Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy

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Background: A carbohydrate-rich drink (CHO) has been shown to reduce preoperative discomfort. It was hypothesized that it may also reduce postoperative nausea and vomiting (PONV).

Methods: Patients undergoing elective laparoscopic cholecystectomy under inhalational anaesthesia (127 women and 45 men; mean(s.d.) 48(15) years) were randomized to either preoperative fasting, intake of CHO (50 kcal/100 ml, 290 mOsm/kg) or placebo. The non-fasting groups were double-blinded; patients ingested 800 ml of liquid on the evening before surgery and 400 ml 2 h before anaesthesia. Nausea and pain scores on a visual analogue scale (VAS) and episodes of PONV were recorded up to 24 h after surgery.

Results: The incidence of PONV was lower in the CHO than in the fasted group between 12 and 24 h after surgery (P = 0.039). Nausea scores in the fasted and placebo groups were higher after operation than before admission to hospital (P = 0.018 and P < 0.001 respectively), whereas there was no significant change in the CHO group. No intergroup differences in VAS scores were seen. The use of anaesthetics, opioids, antiemetics and intravenous fluids was similar in all groups.

Conclusion: CHO may have a beneficial effect on PONV 12–24 h after laparoscopic cholecystectomy.


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Introduction

Despite the development of strategies to prevent and treat postoperative nausea and vomiting (PONV)¹-⁵, it still occurs in 20–30 per cent of adult patients¹,²,⁵,⁶. An even higher incidence has been reported in women, those with a history of motion sickness or previous PONV, non-smokers and with use of opioids¹,⁶,⁷. The choice of anaesthetic as well as the duration and type of surgery may also affect its incidence¹,⁷. From the patient’s perspective, nausea and vomiting may be an even worse experience than pain after surgery⁸. PONV may also delay hospital discharge or necessitate overnight admission after day-case surgery¹,²,⁹, with associated economic consequences. Recently, a multimodal approach, combining several potentially beneficial factors to minimize PONV, has been discussed¹,¹⁰.

Preoperative carbohydrate loading has been shown to reduce postoperative catabolism and insulin resistance¹¹,¹². To facilitate this treatment, a specially designed carbohydrate-rich drink (CHO) has been developed¹³. CHO neither delays gastric emptying¹³,¹⁴ nor affects gastric acidity¹⁴ and is therefore considered safe to use in elective surgical patients without risk factors for pulmonary aspiration¹⁵. In addition to its metabolic effects, CHO has been shown to improve preoperative wellbeing in patients scheduled for elective abdominal surgery¹⁴. Specifically, patients who received CHO were found to be less hungry and less anxious than those receiving placebo (flavoured water) or those fasting overnight¹⁴. Furthermore, a significant increase in preoperative nausea was found in the placebo group, but not in the CHO or fasting groups¹⁴. Similarly, in a trial¹⁶ comparing CHO with placebo given
before laparoscopic cholecystectomy, preoperative nausea and discomfort were less common in the CHO group, but there was no effect on postoperative wellbeing, including nausea and vomiting. The aim of the present study was to further investigate the possible effects of CHO on PONV after laparoscopic cholecystectomy in a randomized clinical trial. This standard surgical procedure is commonly performed either in a day-case setting or with a 1-night hospital stay. Incidences of PONV of up to 38–60 per cent have been reported within 24 h after laparoscopic cholecystectomy and such symptoms may delay discharge from hospital.

**Patients and methods**

Adult patients scheduled for elective laparoscopic cholecystectomy, and who were eligible for intake of preoperative clear fluids according to the guidelines of the Swedish Society of Anaesthesia and Intensive Care, were considered for inclusion. Patients with conditions (including pharmacological treatments) that might impair gastrointestinal motility, gastro-oesophageal reflux and those who had the potential for difficult airway management were therefore excluded. Additional exclusion criteria were diabetes mellitus, American Society of Anesthesiologists physical status grade III or higher and pregnancy. Patients with suspected (jaundice or based on laboratory findings) or documented cholelithiasis were not included, to allow standardization of the surgical trauma. To achieve standardization of the duration of fasting before surgery in each group, patients whose operation was scheduled to start after noon were not included.

