Randomized controlled trial of vagal modulation by sham feeding in elective non-gastrointestinal (orthopaedic) surgery

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Abstract

Background: Enhanced recovery, in part, aims to reduce postoperative gastrointestinal dysfunction (PGID). Acquired – or established- vagal dysfunction may contribute to PGID, even for surgery not involving the gastrointestinal tract. However, direct evidence for this is lacking. We hypothesized that chewing gum reduces morbidity (including PGID) by preserving efferent vagal neural activity postoperatively after elective orthopaedic surgery.

Methods: In a two-centre randomized controlled trial (n=106), we explored whether patients randomized to prescribed chewing gum for five days postoperatively sustained less morbidity (primary outcome, defined by the Postoperative Morbidity Survey), PGID and faster time to become morbidity free (secondary outcomes). In a subset of patients (n=38), cardiac parasympathetic activity was measured by serial Holter monitoring and assessed using time and frequency domain analyses.

Results: Between September 2011 and April 2014, 106 patients were randomized to chewing gum or control. The primary clinical outcome did not differ between groups, with similar morbidity occurring between patients randomized to control (26/30) and chewing gum (21/28; absolute risk reduction (ARR):13% (95% CI: 1–6–32); P=0.26). However, chewing gum reduced PGID (ARR:20% (95% CI: 1–38); P=0.049). Chewing gum reduced time to become morbidity-free (relative risk (RR): 1.62 (95% CI: 1.02–2.58); P=0.04) and was associated with a higher proportion of parasympathetic activity contributing to heart rate variability (11% (95% CI: 1–20); P=0.03).
Conclusions: Chewing gum did not alter overall morbidity, but reduced PGID. These data show for the first time that prescription of sham feeding preserves vagal activity in surgery not directly involving the gastrointestinal tract.

Clinical trial registration: ISRCTN20301599.

Key words: gastrointestinal motility; general surgery; parasympathetic nervous system; postoperative complications; vagus nerve

The mechanisms underlying the potential benefit of specific components of enhanced recovery remain unclear. Enhanced recovery programs, in part, have focused on preventing/reducing postoperative gastrointestinal dysfunction (PGID), particularly after colorectal surgery. However, PGID is common after surgery not directly involving the gastrointestinal tract, and implicated in fuelling distant organ dysfunction. Furthermore, sham feeding appears to be beneficial even at colorectal anatomical sites where vagal innervation is absent.

A ubiquitous feature of major surgery is the relative loss of parasympathetic neural activity. Reduced vagal tone may impair neural cardioprotective mechanisms, augment systemic inflammation and retard restoration of normal gastrointestinal function. The parasympathetic motor supply to the gastrointestinal tract originates from brainstem neurons located in the dorsal motor vagal nucleus and nucleus ambiguous. Circulating inflammatory mediators (e.g. TNFα) inhibit vagal motor-neuron activity. Commonly administered perioperative drugs including propofol, inhalation and neuromuscular blocking agents also inhibit parasympathetic activity at the level of the central nervous system. Morphine blocks central vagal neuronal activity, suppressing insulin- and meal-induced release of gastrointestinal hormones, critical for normal feeding.

PGID may therefore be caused by vagal dysfunction, even in surgeries where the bowel is not handled or traumatized. If parasympathetic dysfunction leading to PGID is common in operations not involving the bowel, clinical interventions such as sham feeding (chewing gum) that reduce postoperative ileus may also be applicable to non-gastrointestinal surgery where vagal activity is reduced perioperatively.

We therefore hypothesized that sham feeding through chewing gum reduces morbidity (including PGID) by preserving efferent vagal neural activity postoperatively, in a randomized controlled trial of patients undergoing elective (non-gastrointestinal) orthopaedic surgery.

