Does Neostigmine Administration Produce a Clinically Important Increase in Postoperative Nausea and Vomiting?

Ching-Rong Cheng, MD, Daniel I. Sessler, MD, and Christian C. Apfel, MD

Outcomes Research Institute and Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, Kentucky

Neostigmine is used to antagonize neuromuscular blocker-induced residual neuromuscular paralysis. Despite the findings of a previous meta-analysis, the effect of neostigmine on postoperative nausea and vomiting remains unresolved. We reevaluated the effect of neostigmine on postoperative nausea and vomiting while considering the different anticholinergics as potentially confounding factors. We performed a systematic literature search using MEDLINE, Embase, Cochrane library, reference listings, and hand searching with no language restriction through December 2004 and identified 10 clinical, randomized, controlled trials evaluating neostigmine’s effect on postoperative nausea and vomiting. Data on nausea or vomiting from 933 patients were extracted for the early (0–6 h), delayed (6–24 h), and overall (0–24 h) postoperative periods and analyzed with RevMan 4.2 (Cochrane Collaboration, Oxford, UK) and multiple logistic regression analysis. The combination of neostigmine with either atropine or glycopyrrolate did not significantly increase the incidence of overall (0–24 h) vomiting (relative risk, 0.91; 95% confidence interval, 0.70–1.18; \( P = 0.48 \)) or nausea (relative risk, 1.24; 95% confidence interval, 0.98–1.59; \( P = 0.08 \)). Multiple logistic regression analysis indicated that there was not a significant increase in the risk of vomiting with large compared with small doses of neostigmine. Contrasting a previous analysis, we conclude that there is insufficient evidence to conclude that neostigmine increases the risk of postoperative nausea and vomiting.


Nausea and vomiting remain among the most common perioperative complications, occurring in approximately 30% of postoperative patients (1–3). Although the origin is generally believed to be multifactorial, there is increasing evidence that patient-specific risk factors play a major role (4). However, drugs specific to anesthesia, including volatile anesthetics, nitrous oxide, and postoperative opioids, are at least as important and, in contrast to the patient-specific risk factors, under the control of anesthesiologists (5,6).

Neostigmine is often used to antagonize residual neuromuscular block. Because anticholinesterases such as neostigmine have cholinergic effects on the gastrointestinal tract (increased motility and gastric acid secretion) and on the heart (bradycardia, cardiac arrest), they are coadministered with anticholinergics such as atropine or glycopyrrolate (7). Atropine is a tertiary amine and can cross the blood-brain barrier to cause central effects. In contrast, glycopyrrolate is a quaternary amine that does not easily cross the blood-brain barrier and thus has no important central effects (8).

Intrathecal neostigmine has been shown to cause severe nausea and vomiting in a dose-dependent manner, probably via action on the brainstem (9). The effect of IV neostigmine on postoperative nausea and vomiting (PONV) remains controversial. Tramér and Fuchs-Buder (10) concluded in their meta-analysis that neostigmine in doses &gt;2.5 mg increases the incidence of PONV. However, a subsequent study (11), not included in their systemic review (10), was unable to confirm an emetogenic effect. Furthermore, the incidence of PONV appears to be reduced when neostigmine is combined with atropine as opposed to glycopyrrolate (12).

If neostigmine were truly emetogenic, it would be reasonable to reconsider its routine use in antagonizing neuromuscular paralysis, especially for patients at increased risk for PONV. Our goal was thus to determine whether neostigmine administration produces a clinically relevant increase in the risk of PONV and to
determine the extent to which risk depends on the coadministration of the anticholinergics.

Methods
We searched for all published full reports of randomized, controlled trials that compared patients given neuromuscular blocking antagonists (intervention) with those allowed to recover spontaneously from neuromuscular block (control group, i.e., placebo or no added anticholinesterase). Included trials were required to have dichotomous outcomes (presence or absence) for postoperative nausea (PON), postoperative vomiting (POV), or adverse events.

