

Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial

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Abstract

Objective To evaluate the influence of preoperative abstinence on postoperative outcome in alcohol misusers with no symptoms who were drinking the equivalent of at least 60 g ethanol/day.

Design Randomised controlled trial.

Setting Copenhagen, Denmark.

Subjects 42 alcoholic patients without liver disease admitted for elective colorectal surgery.

Interventions Withdrawal from alcohol consumption for 1 month before operation (disulfiram controlled) compared with continuous drinking.

Main outcome measures Postoperative complications requiring treatment within the first month after surgery. Perioperative immunosuppression measured by delayed type hypersensitivity; myocardial ischaemia and arrhythmias measured by Holter tape recording; episodes of hypoxaemia measured by pulse oximetry. Response to stress during the operation were assessed by heart rate, blood pressure, serum concentration of cortisol, and plasma concentrations of glucose, interleukin 6, and catecholamines.

Results The intervention group developed significantly fewer postoperative complications than the continuous drinkers (31% *v* 74%, $P = 0.02$). Delayed type hypersensitivity responses were better in the intervention group before ($37 \text{ mm}^2 \text{ v } 12 \text{ mm}^2$, $P = 0.04$), but not after surgery ($3 \text{ mm}^2 \text{ v } 3 \text{ mm}^2$).

Development of postoperative myocardial ischaemia (23% *v* 85%) and arrhythmias (33% *v* 86%) on the second postoperative day as well as nightly hypoxaemic episodes (4 *v* 18 on the second postoperative night) occurred significantly less often in the intervention group. Surgical stress responses were lower in the intervention group ($P \leq 0.05$).

Conclusions One month of preoperative abstinence reduces postoperative morbidity in alcohol abusers. The mechanism is probably reduced preclinical organ dysfunction and reduction of the exaggerated response to surgical stress.

Introduction

During recent years several studies have shown a threefold increase in postoperative morbidity in alcohol misusers who drink at least five drinks (≥ 60 g ethanol) a day.¹⁻⁴ The misusers have prolonged hospital

stay and need more secondary surgery. The most common complications are infections, cardiopulmonary insufficiency, and episodes of bleeding. The pathogenic mechanisms are probably preoperative immunosuppression, preclinical cardiac insufficiency, haemostatic imbalance, and an exaggerated response to surgical stress.² In non-surgical patients such dysfunctions are often reversible after withdrawal from alcohol.⁵

We investigated the influence of 1 month of preoperative abstinence from alcohol on postoperative morbidity in a controlled randomised design.

Methods

Protocol

We planned to evaluate a minimal relevant difference above 50% between the groups. The complication rate in the alcohol misusers was estimated as 67-75%.²⁻⁴ We were willing to accept a high type I failure because of the relatively few side effects of intervention compared with the poor outcome otherwise, whereas we would not overlook a possible benefit in this high risk group ($2\alpha = 0.10$, $\beta = 0.05$). The number of included patients was then calculated to 2×18 . The inclusion criteria were alcohol misuse of five or more drinks (60 g of ethanol) a day without clinical or historical evidence of alcohol related illness (cirrhosis, hepatitis, pancreatitis, polyneuropathy, Wernicke-Korsakoff syndrome) in patients suffering from colorectal disease who probably required elective surgical intervention. Only patients without disseminated malignant disease or signs of bowel obstruction scheduled for intended radical surgery were included.

To avoid surgical delay the patients were included in the trial before the final decision for operation was made. Patients could therefore be excluded later by change of indication or date of operation. Other exclusion criteria were drug abuse, psychiatric disease (other than alcohol abuse), unfamiliarity with Danish language, and withdrawal of informed consent.

Assignment

Within each of three gastrointestinal surgical centres patients were randomised either to intervention, consisting of 1 month of preoperative withdrawal from alcohol and treatment with disulfiram (800 mg disulfiram taken during controlled supervision twice

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weekly until the week before surgery) or to control, which was the routine procedure. The allocation was based on computer generated random numbers. Information on intervention or routine procedure was enclosed in sealed, opaque envelopes with consecutive numbers (written on the envelope and inside on the information). This was performed by a colleague who did not otherwise take part in the study.