Methods

A dual-centre, randomized, single-blinded controlled trial (POM-X: postoperative Morbidity-X) was conducted in two hospitals (University College Hospital, London; Robert Jones and Agnes Hunt Orthopaedic Hospital Oswestry) in the UK. The trial was approved by the NRES Committee London (Camden & Islington; MREC: 11/H0722/3) and registered with Controlled Trials (ISRCTN20301599). The Medicines and Healthcare Products Regulatory Agency designated this as a non-medicinal trial. The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed. Written informed consent was obtained from all patients before surgery. The trial protocol has been available online at www.ucl.ac.uk/anaesthesia/trials. Adult patients undergoing elective joint replacement surgery were eligible for recruitment provided they satisfied the following criteria: ASA grade II-IV; age ≥50 yr; undergoing general anaesthetic or sedation with/without neuraxial/ peripheral nerve block. Exclusion criteria included refusal of consent, established nasogastric/gastrostomy feeding, or unsafe swallow. For patients declining, or with contraindications for neuraxial blockade, local anaesthetic infiltration was performed by the surgical team. Scheduled i.v. (or oral) acetaminophen and morphine (either i.v. patient controlled analgesia or oral, as required) analgesia was prescribed for all patients postoperatively. At Robert Jones and Agnes Hospital, the postoperative analgesic regimen did not routinely use morphine, as all patients were prescribed oxycontin twice per day and oxynorm as required for up to 72 h or patient-controlled analgesia (morphine), plus pregabalin up to 72 h postoperatively. All postoperative management decisions were taken by senior clinicians who retained the discretion to alter any aspect of patient care. Preceding audit showed that both hospitals had similar median lengths of stay. Postoperative management was conducted according to local clinical guidelines. Surgical antibiotic use at the time of the operation at all centres was undertaken according to local microbiology policies, on a prophylactic basis (i.e. preoperative and two subsequent doses). Thus, antibiotic use 48 h postoperatively was seen as a deviation from normal postoperative care.

Randomization and procedures to minimize bias

A randomization list was produced using a computer program (NCSS/PASS, Kaysville, UT, USA) and then concealed using envelopes. Participants were centrally allocated to treatment groups. To minimize the possibility of bias, investigators did not reveal study group allocation to attending surgical and/or physician teams. Patients were randomized to chew a single stick of sugar-free chewing gum four times per day for 30 min, for five days postoperatively [or until discharge]. Chewing gum was prescribed on each patient’s drug chart, and was continued when patients resumed oral food intake. Although we had originally planned patients to commence chewing gum preoperatively, this was impractical for logistic and local practice reasons (and hence never undertaken). Patients randomized to chew gum first did so in the post-anesthetic care unit, as soon as they were able to chew. Surgical and nursing personnel were not informed directly of the arm into which each patient had been randomized. Compliance was
recorded by patient interview. Morbidity outcomes using the Postoperative Morbidity Survey were documented by personnel blinded to treatment allocation.

**Holter monitoring**

In a subset of UCLH patients, baseline three-lead electrocardiographic recordings were made preoperatively, in a quiet environment between 0700–0900 h on the day of surgery, using Lifecard CF digital Holter monitors (Spacelabs Healthcare, Hertford UK). Patients in atrial fibrillation or with frequent ectopy and/or other dysrhythmias were excluded. Data quality criteria were in accordance with Task Force guidelines. Valid recording segments were identified (Pathfinder software, Spacelabs Healthcare, Hertford, UK). Holter data cleaning and analysis were undertaken, blinded to perioperative data and randomization. We analysed time-domain measures from at least one five min recording segment per h (Spacelabs HRV Tools Software, Hertford, UK). This approach is preferable to frequency domain methods when only short-term recordings are possible. Two measures of parasympathetic activity were assessed: 1. the square root of the mean of the sum of the squares of the successive differences between adjacent beat-to-beat intervals (Root Mean Square of the Successive Differences; RMSSD); 2. The proportion of number of pairs of successive beat-to-beat intervals that differ by more than 50 ms, divided by total number of beat-to-beat intervals (pNN50). Frequency-domain analysis was also undertaken, including high-frequency (HF; efferent vagal (parasympathetic) activity) and low frequency (LF) bands, according to Task Force guidelines. Normalized low (LF/n) and high frequency (HF/n) values were also calculated. Normalized values reflect the proportion of total heart rate variability occurring in the high and low frequency bands, respectively. Thus, HF/n specifically reflects changes in parasympathetic regulation. The ratio of power in the low frequency range to the power in the high frequency range, LF/HF, was also calculated. We compared these parameters at baseline (preoperatively) and on postoperative day three, at similar times of day whilst avoiding the period of chewing gum.

