with missing data

We contacted the authors of included studies regarding missing data. Where data were found to be missing and the authors were not accessible, we calculated missing statistics (such as standard deviations (SD)) from other quoted statistics (such as standard errors (SE) or confidence intervals (CIs)). If missing data remained we performed an available case analysis, excluding data where outcome information was unavailable.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant factors across trials, including age, gender, and characteristics of interventions. We assessed statistical heterogeneity by examining the I^2 statistic (Higgins 2002), a quantity which approximately describes the proportion of variation in point estimates that is due to heterogeneity rather than sampling error. If significant heterogeneity was present ($I^2 \geq 50\%$) (Higgins 2002), we investigated trials for possible explanations.
In the case of excessive clinical heterogeneity, no statistical analyses were performed to pool the results. Clinical heterogeneity included the type of intervention, outcome measures reported, and methodological quality.

Assessment of reporting biases

We assessed reporting bias in the quality assessment, particularly aspects regarding methodology. A thorough search for unpublished studies through grey literature searches and contact with known experts in the field also assisted in reducing the risk of publication bias. We planned to use a funnel plot analysis to examine publication bias.

Data synthesis

We entered data from all trials included in the systematic review into Review Manager (RevMan 5.1) and combined data quantitatively, where possible. We presented the main outcomes as dichotomous variables. We calculated weighted mean differences (with 95% confidence intervals (CI)) for outcome measures when possible. We calculated pooled estimates using the fixed-effect model unless there was significant heterogeneity ($I^2 \geq 50\%$), in which case we used the random-effects model.
We calculated 95% CIs for each effect size estimated, using Mantel-Haenszel (MH) for dichotomous outcomes and inverse variance (IV) for continuous outcomes.

The following treatment comparisons were planned: alcohol cessation intervention versus assessment only, and alcohol cessation intervention versus treatment as usual.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses where data were available, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to compare:

- different types of surgery (e.g. orthopaedic and general surgery);

- intensive alcohol cessation intervention and brief intervention.

Intensive interventions were defined as interventions with pharmacological strategies for alcohol withdrawal and relapse prophylaxis. Brief interventions comprised a single session and up to a maximum of four sessions of engagement with a patient and the provision of information and advice that was designed to achieve a reduction in alcohol consumption.

Sensitivity analysis

We planned to performed sensitivity analyses, when possible, to explore risk of bias. We planned to perform sensitivity analyses for self reported alcohol consumption versus self reported alcohol consumption with biochemical validation; and trial factors such as sequence generation, allocation concealment, blinding, and losses to follow up.

RESULTS

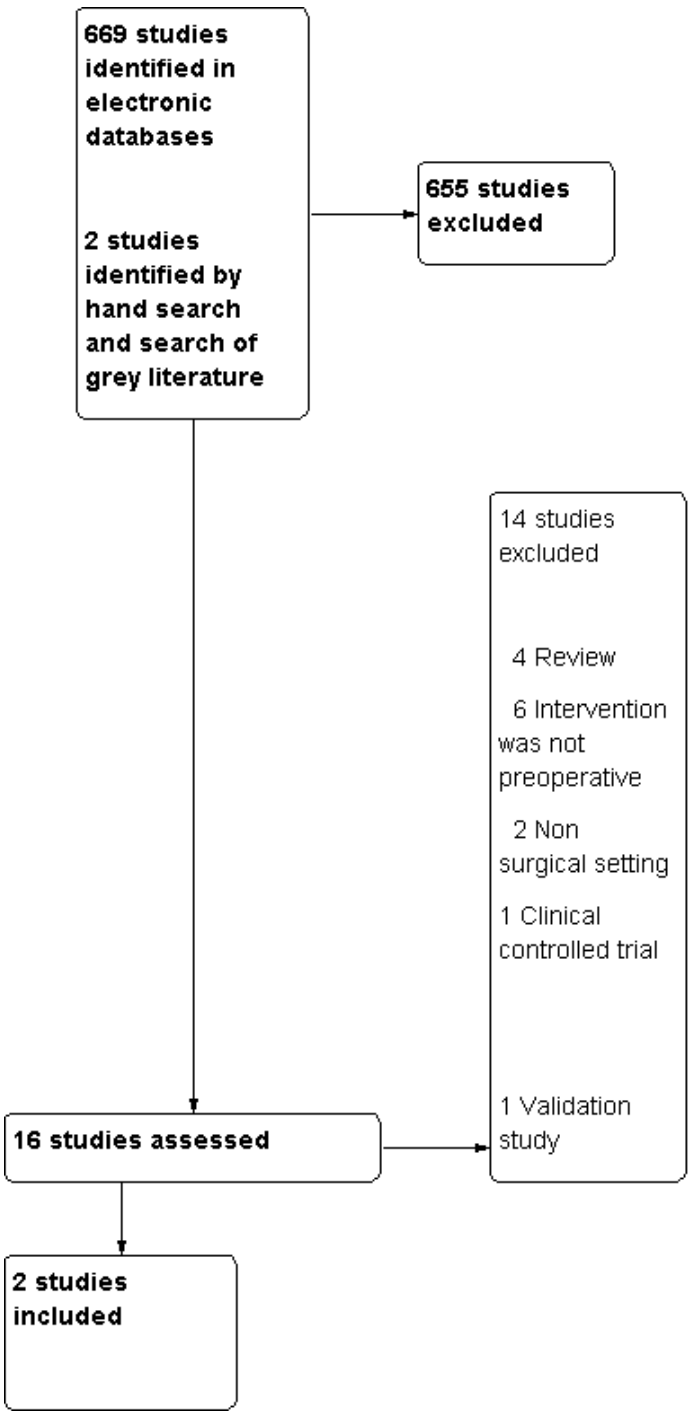
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