Perioperative procedure

Preoperative and intraoperative characteristics included the prognostic nutrition index,⁶ cardiac risk index,⁷ and ASA (American Society of Anesthesiologists) score⁸ (table 1). Thirty patients underwent a liver biopsy during the operation, none had histological signs of hepatitis or cirrhosis. The others had normal results on ultrasound examination and computed tomography of the liver.

Routine prophylaxis included pulmonary physiotherapy; intravenous cefuroxime 3 g and metronidazole 1.5 g or ampicillin 2 g, gentamicin 0.24 g, and metronidazole 1 g at the start of anaesthesia; and low molecular weight heparin; and stockings (TED, Kendan, Vedbæk, Denmark) from the day before surgery until mobilisation. Bowel preparation was different in the three centres: oral saline solution, hyperosmolar electrolyte mixture (Klean Prep, Norgine Lim, Harefield, Middlesex), or no preparation

Table 1 Characteristics of patients undergoing colorectal resection, according to whether they abstained from alcohol in month before operation. Figures are medians (range) unless states otherwise

Detail	Intervention group (no alcohol; n=16)	Control group (n=19)
No of men	16	16
Age (years)	58 (37-75)	61 (50-76)
Body mass index (kg/m ²)	24 (18-30)	28 (19-32)
No of non-smokers	7	8
Smokers (g/day)	20 (5-40)	20 (2-30)
Prognostic nutrition index (%) [*]	51 (14-63)	30 (12-52)
Cardiac risk index (points)	3 (3-15)	3 (3-10)
ASA score	II (II-III)	II (II-III)
No treated for chronic diseases:	5	6†
Heart failure	2	1
Angina pectoris	0	0
Hypertension	1	4
Chronic bronchitis	1	2
Asthma	1	0
IDDM/NIDDM‡	0	0
Operative procedure:		
Resection of transverse colon	1	1
Hemicolectomy	2	3
Sigmoid resection	3	4
Low anterior resection	4	5
Rectal amputation	1	1
Closure of stoma after Hartmann's resection	5	5
Diagnosis benign/malignant:	8/8	9/10
Dukes's type A	1	0
Dukes's type B	2	8
Dukes's type C	5	2
Duration of surgery (min)	185 (110-335)	180 (100-315)
No who did not have transfusion	12	15
Intraoperative transfusion (ml)	900 (600-2100)	1350 (600-3100)
Intraoperative infusion (ml)	2500 (2100-7000)	3000 (1400-4500)

^{*}Values above 50% are associated with increased postoperative morbidity.⁶

†One patient suffered from heart failure and hypertension.

‡IDDM=insulin dependent diabetes mellitus; NIDDM=non-insulin dependent diabetes mellitus.

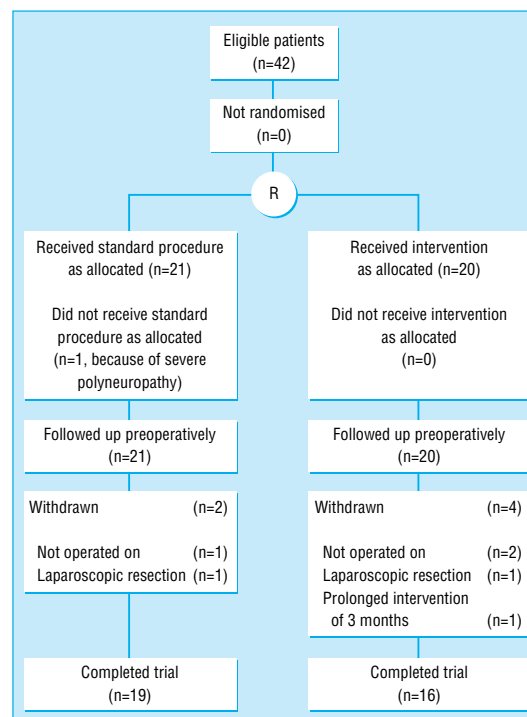


Fig 1 Trial profile of alcoholic patients who underwent colorectal resection. Intervention group abstained from alcohol for 1 month before operation

at all except for preoperative enema (Klyx, Ferring A/S, Copenhagen, Denmark).