Three hospitals in the Stockholm area (Karolinska, St Göran and Ersta Hospital) took part in the study. During the study period (20 months) 174 patients were enrolled, representing approximately 22 per cent of all patients undergoing laparoscopic cholecystectomy in these hospitals. Two patients chose to discontinue the study after surgery, leaving 172 patients for analysis. There was no selection or stratification of patients with regard to the presence of risk factors for PONV. The procedures and purposes of the study were fully explained to, and agreed by, each patient before entering the study. Approval for the investigation was obtained from the Research Ethics Committee at Karolinska Institutet.

The patients were assigned, according to a computer-generated randomization list, to one of three preoperative treatment groups: fasting from midnight, preparation with CHO and placebo treatments, whereas fasting patients were unblinded. CHO and placebo drinks have previously been shown to be indistinguishable in taste, and the products were provided in identical packaging.

During the evening before surgery, patients in the CHO group ingested 800 ml of a clear carbohydrate-rich drink (12.5 per cent carbohydrates, 50 kcal/100 ml, 290 mOsm/kg, pH 5·0, Nutricia preOp; Nutricia, Zoetermeer, The Netherlands). The placebo group consumed the same quantity of flavoured water (0 kcal/100 ml, pH 5·0). All patients were allowed to eat and drink freely before midnight. After midnight, nothing was allowed by mouth, except for a single morning dose of 400 ml of the appropriate drink in the CHO and placebo groups. The morning drink was taken at least 2 h before premedication because of the risk of opioid-induced slowing of gastric emptying.

**Surgery and anaesthesia**

All patients were scheduled for laparoscopic cholecystectomy, and the planned length of hospital stay was 24 h. A standard four-port technique with carbon dioxide insufflation of the peritoneal cavity was used, with an insufflation pressure below 12 mm Hg.

For premedication, ketobemidone 2·5–7·5 mg was given intramuscularly at least 2 h after the morning drink in the CHO and placebo groups and at the corresponding time in the fasted group. General anaesthesia was induced intravenously with thiopental 5 mg/kg and was maintained with isoflurane. Fentanyl 0·1 mg was given before induction and as needed during surgery (0·05–0·1 mg boluses). Atracurium 0·5 mg/kg was given to facilitate endotracheal intubation. A combination of neostigmine and glycopyrrolate (2·5 and 0·5 mg respectively) was given when reversal of muscle relaxation was required. Nitrous oxide (70 per cent in oxygen) was included in the anaesthetic protocol, but could be omitted at the discretion of the anaesthetist or surgeon. In patients with a previous history of PONV, motion sickness or another apparent risk factor for PONV, prophylaxis with intravenous droperidol (1·25 mg) was given at the end of anaesthesia.

Infusion of intravenous fluids was started at the induction of anaesthesia, and continued until the morning of the day of discharge. Non- or low-caloric balanced infusions with a maximum glucose concentration of 25 mg/ml were used.

For postoperative pain relief, acetaminophen 1 g was given rectally during surgery in all patients and continued orally after operation (1 g every 6 h). If insufficient, this was combined with the oral opioids.
codeine (60 mg every 6 h) or dextropropoxyphene (50 mg every 8 h) according to local clinical routines. For treatment of postoperative breakthrough pain intravenous or intramuscular ketobemidone (2.5–5-mg boluses) was used. Rescue medication for PONV was given intravenously at the request of the patient, and after clinical assessment by the attending anaesthetist or surgeon; droperidol 0.5 mg, dixyrazine 10–20 mg or ondansetron 4–8 mg was used.