See Figure 1

Figure 1. Study flow diagram.



The electronic search resulted in 669 potentially relevant studies, which were screened by reviewing titles and abstracts. Two authors (KO, HT) excluded obviously irrelevant studies based on title and abstract. We excluded 655 studies leaving 14 potentially relevant studies. Two independent authors (KO, HT) read the abstracts and full texts for these 14 studies. In addition, we identified two further potentially relevant studies by searching other resources.

Included studies

We identified two relevant studies as eligible to be included in this review (Tønnesen 1999a; Tønnesen 2002;). We included data from these studies, involving 69 participants at entry, in this review. The study characteristics are described in Characteristics of included studies.

Setting and patients

The two studies took place in Denmark (Tønnesen 1999a; Tønnesen 2002). The first study included radical colorectal resection patients (Tønnesen 1999a), the second included elective hip arthroplasty patients (Tønnesen 2002). Both studies aimed to recruit women and men.

Screening

Both studies used self reported alcohol consumption (Tønnesen 1999a; Tønnesen 2002) to identify eligible patients. In Tønnesen 1999a the eligibility criterion was daily alcohol consumption exceeding 60 g/day. In Tønnesen 2002 the eligibility criterion was alcohol consumption exceeding 60 g/day or 420 g/week.

Control

Control groups were defined as treatment as usual in both studies (Tønnesen 1999a; Tønnesen 2002). However, both involved a detailed assessment of patients' alcohol history.

Intervention

The two studies evaluated the effect of intensive alcohol cessation interventions including pharmacological strategies for alcohol withdrawal and relapse prophylaxis (Tønnesen 1999a; Tønnesen 2002).

In Tønnesen 1999a disulfiram (800 mg) was taken under supervision twice weekly until the week before surgery. The intervention aimed at one month preoperative cessation from alcohol.

In Tønnesen 2002 the intervention aimed at three months of preoperative alcohol cessation supported by disulfiram 800 mg/week, 400 mg taken under supervision and 400 mg taken without supervision. Chlordiazepoxide was offered for withdrawal symptoms. The intervention included motivational counselling together with a brief interview (all together about 30 minutes) every week. Project staff were available for the patients by phone in the daytime. All patients received B-vitamins.

Outcome

Both of the included studies reported postoperative complications defined as death or postoperative morbidity requiring treatment. Complications were reported retrospectively one-month postoperatively.

Mortality and length of stay was also reported (Tønnesen 1999a; Tønnesen 2002).

Both studies (Tønnesen 1999a; Tønnesen 2002;) reported postoperative alcohol consumption. They also reported alcohol consumption at time of surgery. Alcohol consumption was self reported and given in AU/day with an AU containing 12 g of ethanol.

In Tønnesen 1999a postoperative alcohol consumption was reported after four to eight weeks.

In Tønnesen 2002 postoperative alcohol consumption was reported after one and three months. In Tønnesen 2002 self reported alcohol consumption was validated by per cent carbohydrate deficient transferrin (CDT%).

Excluded studies

We excluded 13 studies. We have summarized the reasons for exclusion of these possibly relevant studies in the Characteristics of excluded studies. One study (Scand-ankle 2009) was an ongoing trial, and the characteristics of this study can be found in Characteristics of ongoing studies.