Diazepam was used for premedication and intravenous midazolam, low dose fentanyl, nitrous oxide in oxygen, and isoflurane for general anaesthesia. All patients had epidural bupivacaine (0.5% 4-10 ml) plus morphine (2-4 mg) followed by infusion (see below) for supplemental anaesthesia. Continuous epidural infusion of bupivacaine (0.25%) and morphine (0.05 mg/ml) with a rate of 4-8 ml/h for 2-3 days was used in addition to a non-steroidal anti-inflammatory drug or paracetamol for treatment of postoperative pain. Infusion of glucose was not given intraoperatively. After surgery all patients received supplemental nasal oxygen (2 l/min) until next morning. Further oxygen was given on specific indication only. No patient received oxygen on the second night. The patients were mobilised from the day of surgery and recommended to drink and eat freely, except for patients with a rectal anastomosis who had only liquids until the first bowel movement.

The patients were followed up after 1 month, and clinical complications that required treatment were noted within this period. A self care score system (ranging from 0 for normal function to 2 for complete dependence) was repeated daily by the nurses for fluid and food intake, personal and sanitary care, mobility, and mental needs. The maximum score was 12.² Self care requirements were evaluated preoperatively and postoperatively until the 10th postoperative day. If a patient was discharged before then, the score on the last day in hospital was used for the remaining days.

Delayed type hypersensitivity was measured by a skin test (Multitest, Institute Merieux, Lyons, France) consisting of seven simultaneously applied delayed type hypersensitivity antigens: tetanus, diphtheria,

streptococcus, tuberculin, proteus, candida, and *Trichophyton*. The test was applied 2 days preoperatively and at induction of anaesthesia. The cutaneous responses were read as the sum of the indurated areas after 48 hours.

The patients underwent continuous monitoring for electrocardiographic changes by Holter tape recording (Spacelabs 90205, Spacelabs, Redmond, Washington, United States) after the operation and until the third postoperative day, second operation, or assisted ventilation, whichever occurred first. Tachycardia was defined as heart rate above 100 beats/min; arrhythmias as measurable ventricular ectopic activity (> 10 isolated ventricular beats/hour, polymorphic premature ventricular beats, or repetitive forms—that is, pairs, runs, or episodes of ventricular tachycardia) or atrial fibrillation; myocardial ischaemia as decrease in ST level on electrocardiography of more than 1 mV or increase of more than 1.5 mV from baseline measured at 60 ms from the J point.⁹ In two of the three centres arterial oxygen saturation was monitored during the first two postoperative nights (11 00 pm to 7 00 am) at the same time as Holter tape recording, by pulse oximetry (Nellcor N-3000, Nellcor Puritan Bennett, Pleasanton, California). Episodic hypoxaemia was defined as a sudden decrease in arterial oxygen saturation of 5% or more from baseline and constant hypoxaemia as mean saturation < 90%.⁹

Central venous blood was obtained by cannulation of the external jugular vein at the start of the operation and 2, 4, 6, 8, 10 (but not later than 8 00 pm), and 24 hours later. Heart rate and blood pressure was routinely measured every 5 minutes during surgery and every 15 minutes in the recovery ward.

Analysis

Plasma glucose concentration was measured at the bedside (Photometer, Haemocue AB, Ängelholm, Sweden) and serum cortisol concentration at the department of clinical biochemistry (RIA 1277 Gammamaster, LKB-Wallac Oy, Turku, Finland). Blood for analysis of catecholamines was collected in ice cold tubes containing EGTA (ethyleneglycol-bis (aminoethylether)-tetra-acetic acid) and reduced glutathione. Plasma samples were separated within 10 minutes in a refrigerated centrifuge and stored at -80°C until measurement by high pressure liquid chromatographic separation of radioenzyme labelled catecholamines¹⁰ (Amersham International, Buckinghamshire) with a sensitivity of 0.07 µmol/l. The variation within and between assays for measurement of noradrenaline was 3.8% and 8.5% and for adrenaline was 4.2% and 12.2%, respectively. Blood samples for interleukin 6 testing were collected on ice and followed the separating procedure for catecholamines. The tubes contained 7.5 µl/ml of ethylenediaminetetra-acetic acid and 12.5 µl/ml of aprotinin. Interleukin 6 was analysed by a commercially available enzyme linked immunosorbent assay (interleukin 6, Immunotech SA, Marseilles, France) with a detection limit of 3.9 pg/ml. The variation within and between assays was 1.8% and 5.7%. All analyses were performed blinded.

