Droperidol has comparable clinical efficacy against both nausea and vomiting

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Background. Droperidol is commonly noted to be more effective at preventing postoperative nausea (PON) than vomiting (POV) and it is assumed to have a short duration of action. This may be relevant for clinical decisions, especially for designing multiple-drug antiemetic regimens.

Methods. We conducted a post hoc analysis of a large multicentre trial. Within this trial, 1734 patients underwent inhalation anaesthesia and were randomly stratified to receive several antiemetic interventions according to a factorial design, one of which was droperidol 1.25 mg vs placebo. We considered differences to be significant when: (i) point estimates of one outcome are not within the limits of the confidence interval (CI) of the other outcome; and (ii) differences in risk ratio (also known as relative risks, RR) are at least 20%.

Results. Over 24 h, nausea was reduced from 42.9% in the control to 32.0% in the droperidol group, corresponding to a relative risk (RR) of 0.75 (95% CI from 0.66 to 0.84). Vomiting was reduced from 15.6% to 11.8%, and therefore associated with a similar RR of 0.76 (0.59–0.96). In the early postoperative period (0–2 h), droperidol prevented nausea and vomiting similarly, with an RR of 0.57 (0.46–0.69) for nausea and 0.56 (0.37–0.85) for vomiting. In the late postoperative period (2–24 h), the RR was again similar with 0.83 (0.72–0.96) for nausea compared with 0.89 (0.66–1.18) for vomiting but significantly less compared with the early postoperative period.

Conclusions. We conclude that droperidol prevents PON and POV equally well, yet its duration of action is short-lived.

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Despite considerable effort by anaesthetists, postoperative nausea and vomiting (PONV) occurs in one-quarter to one-third of surgical patients.1–4 The term PONV is used frequently in reports to describe both nausea and vomiting; however, the two responses are biologically distinct phenomena and should more appropriately be reported and analysed separately.5 6 Further evidence for this distinction can be found in a recent epidemiologic study by Stadler and colleagues7 who found that although most risk factors are predictive for both outcomes, some appear to be predictive for nausea only.8 It is thus conceivable that a drug used for the prevention of PONV may be, for example, more effective against nausea than vomiting.

Consistent with this notion, authors of a systematic review concluded that droperidol prevents nausea to a greater extent than vomiting,8 and this conclusion has
since been widely accepted.\textsuperscript{3} However, the conclusion of this systematic review is tempered by the fact that few studies separately report all relevant outcomes. Consequently, relative efficacies for nausea and vomiting were determined across different studies rather than strictly from studies that adequately evaluated both responses, making direct comparisons of the outcomes difficult.

We have previously designed\textsuperscript{9} and reported\textsuperscript{10} on an International Multicenter Protocol to assess the single and combined benefits of Antiemetic strategies in a Controlled clinical Trial of factorial design (IMPACT) that investigated the effect of six interventions on PONV. The data set of IMPACT allows us directly to analyse whether droperidol comparably reduces the relative risks (RRs) for nausea and for vomiting, or if there is a clinically relevant difference.

The minimal clinically significant difference (MCSD) is the smallest difference that clinicians and patients would care about. It is possible for the MCSD to be larger than the difference that could be detected as statistically significant in a given situation (especially a clinical trial involving a large population), in which case, a statistically, but not clinically, significant difference might be of little practical importance. For the purposes of this analysis, we considered differences to be clinically significant when: (i) point estimates of one outcome are not within the limits of the confidence interval (CI) of the other outcome; and (ii) risk ratios differences are at least 20%.\textsuperscript{11}

**Methods**

**Protocol**

The details of the underlying protocol for this post hoc analysis are described elsewhere.\textsuperscript{9,10} In brief, adult patients undergoing surgery under general anaesthesia met eligibility criteria, if they had at least two predictors of the simplified risk score for PONV, i.e. their calculated risk for PONV exceeded about 40%.\textsuperscript{12} The considered risk factors were: female gender, previous history of PONV, motion sickness, or both, non-smoking status, and the anticipated use of postoperative opioids.

With ethics committee approval and informed consent, participating patients were randomized to receive a combination of antiemetic interventions utilizing a factorial design. Therefore, all patients were randomized to ondansetron 4 mg vs placebo, dexamethasone 4 mg vs placebo, and droperidol 1.25 mg vs placebo.