**Assessment of nausea and vomiting, and pain**

Two methods were used to assess PONV. The nursing staff objectively recorded episodes of PONV, defined as either spontaneous complaints of nausea or retching or vomiting. Retching was defined as vomiting without production of liquid. Predetermined registration periods were 0–4, 4–12 and 12–24 h after surgery.

In addition, the patients rated their sense of nausea using a 100-mm visual analogue scale (VAS), at the preadmission visit 1 week before surgery and on the day after surgery, that is at about 24 h after operation which was the planned time of hospital discharge. VAS scores for overall pain were obtained in parallel.

**Table 1**  
Demographic and surgical data, and details of anaesthetics, pharmacological treatments and infusions

<table>
<thead>
<tr>
<th></th>
<th>Fasted (n = 58)</th>
<th>Placebo (n = 59)</th>
<th>CHO (n = 55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (F: M)</td>
<td>45:13</td>
<td>41:18</td>
<td>41:14</td>
<td>0.603</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48(14,9)</td>
<td>46(14,9)</td>
<td>48(14,6)</td>
<td>0.855</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25(2,8)</td>
<td>23(2,9)</td>
<td>24(2,3)</td>
<td>0.074</td>
</tr>
<tr>
<td>Ketobemidone in premedication</td>
<td>58(100)</td>
<td>59(100)</td>
<td>55(100)</td>
<td></td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>5(2,1)</td>
<td>5(2,1)</td>
<td>5(2,1)</td>
<td>0.837</td>
</tr>
<tr>
<td>Intraoperative fentanyl</td>
<td>58(100)</td>
<td>59(100)</td>
<td>55(100)</td>
<td></td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>0(2,1)</td>
<td>0(2,1)</td>
<td>0(2,1)</td>
<td>0.416</td>
</tr>
<tr>
<td>Intraoperative nitrous oxide</td>
<td>27(46)</td>
<td>28(47)</td>
<td>23(43)</td>
<td>0.812</td>
</tr>
<tr>
<td>Intraoperative neostigmine and glycopyrrolate</td>
<td>45(78)</td>
<td>44(75)</td>
<td>39(71)</td>
<td>0.718</td>
</tr>
<tr>
<td>Intraoperative droperidol</td>
<td>18(31)</td>
<td>19(32)</td>
<td>20(37)</td>
<td>0.820</td>
</tr>
<tr>
<td>Postoperative droperidol, dixyrazine or ondansetron</td>
<td>23(41)</td>
<td>19(33)</td>
<td>18(33)</td>
<td>0.644</td>
</tr>
<tr>
<td>Postoperative ketobemidone</td>
<td>43(74)</td>
<td>40(67)</td>
<td>32(57)</td>
<td>0.194</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>9(48,8)</td>
<td>7(8,4)</td>
<td>7(8,4)</td>
<td>0.462</td>
</tr>
<tr>
<td>Intraoperative and postoperative infusions</td>
<td>58(100)</td>
<td>59(100)</td>
<td>55(100)</td>
<td></td>
</tr>
<tr>
<td>Infused volume (ml)</td>
<td>2450(552)</td>
<td>2314(638)</td>
<td>2447(521)</td>
<td>0.369</td>
</tr>
<tr>
<td>Infused energy (kcal)</td>
<td>164(105)</td>
<td>143(91)</td>
<td>152(77)</td>
<td>0.541</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>75(41)</td>
<td>67(33)</td>
<td>69(36)</td>
<td>0.535</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>9(36)</td>
<td>5(17)</td>
<td>18(74)</td>
<td>0.308</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>1(30.9)</td>
<td>1(20.9)</td>
<td>1(20.7)</td>
<td>0.918</td>
</tr>
<tr>
<td>No. of patients not discharged 24 h after surgery</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>0.926</td>
</tr>
<tr>
<td>Required an open procedure</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>PONV</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other (pain, psychosocial reasons)</td>
<td>4</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.); †Prophylaxis against postoperative nausea and vomiting (PONV); ‡treatment of PONV. CHO, carbohydrate-rich drink. §χ² test; ¶ANOVA and t test.