Risk of bias in included studies

Details of how and why we rated included studies on the following criteria are provided in the Characteristics of included studies. Figure 2 provides a summary of the overall risk of bias in the two studies, as high, low or unclear. Figure 3 provides details of judgements about each methodological quality item for each study.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

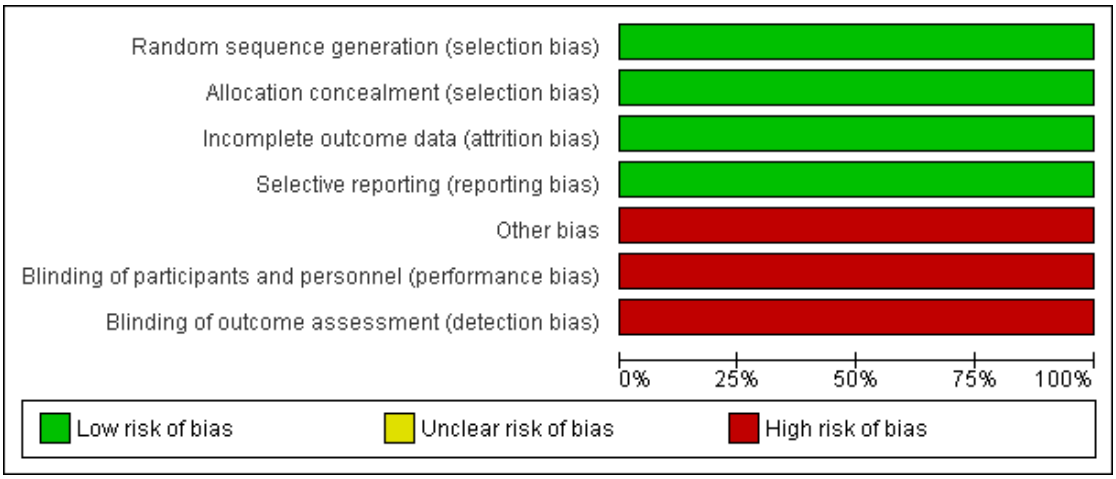
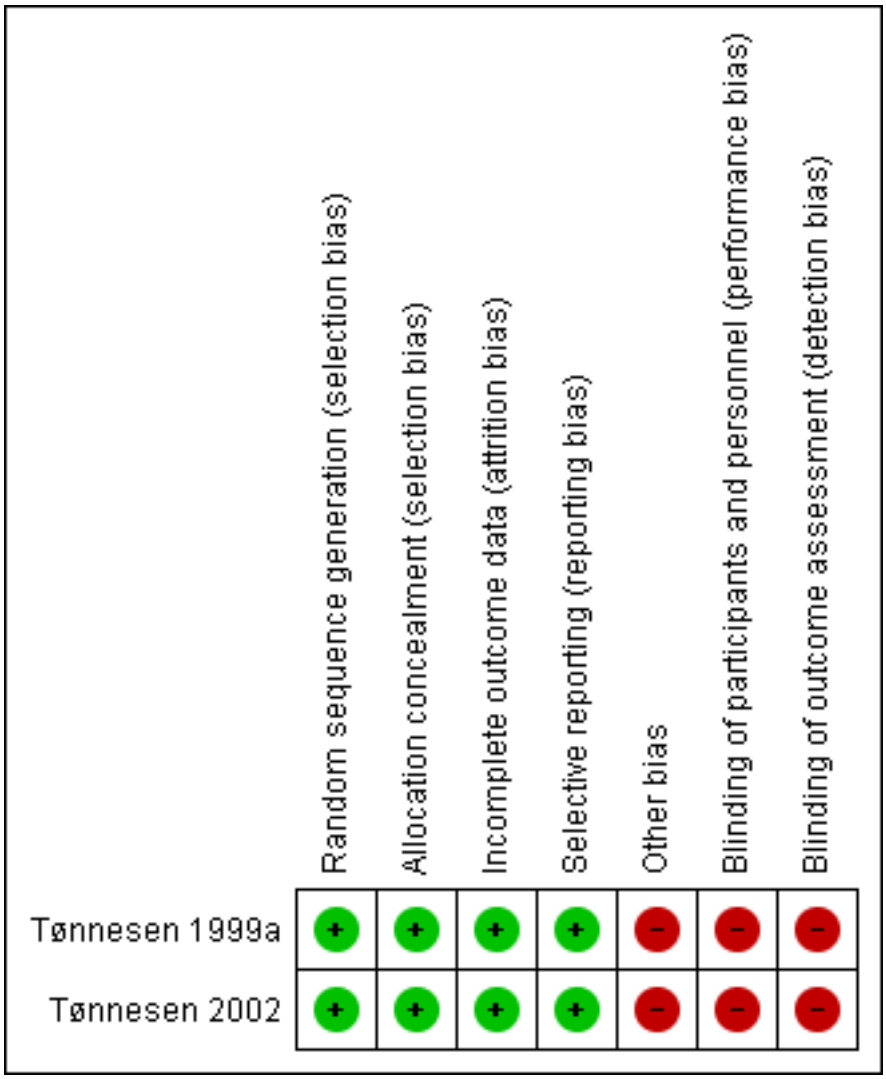


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Sequence generation for randomization was deemed to be adequate in the two studies (Tønnesen 1999a; Tønnesen 2002), both using a computer generated code, off-site data management, and opaque sealed envelopes. Only one of the studies (Tønnesen 2002) used block randomization with stratification for each centre, the blocks did not use varying block sizes.