Patients were monitored for nausea and vomiting for the first 24 h after surgery. The time, severity, and characteristics of any emetic episode were recorded on standardized forms. Patients who experienced postoperative nausea (PON), postoperative vomiting (POV), or both were considered having suffered PONV.\textsuperscript{5} Rescue antiemetic medication was provided in case of symptoms, upon active request, or both.\textsuperscript{9,10}

At 2 and 24 h after surgery, an investigator blinded to treatment recorded emetic episodes and the patient’s self-assessment of their strongest nausea during the preceding time interval using an 11-point verbal rating scale.\textsuperscript{5} The results of this trial are reported previously.\textsuperscript{8,10}

For the current article, we analysed the effect of droperidol on nausea vs vomiting in a sub-data set of 1734 patients who received an inhalation anaesthetic for maintenance of anaesthesia. The factorial design ensured that the additional antiemetic interventions were fully balanced when comparing one intervention vs control.\textsuperscript{9,10}

**Statistical analysis**

The primary outcomes for these analyses were the incidences of nausea (PON), vomiting (POV), and PONV for 24 h after anaesthesia.

Since nausea and vomiting were reported concurrently in the same patients, the outcomes are best described as correlated responses. Currently, there is no adequate statistical test available for comparison of correlated responses to a single intervention. Instead, we calculated RRs with their CIs and considered the difference significant when: (i) the point estimate of one outcome was not within the limits of the CI of the other outcome; and (ii) risk ratio difference was at least 20%.

Results are presented as risk ratios (also known as relative risks, RR) with 95% CIs unless otherwise indicated. All analyses were conducted with SPSS 16.0 (SPSS Inc., Chicago, IL, USA) or STATA 10 (StataCorp LP, College Station, TX, USA).

**Results**

Written informed consent was obtained from 1734 patients. The majority were females (81%), non-smokers (81%), and 34% had a positive history of PONV. Overall, 38% experienced nausea and 14% had at least one episode of vomiting within 24 h after surgery. Patient characteristics and the risk for PONV were similar between the two groups (Table 1).

For the overall 24 h period, PON was reduced from 42.9% in the placebo group to 32.0% in the droperidol group, corresponding to an RR of 0.75 (95% CI 0.66–0.84), or an RR reduction of 25% (Table 2). Vomiting was reduced from 15.6% in the placebo group to 11.8% in the droperidol group, corresponding to an RR of 0.76 (95% CI 0.59–0.96), or an RR reduction of 24% (Table 2). The RRs of 0.75 and 0.76 were clinically similar and CIs of nausea included the point estimate for vomiting and vice versa (Fig. 1).

During the first 2 h after surgery, droperidol prevented nausea and vomiting similarly, with an RR of 0.57 (0.46–0.69) for nausea and 0.56 (0.37–0.85) for vomiting (Table 2). During the late postoperative period (2–24 h), the RR was again similar with 0.83 (0.72–0.96) for nausea and 0.89 (0.66–1.18) for vomiting (Fig. 2).

Additionally, when comparing the efficacy of droperidol in the early (0–2 h) vs the late (2–24 h) postoperative period, the RR reduction decreases from 43% in the early
period to 17% in the late period for nausea and from 44% to 11% for vomiting. Neither the point estimates for nausea nor those for vomiting are included in the 95% CI of the corresponding time interval (Fig. 2).

Discussion

In this analysis of a large, randomized, controlled, multi-centre trial, the RR for nausea was 0.75 and for vomiting 0.76, a difference that is neither statistically significant nor clinically relevant (Fig. 1). In addition, droperidol was significantly more efficacious in reducing PONV in the early (RR 0.57) compared with the late postoperative period (RR 0.81).

The similar efficacy of droperidol for nausea and for vomiting contrasts with the generally accepted notion that has been restated in consensus guidelines of the Society for Ambulatory Anaesthesia in 2007. This notion was based on a systematic review that concluded ‘the antinausea effect is more pronounced than the effect on vomiting’. However, these statements were based on the ratio of the absence of symptoms or the numbers needed to treat. Because both these measures are highly sensitive towards the baseline incidences, they do not allow a direct comparison of the efficacy for two outcomes with different incidences (i.e. nausea being more frequent than vomiting). In fact, when calculating the RRs based on that systematic review, the RR for overall nausea (0–24 h) was 0.76 (58% in the placebo group vs 45% in the droperidol group), and the RR for overall vomiting was 0.56 (46% vs 28%, Fig. 2). Thus, the RRs are again similar and we conclude that the data of that systematic review support our findings that droperidol reduces nausea and vomiting to a similar degree.