**Statistical analysis**

There is no specific procedure by which a power calculation can be performed on outcome measures of ordinal data, such as VAS values. When planning the study, no data were available on the effects of CHO on PONV. Therefore, the sample size was extrapolated from a previous study of the effects of CHO on preoperative VAS scores for wellbeing. A sample size of 50–60 in each of the three study groups had yielded significant differences in the previous study, and this group size was assumed to be sufficient to detect differences in postoperative measurements.

All analyses were performed and presented on the basis of intention to treat. Patients who eventually required an open surgical procedure were therefore included in the analysis. Exclusion of these patients did not significantly affect the variables studied. The Kruskal–Wallis test was used for intergroup testing of VAS data, whereas Wilcoxon’s test was used for intragroup testing. Correlations of VAS data were analysed with the Spearman rank test. Binominal data were analysed with the χ² test and other intergroup
differences were investigated using ANOVA and t test. In addition, for analysis of the occurrence of PONV exact binary logistic regression was used. \( P < 0.050 \) was considered statistically significant.

**Results**

Demographic and surgical data, as well as the use of anaesthetics, intravenous infusions and drugs with a potential effect on PONV, are summarized in Table 1. There were no significant intergroup differences in these variables. There were no complications associated with the intake of CHO or placebo, and there were no major surgical complications.

During the 24 h after surgery, 23 (40 per cent) of the fasted patients, 23 (39 per cent) in the placebo group and 15 (27 per cent) in the CHO group had one or more episodes of nausea or vomiting (\( P = 0.305 \) (Table 2). The incidence of PONV decreased significantly over time in the CHO (\( P < 0.001 \)) and placebo (\( P = 0.006 \)) groups, but not in the fasted group (\( P = 0.067 \)). The incidence of PONV was similar in the three groups during the first 12 h. However, between 12 and 24 h after cholecystectomy significantly more patients in the fasted group than in the CHO group experienced nausea and vomiting (odds ratio (OR) 8.33 (95 per cent confidence interval (c.i.) 1.08 to 333.33); \( P = 0.039 \)). There was no corresponding difference between the placebo and CHO groups (OR 3.89 (95 per cent c.i. 0.37 to 120.00); \( P = 0.401 \)) or between the fasted and placebo groups (OR 2.19 (95 per cent c.i. 0.55 to 10.54); \( P = 0.345 \)). Analysis of the subgroup of women (data not shown) revealed a similar pattern. None

![Fig. 1](image-url)
of the patients who received CHO vomited after the first 4 h, in contrast to several patients in each of the other groups.

There were no differences between treatment groups in VAS scores for pain or nausea before admission to hospital or at 24 h after operation (Fig. 1). However, nausea scores in the fasted and placebo groups were higher after surgery than before admission ($P = 0.018$ and $P < 0.001$ respectively), whereas no significant increase was observed in the CHO group ($P = 0.082$). The 13 patients who had one or more episodes of PONV 12–24 h after operation had significantly higher nausea scores at 24 h than the 159 who did not experience late PONV: median (interquartile range) 43 (57) and 5 (13) mm respectively ($P < 0.001$). There was no difference in preadmission nausea scores between these subgroups ($P = 0.253$).

Pain scores were significantly higher after surgery than at admission in all treatment groups ($P < 0.001$). A correlation between postoperative nausea and pain was seen in the placebo group ($\rho = 0.365$, $P = 0.006$), but not in the two other groups.

**Discussion**

The odds of nausea and vomiting 12–24 h after elective laparoscopic cholecystectomy was found to be higher in patients who fasted overnight than in those who received CHO. In addition, there was a significant postoperative increase in nausea scores compared with preadmission values in the placebo and fasted groups, but not in the CHO group.