Blinding

Due to the nature of the interventions, it was not possible to blind participants or staff providing the interventions. It was, however, possible to blind the outcome assessors. The outcome assessors were not blinded in any of the studies.

Incomplete outcome data

Incomplete data were assessed in both studies (Tønnesen 1999a; Tønnesen 2002;). In Tønnesen 1999a and Tønnesen 2002 the authors reported including patients before the final decision of operation was made and excluded patients after randomization

as they fulfilled the exclusion criteria later on in the preoperative period.

Selective reporting

Selective reporting bias was not recognized in any of the included studies.

Other potential sources of bias

In Tønnesen 1999a only three women were included, all were in the control group; Tønnesen 2002 only included men.
Recruitment seemed to be difficult in both studies as the number needed to screen to identify eligible patients was extremely high. Under-reporting of alcohol consumption may partly explain this problem and may contribute to selection bias as certain groups of patients may consider alcohol use as particularly sensitive information. Reluctance among staff to address patients' alcohol use may also contribute to the problem.

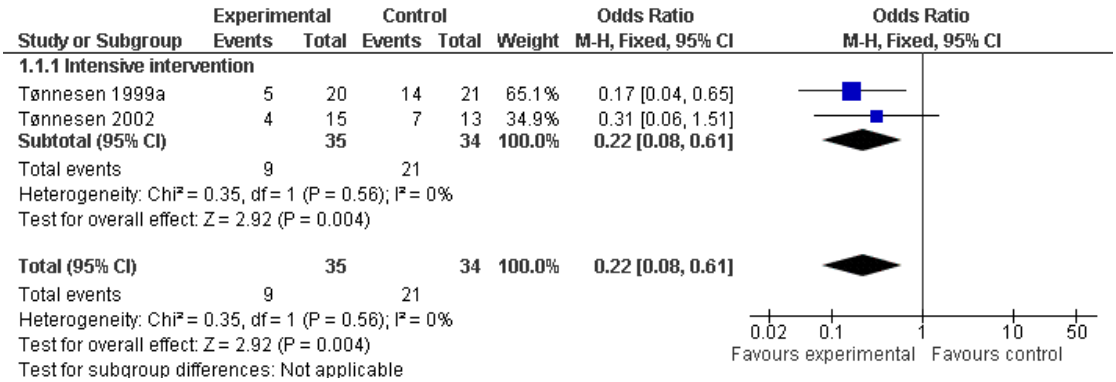
Effects of interventions

See: **Summary of findings for the main comparison** Preoperative alcohol cessation intervention versus treatment as usual for hazardous drinking
Only one of the studies (Tønnesen 2002) reported the number needed to screen (NNS) to identify patients eligible for inclusion. About 1900 patients were screened with a self administrated questionnaire: 1486 patients returned a filled questionnaire and 1133 underwent a hip replacement. Only 48 of these patients were eligible for inclusion; 25 were not included leaving 28 patients for randomization. The other study (Tønnesen 1999a) appeared to find similar problems with recruitment as the study took two and a half years to recruit 41 patients.
In Tønnesen 1999a the preoperative alcohol consumption was 84 g (60 to 480 g) per day in the intervention group and 72 g (60 to 480 g) per day in the control group at inclusion. All patients in the intervention group completed the programme of complete alcohol cessation, while the control group continued their drinking habits. In Tønnesen 2002 the preoperative alcohol consumption at inclusion was 72 g (60 to 156 g) per day in the intervention group and 72 g (60 to 96 g) per day in the control group. Of the 10 patients In the intervention group, nine stopped drinking and one reduced the alcohol intake from five to one AU/day. In the control group alcohol consumption was reported to be unchanged. CDT% was used as a biomarker.

Postoperative complications

Tønnesen 1999a and Tønnesen 2002 reported postoperative complications for 69 patients in total.
In the meta-analysis there was a significant reduction in the complication rate (OR 0.22; 95% CI 0.08 to 0.61; P = 0.004) (Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Preoperative alcohol cessation intervention versus treatment as usual, outcome: 1.1 Postoperative complications.