Table 2 Clinical complications after colorectal resection, according to whether patients had abstained from alcohol in month before operation

Detail	Intervention group (no alcohol; n=16)	Control group (n=19)	P value*
No of minor complications:	5	17	
Wound infections (requiring surgical intervention)	3	4	
Wound haematoma (surgical intervention)	0	1	
Pneumonia (stethoscopy and x ray confirmation)	0	5	
Thrombophlebitis (venography)	1	0	
Haematemesis	0	1	
Subileus (retention ≥ 7 days)	0	1	
Dehydration (readmission for IV rehydration)	0	2	
Urinary infection (≥ 10 ⁵ bacteria/ml)	1	2	
Fistula (external)	0	1	
No of major complications:	5	14	
Fascial rupture	0	3	
Intra-abdominal bleeding (requiring surgical intervention and transfusion)	0	1	
Intra-abdominal abscess (drainage)	1	2	
Anastomotic leakage (surgical intervention)	2	2	
Ileus (surgical intervention)	0	1	
Cardiopulmonary insufficiency (intensive care)	1	4	
Acute myocardial infarction (increased enzymes, ECG changes)	0	0	
Sepsis (bacteraemia and fever)	1	1	
Pulmonary embolism (positive ventilation/perfusion scintigraphy)	0	0	
Psychosis (hallucinations requiring pharmacological treatment)	0	0	
No of patients with:			
Any complication	5/16	14/19	0.02
Major complications	2/16	8/19	0.07
Minor complications	4/16	11/19	0.09
Patients who required secondary surgery:			
Intraperitoneal	2/16	8/19	0.07
Superficial	3/16	4/19	1.00
Mortality	1/16	2/19	1.00

*Fisher's exact test.

Statistics

Mann-Whitney test and Fisher's exact test were used for statistical analyses. Data monitored over time were compared by the area under the curve to reduce the number of tests. The level of significance was 0.05. Data are given as median (range).

Ethics

The study was approved by the scientific ethics committees of Copenhagen (KA 92043). The ethical considerations before this study included randomisation to a group without intervention. In our opinion, it is not common practice to intervene against asympto-

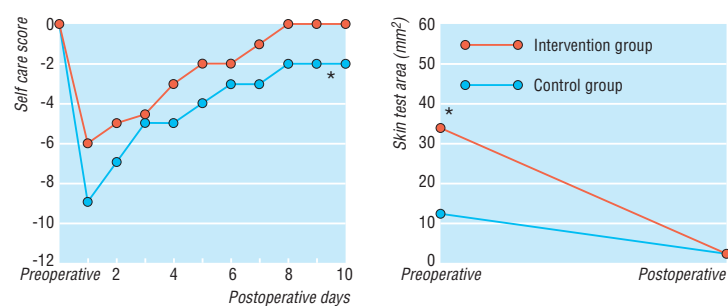


Fig 2 Median values for self care and skin test areas after colorectal surgery in alcohol misusers. *Significance between groups (area under curve) P=0.04 for self care and P=0.02 for skin test