**Trial endpoints**

In accordance with CONSORT guidelines, the primary effect estimate was the difference in risk (absolute risk reduction (ARR); 95% confidence intervals (95% CI)) of acquiring postoperative morbidity throughout the hospital admission, as defined by the Postoperative Morbidity Survey (POMS; Table 1). Rather than collect quantitative data on opiate use, we used the POMS-defined criteria for pain which is de

<table>
<thead>
<tr>
<th>Morbidity type</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>De novo requirement for supplemental oxygen or other respiratory support (e.g. continuous positive airway pressure or mechanical ventilation)</td>
</tr>
<tr>
<td>Infectious</td>
<td>Currently on antibiotics or temperature &gt;38°C in the last 24 h</td>
</tr>
<tr>
<td>Renal</td>
<td>Presence of oliguria (&lt;500 ml d⁻¹), increased serum creatinine (&gt;30% from baseline value), or urinary catheter in place for a non-surgical reasons</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Unable to tolerate an enteral diet (either by mouth or feeding tube) for any reason, including nausea, vomiting and abdominal distension</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Diagnostic test or therapy in last 24 h for any of the following reasons: de novo myocardial infarction or ischaemia, hypotension (requiring drug therapy or fluid &gt;200 ml h⁻¹), atrial or ventricular arrhythmia or pulmonary oedema</td>
</tr>
<tr>
<td>Neurological</td>
<td>Presence of a de novo focal deficit, coma or confusion/delirium</td>
</tr>
<tr>
<td>Wound complications</td>
<td>Wound dehiscence requiring surgical exploration or drainage or pus from the wound</td>
</tr>
<tr>
<td>Hematological</td>
<td>Requirement for any of the following within last 24 h: blood, platelets, fresh frozen plasma or cryoprecipitate</td>
</tr>
<tr>
<td>Pain</td>
<td>Surgical wound pain significant enough to require parenteral opiates or regional anaesthesia</td>
</tr>
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**Statistical analysis**

Categorical data are summarized as absolute values (percentage). Continuous data are presented as mean (95% confidence intervals). Holter data were analysed using two way ANOVA (time x treatment allocation), with post-hoc Tukey-Kramer tests to identify within and between factor differences. Time to become morbidity free and length of hospital stay were analysed by intention to treat. Length of stay was calculated by Kaplan–Meier analysis, with unadjusted comparison of groups by Mantel–Cox log rank test. Risk ratios for the time-to-become morbidity free and time-to-discharge from hospital were calculated by Cox regression modeling, taking into account the following independent variables: age, gender, hospital, operation type, diabetes mellitus, preoperative cardiovascular disease (ischaemia/heart failure/dysrhythmias), PCA opiate use and presence/absence of chewing gum. We censored data for patients no longer remaining in hospital, as we could not ascertain whether (although unlikely) they sustained morbidity post-discharge. P < 0.05 was considered significant. All statistical analyses were undertaken using NCSS 8 (Kaysville, UT, USA).
Power calculation

We estimated that ≥50% of patients would sustain any POMS-defined morbidity by postoperative day five. On the basis that morbidity was expected to be twice as prevalent in the group who do not chew gum, the expected outcome was that 33% of patients in the intervention group would sustain morbidity vs 66% of the patients non-randomized to chew gum. With a 5% significance level and 80% power, at least 53 patients per group would be required for the study. For the heart rate variability study, on the basis of preceding data exploring the role of sham feeding in functional dyspepsia, we estimated that at least 14 patients per randomization arm would be required. Assuming an incomplete data collection rate of ~25% as a result of ECG artifacts or early discharge, we estimated that at least 37 patients would be required for Holter-based analysis.