There was little clinical heterogeneity between the two studies, both regarding outcomes and the intensity of the interventions. Both studies reported postoperative complications retrospectively, for one month following surgery, and the alcohol cessation programmes were intensive and included pharmacological therapy.

In-hospital and 30-day mortality

Both studies, involving a total of 69 patients at entry, reported

mortality. The analysis did not show significant difference in the number of deaths between control and intervention groups (OR 0.39; 95% CI 0.06 to 2.83; P = 0.35) (Analysis 1.2). The number of deaths was low, thus there is uncertainty about the result.

Length of stay

Length of stay was reported in both studies. The analysis did not show a significant difference in length of stay between the control and intervention groups (mean difference 0.00; 95% CI -3.84 to 3.84; P = 1.00) (Analysis 1.3).

Hazardous drinking and alcohol use disorder (AUD)

Tønnesen 2002 and Tønnesen 1999a reported the effect of preoperative alcohol cessation intervention on hazardous drinking one month and three months after surgery. No significant reductions were found (OR 2.00; 95% CI 0.57 to 7.06; P = 0.28 and OR 18.47; 95% CI 0.93 to 368.76; P = 0.06 respectively) (Appendix 9).

No studies reported the effect of preoperative alcohol cessation intervention on the number of AUD patients in the postoperative period.

Postoperative alcohol consumption

Tønnesen 1999a reported postoperative alcohol consumption one month after surgery. The median alcohol consumption was 0 g/day (range 0 to 84 g/day) in the intervention group and 12 g/day (range 0 to 132 g/day) in the control group. The difference was not significant. Tønnesen 2002 reported the effect of alcohol cessation intervention on postoperative alcohol consumption at one and three months postoperatively. Alcohol consumption was significantly lower in the intervention group after one month (P = 0.05; the mean difference and 95% CI were not reported) but not after three months (mean difference -147.00; 95% CI -323.62 to -29.62; P = 0.10) (Appendix 9).

DISCUSSION

Summary of main results

This systematic review assessed the effectiveness of preoperative alcohol cessation interventions on postoperative complication rates and alcohol use. We included two studies involving a total of 69 patients. The two RCTs evaluated the effect of intensive alcohol cessation interventions including pharmacological strategies for alcohol withdrawal and relapse prophylaxis.

Our primary outcome measure was postoperative complications and in-hospital and 30-day mortality. Meta-analysis showed an effect on the overall complication rates (OR 0.22; 95% CI 0.08 to 0.61; P = 0.004). No significant reduction of in-hospital and 30-day mortality was found (OR 0.39; 95% CI 0.06 to 2.84; P = 0.35).

Secondary outcomes included length of stay and postoperative alcohol use. One study reported an effect of the alcohol cessation intervention on postoperative alcohol consumption at one month postoperatively (P = 0.05). Otherwise no significant reduction was found.

Overall completeness and applicability of evidence

Study participants

The studies used different methods to identify hazardous drinkers (daily alcohol consumption (quantity x frequency); weekly alcohol consumption (quantity x frequency)). Despite this there was consistency in baseline alcohol consumption levels for the included patients.

Although the two studies were open for both sexes, one of the studies managed to recruit men only (Tønnesen 2002). The other included a small number of women, but all of them were allocated to the control group (Tønnesen 1999a). No conclusion on gender effect can be drawn from our review due to an insufficient number of studies reporting outcomes for women.

Intervention

There was not substantial clinical heterogeneity between the studies. Both studies involved high intensity interventions including disulfiram and pharmacological strategies for withdrawal prophylaxis. No RCT reported the effect of brief alcohol intervention on postoperative complications.

Length of follow up

The postoperative period for which the postoperative complications were recorded was one month in both studies (Tønnesen 1999a; Tønnesen 2002).

Postoperative alcohol intake was reported at four to eight weeks in Tønnesen 1999a and at one and three months in Tønnesen 2002.

Completeness and applicability of evidence

Both included studies were written in English and conducted in Denmark. Thus, the applicability of the evidence may be limited to the Danish healthcare systems. The majority of the participants were men, and the results may not apply for women.

Quality of the evidence

Both RCTs (Tønnesen 1999a; Tønnesen 2002) reported adequate methods of randomization and allocation concealment. Due to the nature of the intervention it was not possible to blind the participants for the intervention. However, the outcome assessors could have been blinded, but none of the studies used blinded assessors. Lack of blinding may have influenced the effect size (Higgins 2011).

In both studies the authors reported including patients before the final decision of operation was made, and then excluded patients after randomization as they fulfilled the exclusion criteria later on in the preoperative period. In the meta-analysis for this review the number of randomized patients was used to describe the number of patients at entry.