The patients were unselected with regard to the presence of risk factors for PONV\(^{1,6,7}\), and the sex ratio was similar in the three groups. The perioperative care and anaesthetic technique in the study were in accordance with local clinical practice, and all patients received volatile anaesthetics and long-acting opioids. These drugs may have increased the risk of PONV\(^{1,6,7}\), but the pharmacological treatment, including use of prophylactic antiemetics, did not differ between study groups. The baseline risk for PONV was therefore assumed to be equal in the three groups.

A VAS has been used previously for the assessment of postoperative nausea in laparoscopic cholecystectomy\(^{19,20}\). In the present study, such scoring was combined with an objective registration of PONV episodes in an effort to increase the accuracy of the evaluation. Patients who experienced late PONV (12–24 h after surgery) were found to have significantly higher VAS scores for nausea (at 24 h) than those who did not, supporting an association between the two methods.

There are no generally accepted definitions of early and late registration periods for PONV. To determine the immediate postoperative emetic effects of anaesthesia and surgery, an initial registration period of 4 h was chosen for the objective assessment of nausea and vomiting. The choice of a late registration period, 12–24 h after surgery, was believed to be of clinical significance as events during this period may delay discharge or necessitate overnight admission after laparoscopic day-case surgery\(^9\). In the present study, three patients (1.7 per cent) could not be discharged from hospital after 24 h owing to intractable late PONV. None of these patients received preoperative CHO.

Median pain and nausea scores before admission were low. The pain scores at 24 h after surgery were higher than expected, considering that opioids were administered to control breakthrough pain. However, similar VAS pain scores on the day after laparoscopic cholecystectomy have been reported previously\(^{16,17}\). An increased scatter in nausea VAS scores was seen at 24 h. Non-parametric ranking statistical analysis showed that nausea was worse after surgery than before admission in the fasting and placebo groups, but not in the CHO group. Although significant versus non-significant differences in small numbers of patients should be interpreted with caution, the present data suggest that CHO might reduce nausea and vomiting after laparoscopic cholecystectomy.

A recently published placebo-controlled study of 94 patients from Denmark\(^{16}\) was unable to show any significant beneficial effects of CHO on postoperative wellbeing, including PONV, after laparoscopic cholecystectomy\(^{16}\). Unfortunately, there was no fasting group in the Danish...
investigation, which makes comparison with the present study difficult. Furthermore, the anaesthetic protocol as well as the registration periods and method of assessment of PONV were different. The latter may offer some explanation for the difference in the 24 h incidence of PONV (35.5 per cent in the present study and 60.5 per cent in the Danish study). A weakness shared by both studies is the relatively small sample sizes (about 50 per group). With such a small number of patients, the risk of a Type II error increases. In the present study a significant difference in the incidence of PONV was confirmed only between the CHO and fasting groups 12–24 h after surgery. The lack of significant differences between the other groups may be related to the small sample size. Given that the incidence of PONV would remain the same in all groups as in the current study, a sample size of about 150 per group would be expected to detect differences between all three groups.

The relationship between perioperative compensatory hydration and PONV or postoperative wellbeing has not yet been clarified. Although perioperative hydration was found to reduce PONV in some recent studies, others have found that excessive fluid administration may not only potentially cause PONV, but also increase morbidity. In the present study, the intravenous infusion volumes were about 2400 ml per 24 h in all three groups. These volumes may seem somewhat high in the light of recent findings, but were given according to the clinical routines at the time of the study. Such volumes may have obscured the hydration effects of the oral fluid given before surgery in the CHO and placebo groups.

The exact mechanism by which CHO affects PONV needs to be clarified. The effects of its high carbohydrate content, its distinct effects on body metabolism (insulin release) and probable parallel effects on the hypothalamic serotonin system require further investigation.

The present data suggest that the metabolic setting at the onset of surgery influences late nausea and vomiting after elective laparoscopic cholecystectomy. CHO may therefore have a role in a multimodal approach to minimize PONV.

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