Results

We enrolled 106 patients between September 2011 and April 2014 (Fig. 1). Baseline characteristics were similar between the groups (Table 2). Five patients were enrolled, randomized but subsequently excluded because of unscheduled cancellation of their operation, or a change in anaesthetic technique that breached inclusion criteria. Intraoperative duration and management were similar across groups (Table 3). Pain medication and opiate use was similar between groups (Table 3). Cardiac output monitoring or goal-directed therapies were not used in any patients. There were no adverse events linked to prescription of chewing gum.

Primary clinical outcome: postoperative morbidity

Similar overall morbidity was recorded on postoperative day five between patients randomized to control (26/30) or chewing gum (21/28; ARR:12% (95% CI: −9–32); P=0.26)

Secondary clinical outcomes

Randomization to chewing gum was associated with quicker resolution of morbidity (risk ratio: 1.62 (95% CI: 1.02–2.58); P=0.04;
PGID was associated with prolonged hospital stay (Fig. 2), with all but one patient per group having resumed oral diet by postoperative day five. However, by postoperative day five, 2/28 patients randomized to chewing gum reported PGID, compared with 8/30 patients allocated to the control arm [ARR: 20% (95% CI: 1–38); \( P = 0.049 \)]. Duration of hospital stay was shorter in patients randomized to chew gum [risk ratio: 1.69 (1.07–2.67); \( P = 0.03 \); Fig. 2; Table 4].

Effect of chewing gum on postoperative parasympathetic activity

Serial heart rate data was successfully captured pre and postoperatively in 33/38 patients at UCLH, with 15 patients who had been randomized to control and 18 who had been randomized to chewing gum. Median recording time preoperatively was seven h (IQR: 4–8 h). Median recording time on postoperative day three was three h (IQR: 2–4 h). Heart rate increased in both arms postoperatively (Fig. 3a), while mean arterial blood pressure was lower during the postoperative period (Fig. 3b). Time and frequency domain measures of parasympathetic activity were reduced postoperatively.

Table 2 Baseline patient characteristics: POM-X pilot RCT. CKD, chronic kidney disease; UCLH, University College London Hospital; RJAH, Robert Jones and Agnes Orthopaedic Hospital. Data presented as mean (95% CI), or n (%)

<table>
<thead>
<tr>
<th></th>
<th>No gum (n=49)</th>
<th>Gum (n=52)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>62 (59–65)</td>
<td>65 (63–67)</td>
</tr>
<tr>
<td>Male (n,%)</td>
<td>19 (38.7)</td>
<td>20 (37.8)</td>
</tr>
<tr>
<td>BMI (kg m(^{-2}))</td>
<td>31.1 (28.9–33.3)</td>
<td>30.6 (29.1–32.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (32.4%)</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>26 (53.1%)</td>
<td>27 (51.9%)</td>
</tr>
<tr>
<td>CKD (≥ stage 3)</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11 (22.4%)</td>
<td>5 (9.6%)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>19 (38.8%)</td>
<td>20 (38.5%)</td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>19 (38.8%)</td>
<td>29 (55.7%)</td>
</tr>
<tr>
<td>Revision hip/knee</td>
<td>11 (22.4%)</td>
<td>3 (5.8%)</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCLH</td>
<td>26</td>
<td>39</td>
</tr>
<tr>
<td>RJAH</td>
<td>23</td>
<td>13</td>
</tr>
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</table>
irrespective of trial intervention (Fig. 3c–r; Supplementary Fig. S1). Both time domain measures (pNN50 and RMSSD) of parasympathetic activity were higher in patients randomized to chew gum postoperatively (Fig. 3d–k). Frequency domain analysis showed that normalized high frequency (effenter vagal activity) was higher in patients randomized to chew gum postoperatively (Fig. 3f and h). An increase in normalized low frequency was observed in patients randomized to control (Fig. 3e and h), which may be indicative of relative sympathetic hyperactivity. Lack of PGID was associated with higher RMSSD on postoperative day three (Supplementary Fig. S2).