In any case, both studies were small and in reality not powered to find a difference in mortality nor in the relatively rare postoperative complications.

Potential biases in the review process

The review was conducted according to our published protocol. After advice from the Cochrane Anaesthesia Review Group, we excluded controlled clinical trials (CCT). Thus Shourie 2006 was excluded as this study originally set out to be a RCT but was converted to a CCT after only including a few patients.

The search of electronic databases was considered adequate, and we performed a thorough search for unpublished studies through grey literature searches. One additional study (Tønnesen 2002) was identified through contact with known experts. This was an unpublished trial. We did not produce a funnel plot analysis to examine publication bias due to the small number of studies identified.

There were limited data on postoperative alcohol use in the included studies. We contacted relevant authors for data on hazardous drinking and AUD, but did not obtain adequate information to make such analyses. The small number of studies also limited the possibility of performing subgroup analysis and sensitivity analysis as planned.

One of the co-authors of this review has authored both studies (Tønnesen 1999a; Tønnesen 2002) which were included in this review. This is declared in the Declarations of interest section. To avoid potential bias, KO and HT independently assessed the congruence of trials with the review's inclusion criteria (Appendix 5). In case of disagreements a third author (AM) would have been contacted for discussion. However, no disagreement was found.

Agreements and disagreements with other studies or reviews

No comparable systematic reviews were found. One narrative review (Tønnesen 2009) performed on preoperative alcohol and smoking cessation interventions was identified. This review identified two studies (Tønnesen 1999a; Shourie 2006) and concluded that all patients presented for surgery should be questioned about hazardous drinking, and that interventions appropriate for the surgical setting should be applied. It further concluded that interventions must be intensive to obtain sufficient effect on postoperative complications. In our review we found evidence that intensive interventions including pharmacological strategies may be effective in prevention of postoperative complications but the evidence remains weak. We found no evidence for the effect of brief intervention on postoperative complications.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the findings of two studies, it appears that intensive preoperative alcohol cessation interventions including pharmacological strategies for relapse prophylaxis and withdrawal symptoms may significantly reduce postoperative complication rates. We found no effect of preoperative alcohol cessation intervention on mortality rates and length of stay. The number needed to screen to identify eligible patients was extremely high. The studies were small and influenced by several methodological flaws. Brief intervention was not examined in any of the included studies.

More knowledge is needed to clarify the most beneficial intervention programme, including the duration of preoperative abstinence or reduced alcohol consumption.

There was insufficient evidence to make conclusions on the effect of postoperative alcohol use. Due to the lack of studies, it was not possible to investigate the effect of the interventions in different subgroups of participants. In general, few women were included in the studies that were retrieved. The strength of evidence limits our capacity to draw robust conclusions.

Implications for research

The effect of a preoperative alcohol cessation intervention is promising and should be further explored in an effort to reduce the adverse effects of alcohol use on surgical outcomes. Recruitment to preoperative alcohol cessation intervention studies seems to be difficult. The timing, duration, and intensity of alcohol cessation interventions need to be subject to further investigation.

Finally, we need large randomized controlled trials powered to detect effects on mortality. As we know that these studies are very difficult to perform, large cohort studies or cluster randomized trials may add to the bank of evidence.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Tønnesen 1999a

Methods	RCT
Participants	Country of region: Denmark three centres; N = 41; Age: 37-76 years; Sex: mixed Clinical setting: Gastrointestinal surgery Inclusion criteria: Type of surgery, radical colorectal resection; Alcohol: ≥60 g/day Exclusion criteria: Clinical or historical evidence of alcohol related disorder (cirrhosis, hepatitis, pancreatitis, polyneuropathy, Wernicke-Korsakoff syndrome), disseminated malignant disease, bowel obstruction, drug abuse, psychiatric disease (other than alcohol abuse), insufficient Danish language skills, and withdrawal of informed consent
Interventions	Intensive intervention: Disulfuram (800mg) taken under supervision twice weekly until the week before surgery. The intervention aimed at one month preoperative withdrawal from alcohol Control group: Routine procedure (N = 21)
Outcomes	Follow up during admission: Daily until the 10th day actively: a self care score system (ranging from 0 for normal function and two for complete dependence) was repeated daily by nurses for fluid and food intake, personal and sanitary care, mobility and mental needs Follow up perioperatively: 1. Delayed type hypersensitivity measured by a skin test (applied at induction of anesthesia and measured at 48 hours) 2. Continuous EKG monitoring by Holter tape recording after the operation and until the third postoperative day, second operation, or assisted ventilation, whichever occurred first 3. In 2/3 centres arterial O_2 saturation was monitored during the first two postoperative nights 4. Serum cortisol, plasma glucose, plasma noradrenalin, plasma adrenaline, plasma interleukin-6 at start of operation, at 2, 4, 6, 8, 10 (not later than 8.00pm) and 24 hours 5. Heart rate and blood pressure was measured at 5 minutes intervals during surgery and 15 minutes intervals in the recovery ward 6. AU/day (self reported) Follow up at one month: 1. Postoperative complications retrospectively recorded for 1 month following surgery 2. Length of stay Follow up at four to eight weeks AU/day (self reported)
Notes	Median alcohol consumption before inclusion was 84g/day (60 to 480g/day) in the intervention group, and 72g/day (60 to 480g/day) in the control group