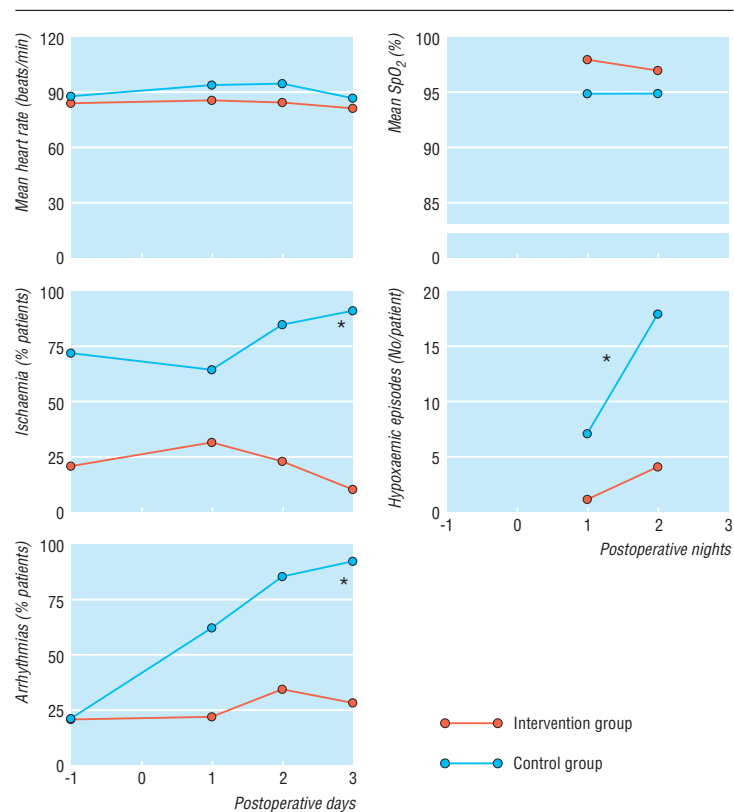


Fig 3 Median values on perioperative electrocardiography of all patients (n=16+19) and postoperative pulse oximetry of patients from two centres (n=14+12) undergoing colorectal surgery. *Significance between groups (area under curve) $P \leq 0.05$

matic alcohol misuse in the preoperative period before major colorectal surgery, usually indicated for cancer. According to the recent knowledge of alcohol misuse as a potentially important risk factor at surgery,⁵ it was considered important and ethically justified to perform the study. Therefore, we compared the standard procedure (non-intervention) with preoperative withdrawal, being aware of stress caused by abstinence as well as personal stress induced by changing lifestyle.

Results

From November 1995 to May 1998, 42 patients fulfilled the narrow criteria for inclusion (fig 1). No patient refused to enter the study or died in the preoperative period. The two groups were comparable with regard to preoperative and intraoperative characteristics (table 1). Before inclusion, the daily median alcohol consumption was 7 drinks (range 5-40), equivalent to 84 g of ethanol (60-480 g), in the intervention group and 6 (5-40) in the control group. All intervention patients completed the withdrawal programme of total abstinence from alcohol, including the two patients who did not require surgery. The control group continued their drinking habits until surgery. Postoperatively, until the day of follow up, the alcohol consumption was low in both groups, 0 (0-7) and 1 (0-11) drink a day, respectively.

The intervention group developed significantly fewer complications (minor and major), compared with the control group (table 2) and required significantly less nurse care postoperatively (fig 2).

There was no significant difference in length of hospital stay: 8 days (3-41) versus 10 (4-46), respectively. Before the operation the delayed type hypersensitivity reactions were significantly larger in the abstinence group compared with the control group, while there was no difference postoperatively (fig 2). Myocardial ischaemia and arrhythmias occurred less often in the intervention group; there were also significantly fewer episodes of sudden hypoxaemia. All patients had a mean arterial oxygen saturation above 90% on all study nights (fig 3). The response surgical stress, as assessed by heart rate and plasma concentrations of catecholamines and interleukin 6, was significantly smaller in the intervention group, while mean arterial pressure, serum concentration of cortisol, and plasma concentration of glucose did not differ significantly between the groups (fig 4).

Discussion

Our results show that 1 month of preoperative abstinence in alcohol misusers reduces postoperative morbidity. Correspondingly, the need for nurse care was lowered. The high complication rate in the control patients, who continued to drink, is comparable with that seen in previous studies in alcohol misusers.¹⁻⁴ Although reduced, the postoperative morbidity in the intervention group was still higher (31%) than that seen in most studies in unselected colorectal patients, though a wide range has been reported.^{11 12} The mechanism of the improved outcome after intervention is probably reversibility of the ethanol induced organ dysfunction as a result of abstinence.⁵

Specific complications

Postoperative infections are related to preoperative immunosuppression.¹³ The preoperative immune response in the intervention group improved significantly compared with the response in the control patients. There was no significant difference with regard to infectious outcome (25% v 53%; $P = 0.17$) between the groups. The postoperative immune response was low in both groups. The improved immunity after abstinence corresponds with our previous results in alcohol misusers who did not undergo surgery.¹⁴

Holter recording before surgery showed that in the group who did not abstain from alcohol misuse there were significantly more patients with myocardial ischaemia, which may explain the increased incidence of postoperative ischaemia seen in this group compared with the intervention group. These results may reflect alcohol induced cardiomyopathy, which improves after 1-3 months of sobriety.^{15 16} As postoperative myocardial ischaemia is related to serious cardiac complications,¹⁷ 1 month of abstinence may improve cardiac outcome in alcohol abusers.