**Discussion**

The primary outcome of this study was that chewing gum did not reduce morbidity as assessed by POMS on postoperative day five. We have, however, demonstrated for the first time that autonomic modulation by sham feeding occurs postoperatively. This study supports the concept that chewing gum maintains efferent vagal tone and that this approach may have a role in reducing PGID, even in non-GI tract surgery. This provides mechanistic data to support a key feature of many enhanced recovery programmes, which have focused on reducing gastrointestinal-related morbidity. Although enhanced recovery has largely been addressed in patients undergoing intra-abdominal surgery, our data confirm that reducing gastrointestinal morbidity after extra-abdominal surgery may reduce length of hospital stay.

Remarkably, nine systematic reviews have broadly reached the same conclusion in advocating chewing gum to reduce postoperative ileus.\textsuperscript{21–29} None of these studies have confirmed an autonomic impact of sham feeding, which is of particular importance given the challenges surrounding blinding of the intervention. We are unaware of any clinical study that has explored this question in operations not involving bowel manipulation, a potential confounding factor that introduces significant uncertainty as direct (vagally innervated) neural injury may occur. Furthermore, animal neuroanatomical tracing studies demonstrate that vagal innervation of the proximal and distal colon differs
Vagal modulation of postoperative morbidity

Central vagal activation reduces surgical inflammation in experimental postoperative ileus. This is likely to be mediated via neuromodulation of resident macrophages in the gut, where efferent vagal nerve fibers synapse with enteric cholinergic neurons.

Preservation of parasympathetic innervation is likely to protect other organs perioperatively, beyond the gastrointestinal tract. Cardioprotection against ischaemia/reperfusion injury is critically dependent upon the activity of a distinct population of vagal pre-ganglionic neurons, at least in the context of afferent neural input that initiates remote preconditioning reflexes. Direct vagal stimulation reduces inflammation through increased coagulation factor activity. Vagal stimulation also reduces the pathophysiological sequelae of experimental neurologic and acute lung injury.

The inherent limitation of not blinding patients who received chewing gum is difficult to circumnavigate. However, without conducting this study first, devising alternative innovative paradigms is impractical. A further possible limitation was the imbalance between revision procedures between groups, although primary knee surgery (which is associated with longer hospital stay than hip surgery) was more frequent in those randomized to sham feeding. The assumptions underpinning the Cox regression analyses may have underestimated the contribution of other confounding variables. Furthermore, a trend for more patients randomized to gum requiring PCA morphine was observed by chance, which should increase the likelihood of gastrointestinal symptoms postoperatively. A significant strength of these data is the confirmation that sham feeding has an effect on parasympathetic autonomic function, an analysis that was blinded to clinical outcomes. In contrast to other studies, we continued to prescribe chewing gum even when oral diet resumed. We cannot exclude those patients who received gum, gained benefit purely from the belief that a positive intervention can only be beneficial. However, if that was the case, we still found a positive association with preserved autonomic function, which remains consistent with...
the over-arching hypothesis. Nevertheless, we conducted an adequately powered study in a highly phenotyped surgical population. The patient demographic may not be extrapolatable to older patients with more frequent, and serious, co-morbidities associated with established autonomic dysfunction. We did not test for other postoperative autonomic alterations, including orthostatic intolerance which is associated with delayed recovery.41 42

These data provide two immediate clinical implications. We have demonstrated for the first time that autonomic modulation by resuming early (sham) feeding can occur postoperatively. This finding may be applicable to other pathophysiology in the perioperative period involving parasympathetic dysfunction, including the development of atrial fibrillation and myocardial injury.43 44 Second, chewing gum is a cheap, readily available intervention associated with negligible harm. It thus appears reasonable to advocate use of chewing gum beyond the colorectal surgical arena.

In conclusion, no effect of chewing gum on morbidity was demonstrated other than PGID, but this may reflect a lack of power in the presence of confounding factors including age-related established autonomic dysfunction. A significant effect of chewing gum on vago-vagal efferent activity was demonstrated, suggesting that further clinical trials are warranted. Innovative autonomic interventions aimed at preventing PGID may reduce postoperative organ dysfunction in surgery not directly involving the gastrointestinal tract.

Authors’ contributions
Study design/planning: G.L.A
Study conduct: S.K., N.J., A.S., POM-X investigators
Revising paper: all authors

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

Declaration of interest
None declared.

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