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: −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).

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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 motoneuron 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: a. 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 nasso-gastric/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 oxycodone 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\(^4\) 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.\(^30\) 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.\(^30\) 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 defined as: surgical wound pain significant enough to require parenteral opiates or regional anaesthesia. Morbidity data were collected prospectively on designated postoperative days three, five, seven, 14). Secondary outcomes were PGID as defined by POMS (inability to tolerate normal diet, and/or nausea/vomiting, or requiring anti-emetic medication) on postoperative day five, time to become morbidity free and parasympathetic time-domain heart rate variability measures. Time to become morbidity free was defined as the first day of POMS data collection, when no POMS-defined morbidity was evident. Length of hospital stay was defined as the number of days of admission including the day of surgery and day of discharge. Automated validation checks including plausibility ranges for clinical and physiological parameters were made. Further manual data checks for POMS classification and basic patient characteristics were performed through verification of source data.

<table>
<thead>
<tr>
<th>Morbidity type</th>
<th>Criteria</th>
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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 reason</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>
</tbody>
</table>

### 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 $\geq 50\%$ 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 $\sim 25\%$ 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); $P=0.04$;
Fig. 2: Effect of sham feeding on postoperative morbidity and length of hospital stay. (a) Serial changes in POMS in each trial centres, stratified by randomization to chewing gum or control. POD- postoperative day. (b) Kaplan-Meier plot showing effect of sham feeding on time to become morbidity free (unadjusted hazard ratio: 0.79 (95% CI: 0.54–1.18); P=0.16, by log-rank test). (c) Impact of PGID on postoperative day five on length of stay in trial cohort on hospital stay (hazard ratio: 2.14 (95% CI: 1.30–3.51); P=0.003, by log-rank test). (d) Kaplan-Meier plot showing effect of sham feeding on length of hospital stay (unadjusted hazard ratio: 0.82 (95% CI: 0.55–1.22); P=0.09, by log-rank test).

### Table 2: Baseline patient characteristics: POM-X pilot RCT.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No gum (n=49)</th>
<th>Gum (n=52)</th>
</tr>
</thead>
<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>1 (2%)</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>
</tbody>
</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–s). Frequency domain analysis showed that normalized high frequency (efferent vagal activity) was higher in patients randomized to chew gum postoperatively (Fig. 3r and s). An increase in normalized low frequency was observed in patients randomized to control (Fig. 3a and i), 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. None of these studies have considered PGID, which is of particular importance given the challenges surrounding blinding of the intervention. We are unaware of any clinical study that has explored the autonomic impact of sham feeding, which is of particular importance given the challenges surrounding blinding of the intervention.
substantially, so it remains unclear whether direct gut innervation can account for the beneficial effects of sham feeding, in a wide range of colorectal procedures. As the neurophysiological basis of PGID may originate from brainstem neuronal dysfunction, the addition of novel data supporting the use of sham feeding via prescribed chewing gum in orthopaedic patients significantly extends this literature. Thus, our data suggest that at least part of this beneficial effect may be applicable beyond gastrointestinal surgery.

Central vagal activation reduces surgical inflammation in experimental postoperative ileus. This is likely to be mediated by 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 acetylcholine acting on alpha-7 nicotinic receptors on splenic macrophages. Vagal nerve stimulation also attenuates hemorrhage in experimental soft tissue injury, an effect possibly mediated 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 inflammation through acetylcholine.

Fig 3 Effect of sham feeding on cardiovascular and autonomic variables. (A) Serial changes in heart rate perioperatively. Shaded area represents measurements made postoperatively. P value refers to pre vs. postoperative comparison (analysed by two-way ANOVA). (B) Serial changes in arterial pressure perioperatively. Shaded area represents measurements made postoperatively. P value refers to pre vs. postoperative comparison (analysed by two-way ANOVA). MAP: mean arterial pressure. (c) SDNN (standard deviation of successive beat-to-beat intervals) in patients randomized to gum or control (pre and postoperative median (25–75 centile) values). P value refers to between group comparisons postoperatively (two-way ANOVA). (d) Parasympathetic activity as indicated by pNN50 (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) in patients randomized to gum or control. Median (25–75 centile) values shown; P value refers to between group comparisons postoperatively (two-way ANOVA). (e) Parasympathetic activity as indicated by Root Mean Square of the Successive Differences (RMSSD) in patients randomized to gum or control (median (25–75 centile)). P value refers to between group comparisons postoperatively (two-way ANOVA). (f) Normalized high frequency band (efferent vagal activity) derived from frequency domain analysis in patients randomized to gum or control. Median (25–75 centile) values; P value refers to between group comparisons postoperatively (two-way ANOVA). (g) Normalized low frequency band derived from frequency domain analysis in patients randomized to gum or control. Median (25–75 centile) values; P value refers to between group comparisons postoperatively (two-way ANOVA).
the over-arching hypothesis. Nevertheless, we conducted an ade-
quately powered study in a highly phenotyped surgical popula-
tion. The patient demographic may not be extrapolatable to older
patients with more frequent, and serious, co-morbidities asso-
ciated with established autonomic dysfunction. We did not test
for other postoperative autonomic alterations, including orthostat-
ic 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 peri-
operative period involving parasympathetic dysfunction, includ-
ing the development of atrial fibrillation43 44 and myocardial
injury.12 Second, chewing gum is a cheap, readily available inter-
vention associated with negligible harm. It thus appears reason-
able to advocate use of chewing gum beyond the colorectal
surgical arena.

In conclusion, no effect of chewing gum on morbidity was de-
monstrated 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 chew-
ing gum on vagal efferent activity was demonstrated, suggesting
that further clinical trials are warranted. Innovative autonomic
interventions aimed at preventing PGID may reduce postopera-
tive 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.

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