Risk of bias

Tønnesen 1999a (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated code
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes with consecutive numbers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow up: 2/21 control group and 4/20 intervention group. Intention-to-treat analysis was not performed. The authors report including patients before the final decision of operation was made, and that three patients in the control group and four patients in the intervention group were excluded after randomization
Selective reporting (reporting bias)	Low risk	Selective reporting was not identified
Other bias	High risk	Only three women were include, all were in the control group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	No

Tønnesen 2002

Methods	RCT
Participants	Country of region: Denmark, six centres; N = 28; Age: 39-75 years; Sex: mixed Clinical setting: Othopaedic surgery Inclusion criteria: Type of surgery, elective hip arthroplasty; Alcohol: ≥60 g/day or 420g/week Exclusion criteria: Uncompensated/uncontrolled chronic medical disease (such as liver cirrhosis, diabetes mellitus, severe heart- or lung disease), psychiatric disease, insufficient Danish language skills, no or subacute surgery and withdrawal of informed consent
Interventions	Intensive intervention: Aimed at three months of preoperative withdrawal from alcohol, supported by disulfiram 800mg/week, 400mg taken under supervision, and 400mg taken without supervision. Chlordiazepoxide was offered for withdrawal symptoms. The intervention included motivational counselling together with a brief interview (all together about 30 minutes) every week. Project staff were available for the patients by phone in the daytime. All patients received B-vitamins Control group: Routine procedure (N = 13)

Tønnesen 2002 (*Continued*)

Outcomes	Follow up during admission: 1. A self care score system (ranging from 0 for normal function to two for complete dependence) was repeated daily by nurses for fluid and food intake, personal and sanitary care, mobility and mental needs 2. AU/day (self reported) and biochemically validated (CTD%) Follow up at one month: 1. Postoperative complications defined by death or postoperative morbidity requiring treatment was retrospectively recorded 2. Harris Hip Score 3. Length of stay 4. AU/day (self reported) and biochemically validated (CTD%) Follow up at three months 1. AU/day (self reported) and biochemically validated (CTD%)
Notes	Only men were included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated code (block randomization with stratification for each centre)
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes with consecutive numbers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow up: 4/13 control group and 5/15 intervention group. The authors report including patients before the final decision of operation was made, four patients in the control group and five patients in the intervention group were excluded after randomization as they fulfilled the exclusion criteria in the preoperative period. They report both intention-to-treat and per protocol analysis based on the remaining patients
Selective reporting (reporting bias)	Low risk	Selective reporting was not identified
Other bias	High risk	Only men were included
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	No

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

Study	Reason for exclusion
Antti-Poika 1988	Intervention was not preoperative. Participants recruited from orthopaedic and trauma centre
Bejou 2000	Review of article, not primary research.
Chiang 1995	Review of articles, not primary research.
Forsberg 2000	Intervention was not preoperative. Participants recruited from emergency surgical ward. No control group. Comparison of two types of brief intervention
Gentilello 1999	Intervention was not preoperative. Participants recruited from level one trauma centre
Heather 1996	Participants recruited from general hospital wards.
Holloway 2007	Participants recruited from general medical and surgical wards
Schermer 2006	Intervention was not preoperative. Participants recruited from trauma centre
Shourie 2006	Controlled clinical trial.
Sommers 2006	Intervention was not preoperative. Participants recruited from level one trauma centre
Soria 1981	Review of articles, not primary research.
Vagts 2002	Review of articles, not primary research.
Watson 1999	Validation study of screening procedure.