Hypoxaemia after major surgery may contribute to cardiac and wound complications.¹⁸ The increased development of sudden episodic hypoxaemia in the patients who continued to drink may be due to the altered sleep physiology described in chronic alcohol abusers,¹⁹ although a relation to the higher incidence of pulmonary complications in this group cannot be excluded. Sleep deterioration with high prevalence of apnoeic and hypopnoeic episodes may continue for

3-6 weeks in detoxified misusers.^{19, 20} The incidence of postoperative episodic hypoxaemia in the intervention group is comparable with that seen in a group of unselected surgical patients.¹⁸

Surgical stress response

Response to surgical stress is mediated by cytokines and hormones, and excess stress is thought to be deleterious. Surgical trauma increases the activity of the hypothalamic-pituitary-adrenal axis and the sympathetic activity more in chronic misusers than in non-misusers.² We found that the response to surgical stress was reduced in the intervention group, as measured by heart rate and catecholamine concentrations, while serum cortisol concentration was only insignificantly lower in the intervention group. These results are in accordance with those from studies in non-surgical patients, which reported normalised reaction of the central part of the hypothalamic-pituitary-adrenal axis as well as normalised catecholamine response to (non-surgical) stress within 1 to 4 weeks after withdrawal.^{21, 22} The cortisol synthesis and metabolism, however, may still be disturbed after this period,²¹ which may explain the comparable high concentrations of serum cortisol in the groups.

The response to surgical stress includes production of interleukin 6, which besides immunological functions is the determinant stimulator of hepatocytes to produce acute phase proteins. Transient increased plasma concentrations of interleukin 6 after surgical intervention are associated with the injury severity and predict postoperative complications.²³ In our study the interleukin 6 response was increased in both groups of patients compared with studies of unselected patients undergoing open colorectal resection.²⁴ Similar to the enhanced hormonal response, the patients who continued to drink also showed significantly increased interleukin 6 concentrations compared with the abstinent group. High concentrations, above 5000 pg/ml, were found exclusively in patients who developed major complications. The clinical consequences of a smaller stress response in the intervention group may be a lower load on the already recovering target organs. Altogether, the smaller response may therefore contribute to the reduced postoperative morbidity.

Bias

The complete compliance with abstinence in the intervention group was probably because of the well known effect of brief intervention²⁵ and the high level of motivation from the patients as well as information about the study. Though we have treated only the alcohol misuse, the intervention group may have changed other variables of lifestyle simultaneously. This was, however, not monitored. Other sources of bias include non-significant differences between the groups (table 1). Lower body mass index, fewer patients with hypertension, and less bleeding may contribute to the improved outcome in the intervention group, while a poorer prognostic index may act in the opposite direction.

The study population was identified by a specific interview concerning daily consumption, based on the memory of the patients. Underestimation is more pronounced with increasing drinking,²⁶ and inclusion of non-misusers therefore seems improbable. In conclu-