In the early postoperative period, the RRs for nausea and vomiting were 0.57 and 0.56, respectively. This is again similar to the data published in the systematic review where the RRs for nausea and vomiting were 0.48 (33% vs 16%) and 0.48 (29% vs 14%). Thus, the RRs for nausea and for vomiting are again similar. This was also the case when we compared the RRs for the late postoperative period of our data.

Another notable result of our analysis is the higher efficacy of droperidol to prevent PONV in early postoperative compared with the late postoperative period with RR of 0.57 vs 0.81 (Table 2, Fig. 3). This is consistent with the short half-life of droperidol of about 2 h and previous studies such as a paper from Australia where the RRs in the early and late period were 0.72 (53% vs 38%) and

| Table 2 RR, absolute risk reduction, and number-needed-to-treat. Results presented as number of patients (% of total) |
|---------------------------------|-----------------|-------------------|-----------------|-----------------|-----------------|-----------------|
| Interval | Symptom | Control (n=867) | Droperidol (n=867) | Relative risk (95% CI) | P-value | Absolute risk reduction (%) | Number-needed-to-treat |
| 0–2 h Nausea | 223 (25.7) | 126 (14.5) | 0.57 (0.46–0.69) | <0.001 | 11.2 | 9 |
| Vomiting | 59 (6.8) | 33 (3.8) | 0.56 (0.37–0.85) | 0.005 | 3 | 33 |
| Nausea, vomiting, or both | 231 (26.6) | 132 (15.2) | 0.57 (0.47–0.69) | <0.001 | 11.4 | 9 |
| Rescue treatment | 31 (3.6) | 6 (0.7) | 0.19 (0.08–0.46) | <0.001 | 2.9 | 35 |
| 2–24 h Nausea | 284 (32.8) | 237 (27.4) | 0.83 (0.72–0.96) | 0.013 | 5.4 | 19 |
| Vomiting | 88 (10.2) | 78 (9) | 0.89 (0.66–1.18) | 0.414 | 1.2 | 83 |
| Nausea, vomiting, or both | 296 (34.2) | 241 (27.8) | 0.81 (0.71–0.94) | 0.003 | 6.4 | 16 |
| Rescue treatment | 18 (2.1) | 17 (2.0) | 0.94 (0.49–1.82) | 0.86 | 0.1 | 867 |
| 0–24 h Nausea | 372 (42.9) | 277 (32) | 0.75 (0.66–0.84) | <0.001 | 11 | 9 |
| Vomiting | 135 (15.6) | 102 (11.8) | 0.76 (0.59–0.96) | 0.021 | 3.8 | 26 |
| Nausea, vomiting, or both | 382 (44.1) | 283 (32.6) | 0.74 (0.66–0.84) | <0.001 | 11.5 | 9 |
| Rescue treatment | 47 (5.4) | 21 (2.4) | 0.45 (0.27–0.74) | 0.001 | 3 | 33 |
1.00 (15% vs 15%). Because of the short half-life, a longer antiemetic coverage may better be achieved through multiple recurrent small doses instead of one large bolus. This may be the reason why droperidol added to morphine in a patient-controlled analgesic pump has been shown by Tramer and colleagues to be highly effective in providing a full 24 h antiemetic coverage.

The short-lived antiemetic coverage of a single dose of droperidol is further corroborated by our data where the RR for antiemetic rescue treatment was 0.19 in the early and 0.94 in the late postoperative period (Table 2, Fig. 3).

The results of our large multicentre trial suggest that droperidol reduces the risk for nausea and vomiting equally. The RR reductions for both symptoms were comparable. Therefore, for clinical practice and also for designing clinical trials with multiple antiemetic strategies, it is not necessary to consider anti-nauseous and anti-vomiting efficacies for droperidol separately. However, the antiemetic property of a single bolus is short-lived because of the short plasma half-life of droperidol.

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