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

Scand-ankle 2009

Trial name or title	Scand-ankle
Methods	RCT
Participants	Country of region: Denmark, Sweden and Norway, four centres; N = 160; Age: 18→ years; Sex: mixed Clinical setting: Othopaedic surgery Inclusion criteria: Type of surgery osteosynthesis, ankle fracture; Alcohol: ≥252g/week, randomization within 24 hours after entering the hospital Exclusion criteria: Major trauma involving other fractures or major lesions. Preoperative severe psychiatric disorder (including addiction to drugs, severe alcohol dependence; defined as experience of delirium or seizures during abstinence from alcohol, dementia) or conditions of reduced ability to give informed consent. Pathological fractures. Pregnancy and lactation. Allergy to benzodiazepines, anaesthesia, pain treatment or

Scand-ankle 2009 (*Continued*)

	disulfiram. Uncompensated chronic diseases (including fulminant cardiac or liver insufficiency, which are contraindications for disulfiram). ASA score 4-5. Cancelled operation. Withdrawal of informed consent
Interventions	Intensive intervention: Aimed at one month postoperative withdrawal from alcohol, supported by disulfiram 400mg/week, 200mg taken under supervision, and 200mg taken without supervision. Chlordiazepoxide offered for withdrawal symptoms. B-vitamins. The intervention included motivational counselling together with a brief interview (all together about 30 minutes) every week. Project staff available for the patients by phone Control group: Routine procedure (N = 80)
Outcomes	Primary outcomes: Follow up at 6 weeks, 3, 6, 9 and 12 months 1. Postoperative complications defined by death or postoperative morbidity requiring treatment. Retrospectively recorded at follow up. X ray at 12 months 2. Timeline follow back (AU/week), CIWA score, AUDIT (12 months) 3. Cost-effectiveness secondary outcomes: Follow up at 6 weeks, 3, 6, 9 and 12 months: 1. Length of stay 2. Nursing care 3. Convalescence 4. SF-36 5. CIWA 6. Alcohol markers 7. Estimates of cost-effectiveness regarding changes in QALY
Starting date	December 2009
Contact information	Hanne Tønnesen, MD, DMSc. Phone:+45 353 13 531. Mail: hanne.tonnesen@bbh.regionh.dk
Notes	

DATA AND ANALYSES

Comparison 1. Preoperative alcohol cessation intervention versus treatment as usual

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative complications	2	69	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.08, 0.61]
1.1 Intensive intervention	2	69	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.08, 0.61]
2 In-hospital and 30-day mortality	2	69	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.06, 2.83]
2.1 Intensive intervention	2	69	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.06, 2.83]
3 Length of stay	2	69	Mean Difference (IV, Fixed, 95% CI)	0.0 [-3.84, 3.84]
3.1 Intensive intervention	2	69	Mean Difference (IV, Fixed, 95% CI)	0.0 [-3.84, 3.84]

WHAT'S NEW

Last assessed as up-to-date: 22 September 2011.

Date	Event	Description
8 March 2013	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: KO (Kristian Oppedal), BP (Bolette Pedersen), HT (Hanne Tønnesen), AMM (Ann Merete Møller)

Co-ordinating the review: KO

Undertaking manual searches: KO, HT

Screening search results: KO, HT, AMM

Organizing retrieval of papers: KO

Screening retrieved papers against inclusion criteria: KO, BP, HT, AMM

Appraising quality of papers: KO, HT, AMM

Abstracting data from papers: KO, BP, HT

Writing to authors of papers for additional information: KO, BP

Providing additional data about papers: KO

Obtaining and screening data on unpublished studies: KO, BP, HT

Data management for the review: KO, BP, HT, AMM

Entering data into Review Manager (RevMan 5.1): KO, BP

RevMan statistical data: KO, BP, HT, AMM

Other statistical analysis not using RevMan: KO, BP

Double entry of data: (data entered by person one: KO; data entered by person two: HT)

Interpretation of data: KO, BP, HT, AMM

Statistical inferences: KO, BP, HT, AMM

Writing the review: KO, BP, HT, AMM

Securing funding for the review: KO

Performing previous work that was the foundation of the present study: KO, HT, AMM

Guarantor for the review (one author): KO

Person responsible for reading and checking review before submission: KO

DECLARATIONS OF INTEREST

Hanne Tønnesen has authored both studies (Tønnesen 1999a; Tønnesen 2002) which were included in this review.

Other authors: none known.

To avoid potential bias, HT and KO independently chose, evaluated, and abstracted the included studies. In case of disagreement, a third author would have been contacted. However, there were no disagreements.

SOURCES OF SUPPORT

Internal sources

- Alcohol and Drug Research Western Norway, Norway.

Salary, Kristian Oppedal

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

During the review process the Cochrane Anesthetic Research Group advised us not to include controlled clinical trials in the review. This was a change from the original published protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Elective Surgical Procedures; Alcohol Drinking [adverse effects; *prevention & control]; Postoperative Complications [*prevention & control]; Preoperative Care [*methods]; Randomized Controlled Trials as Topic; Secondary Prevention; Substance Withdrawal Syndrome [prevention & control]

MeSH check words

Humans