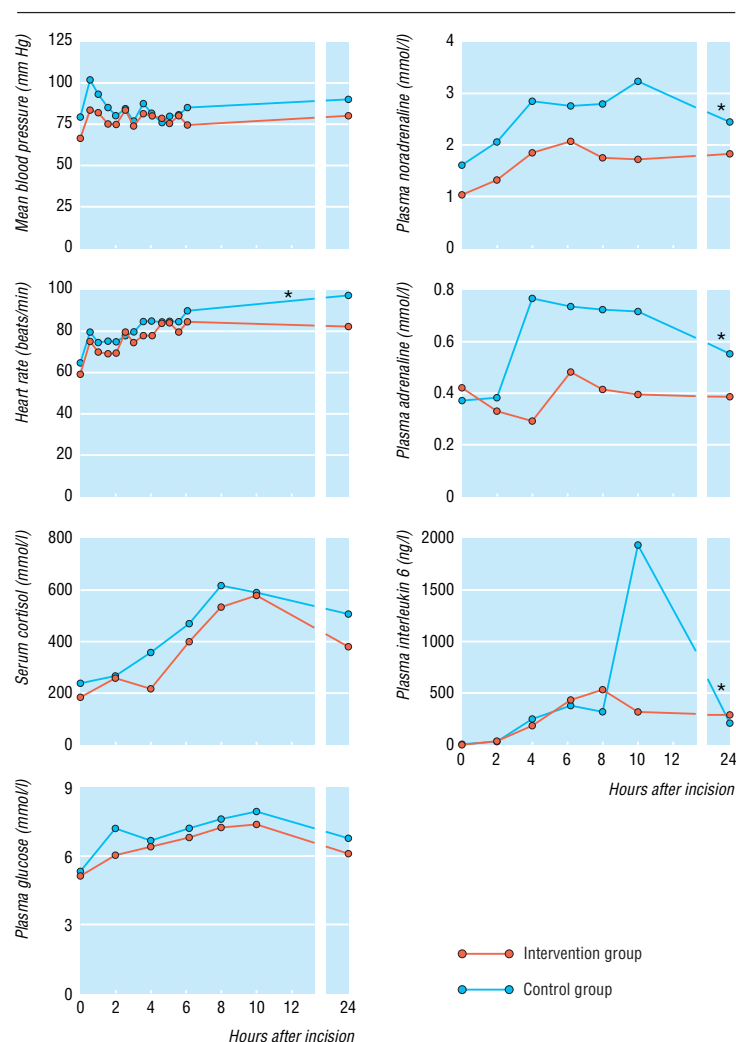


Fig 4 Median values for responses to surgical stress. *Significance between groups (area under curve) $P \leq 0.05$

sion, alcohol misuse should be included in the preoperative assessment of surgical risk and withdrawal recommended for at least 1 month before the operation whenever possible.

We thank Professor Per Christoffersen, department of pathology, Hvidovre Hospital, for histological examination of

Key messages

- Recent data have shown alcohol misusers to have a threefold increase in postoperative morbidity
- In misusers recovery from organ dysfunction induced by alcohol is seen after abstinence
- Abstinence from alcohol for 1 month before surgery reduces postoperative morbidity after colorectal surgery
- Mechanisms may involve reduced responses to surgical stress and improved cardiac and immune dysfunction
- Withdrawal from alcohol before an operation is recommended in alcohol abusers

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Contributors: HT initiated the research and coordinated the formulation of the primary study hypothesis, discussed core ideas, designed the protocol, collected and analysed the data, and wrote the paper. JR participated in the study design, analyses (pulse oximetry), interpretation of the data, and writing the paper. HJN participated in the study design, analyses (immune response), and interpretation of the data and edited the paper. VR participated in the data analyses (Holter tape recording) and edited the paper. CH and IKP participated in study design, data collection, and paper editing. HK discussed core ideas and participated in the protocol design, interpretation of the data, and writing the paper. HT, JR, and HK are guarantors of the paper.

- Spies CD, Nordmann A, Brummer G, Marks C, Conrad C, Berger C, et al. Intensive care unit stay is prolonged in chronic alcoholic men following tumor resection of the upper digestive tract. *Acta Anaesthesiol Scand* 1996;40:649-56.
- Tønnesen H, Petersen KR, Højgaard L, Stokholm KH, Nielsen, HJ, Knigge U, et al. Postoperative morbidity among symptom-free alcohol misusers. *Lancet* 1992;340:334-7.
- Felding C, Jensen LM, Tønnesen H. Influence of alcohol intake on postoperative morbidity after hysterectomy. *Am J Obstet Gynecol* 1992;166:667-70.
- Tønnesen H, Schütten BT, Jørgensen BB. Influence of alcohol on morbidity after colonic surgery. *Dis Colon Rectum* 1987;30:549-51.
- Tønnesen H. The alcohol patient at surgery. *Alcohol Alcohol* (in press).
- Simms JM, Smith JAR, Woods HE. A modified prognostic index based upon nutritional measurements. *Clin Nutr* 1982;1:71-9.
- Goldman L, Caldara DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, et al. Multifactorial index of cardiac risk in non-cardiac surgical procedures. *N Engl J Med* 1977;297:845-50.
- American Society of Anesthesiologists. New classification of physical status. *Anesthesiology* 1965;24:111.
- Rosenberg J, Rasmussen V, von Jessen F, Ullstad T, Kehlet H. Late postoperative episodic and constant hypoxaemia and associated ECG abnormalities. *Br J Anaesth* 1990;65:684-91.
- Appel E, Bayer P, Hajdu P, Palm D, Shofer J, Uihlein M. Determination of plasma catecholamines by means of radioenzymatic labelling and high pressure liquid chromatographic separation. *Naunyn Schmiedeberg Arch Pharmacol* 1981;315:233-9.

- Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. *J Am Coll Surg* 1997;185:105-13.
- Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey SG, Brewer D, et al. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. *Dis Colon Rectum* 1995;38:480-7.
- Christou NV. Host-defence mechanisms in surgical patients: a correlative study of the delayed hypersensitivity skin-test response, granulocyte function and sepsis. *Can J Surg* 1985;28:39-49.
- Tønnesen H, Kaiser AH, Nielsen BB, Pedersen AE. Reversibility of alcohol-induced immune depression. *Br J Addict* 1992;87:1025-8.
- Kelbæk H, Nielsen BM, Eriksen J, Rabøl A, Christensen NJ, Lund JO, et al. Left ventricular performance in alcoholic patients without chronic liver disease. *Br Heart J* 1987;58:352-7.
- La Vecchia L, Bedogni F, Loredana B, Bevilacqua P, Ometto R, Vincenzi M. Prediction of recovery after abstinence in alcoholic cardiomyopathy: role of hemodynamic and morphometric parameters. *Clin Cardiol* 1996;19:45-50.
- Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med* 1995;333:1750-6.
- Rosenberg J, Kehlet H. Late postoperative hypoxemia. In: Kinney JM, Tucker HN, eds. *Physiology, stress and malnutrition: functional correlates, nutritional intervention*. New York: Lippincott-Raven Publishers, 1997.
- Williams HL, Rundell OH Jr. Altered sleep physiology in chronic alcoholics: reversal with abstinence. *Alcohol Clin Exp Res* 1981;5:318-25.
- Le Bon O, Verbanck P, Hoffmann G, Murphy JR, Staner L, De Groot D, et al. Sleep in detoxified alcoholics: impairment of most standard sleep parameters and increased risk for sleep apnea, but not for myoclonias—a controlled study. *J Stud Alcohol* 1997;58:30-6.
- Marchesi C, Chiodera P, Ampollini P, Volpi R, Coiro V. Beta-endorphin, adrenocorticotropic hormone and cortisol secretion in abstinent alcoholics. *Psychiatr Res* 1997;72:187-94.
- Martin PR, Gibbs SJ, Nimmerrichter AA, Riddle WR, Welch LW, Willcutt MR. Brain proton magnetic resonance spectroscopy studies in recently abstinent alcoholics. *Alcohol Clin Exp Res* 1995;19:1078-82.
- Damas P, Ledoux D, Nys M, Vrindts Y, De Groot D, Franchimont P, et al. Cytokine serum level during severe sepsis in human IL-6 as a marker of severity. *Ann Surg* 1992;215:356-62.
- Stage JG, Schulze S, Møller P, Overgaard H, Andersen M, Rebsdorf-Pedersen VB, et al. Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. *Br J Surg* 1997;84:391-6.
- World Health Organisation. A cross-national trial of brief interventions with heavy drinkers. *Am J Public Health* 1996;86:948-55.
- Popham RE, Schmidt W. Words and deeds: the validity of self report data on alcohol consumption. *J Stud Alcohol* 1981;42:355-8.

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Impact of breast feeding on admission for pneumonia during postneonatal period in Brazil: nested case-control study

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Abstract

Objective To determine whether breast feeding protects infants against pneumonia and whether the protection varies with age.

Design Nested case-control study.

Setting Pelotas, southern Brazil.

Subjects Cases were 152 infants aged 28-364 days who had been admitted to hospital for pneumonia. Controls were 2391 cases in a population based case-control study.

Main outcome measure Odds ratio of admission for pneumonia according to type of milk consumed (breast milk alone, breast and formula milk, or formula milk and other fluids only), use of fluid supplements apart from formula milk, and use of solid supplements.

Results Infants who were not being breast fed were 17 times more likely than those being breast fed without formula milk to be admitted to hospital for

pneumonia (95% confidence interval 7.7 to 36.0). This relative risk was 61 (19.0 to 195.5) for children under 3 months old, decreasing to 10 (2.8 to 36.2) thereafter. Supplementation with solids was associated with a relative risk of 13.4 (7.6 to 23.5) for all infants and 175 (21.8 to 1405.1) for those under 3 months old.

Conclusion Breast feeding protects young children against pneumonia, especially in the first months of life. These results may be used for targeting intervention campaigns at the most vulnerable age groups.

Introduction

Pneumonia is the leading cause of death in children under 5 years old worldwide,^{1,2} and breast milk is the most important food in the first year of life.³

Several studies in less developed countries have assessed the effect of breast feeding on the risk of developing acute lower respiratory infections, particu-