We searched systematically for relevant reports without any language restrictions in MEDLINE (1966–2004), EMBASE (1980–2004), and Cochrane Library (2004, Issue 4); the date of our last electronic search was December 8, 2004. We used the free text terms “nausea, vomiting, emesis, neostigmine, prostigmine, edrophonium, antagonism, and neuromuscular block” in any combination for the search. A manual scan was performed through the reference lists of all studies in the search results until no further relevant references could be identified.

Authors of the original publication were contacted if analyses end-points were insufficiently reported. We sought to obtain separate data for PON and POV and for the early, delayed, and overall study period of 24 h (13). Two authors (RC and CCA) independently read each retrieved report to assess the adequacy of randomization and blinding. The 5-point Oxford score was used to assess the quality of the study design (14) and differences were resolved by consensus.

We obtained information on patients, anesthetics, type and dose of anticholinergics, type and dose of anticholinesterases, and intervention-related adverse effects from each included report. Dichotomous data on harm and efficacy were extracted from the published reports. Extracted outcome data were early PON, early POV (0–6 h postoperative cumulative incidence), delayed PON, delayed POV (6–24 h postoperative cumulative incidence), overall postoperative PON, and overall POV (0–24 h postoperative cumulative incidence), as well as data on clinically diagnosed adverse events.

Data extracted from the relevant studies were entered into RevMan 4.2 (Review Manager, Cochrane Collaboration, UK) and analyzed. The relative risk (RR) with the corresponding 95% confidence intervals (CI) was calculated for each study. The results were pooled together using the Mantel-Haenszel method for combining trials. The individual effect sizes were weighted according to the reciprocal of their variance. A random effect model was used and heterogeneity was determined under the assumption (null hypothesis) that there were no differences in treatment effect between trials. Results are presented as RR (95% CI). The comparisons of neostigmine versus control were also divided into subgroups based on whether atropine or glycopyrrolate was given.

Multiple logistic regression analysis was used to investigate the relationship of the dose of neostigmine and POV. The analysis was corrected by center, with the largest center being the reference group (SPSS version 12.0 for windows, SPSS Inc., Chicago, IL). An absolute increase of 10% or a relative increase of 25%, i.e., a quarter of the incidence, was considered to be clinically important.

Results
We found 15 reports that met our criteria. Five of these were subsequently excluded: two did not have control groups (15,16), another did not report PONV results (17), the data of one other study were insufficient to be considered in the analysis, despite getting more information from the authors (18), and in the last excluded study, only the combination of edrophonium and atropine was compared with placebo (19). In one trial, although only data on PONV were published, the authors generously provided the detailed data so that their study could be included in the analysis (11). We therefore performed meta-analyses on 10 comparisons of neostigmine versus an inactive control with 933 study patients (Table 1) (11,20–28). All trials were randomized, except one that had a pseudo-randomization; we only included those patients who received standard anesthesia (n = 41) or no reversal (n = 40) after cholecystectomy from this study (28).

Early (0–6 h) PON was reported as an outcome in 6 trials (Table 2) (11,20–23,25): 5 with glycopyrrolate (11,21–23,25) and 1 with atropine (20). The RR of suffering PON in this early period was 1.24 (0.86–1.80; P = 0.25). Early POV (0–6 h) was reported in 8 studies. Patients in six of them received glycopyrrolate (11,21–23,25,27); patients in the other two received atropine (20,26). The RR for POV in the early postoperative period was 1.05 (0.72–1.55; P = 0.79).

Delayed (6–24 h) PON as an outcome was included in 4 studies with a RR of 1.09 (0.76–1.57; P = 0.64) (11,21,23,25). All were with neostigmine combined with glycopyrrolate versus control. Delayed POV was an outcome in 4 studies; all were with glycopyrrolate. The RR was 1.01 (0.58–1.78; P = 0.96) (11,21,23,25).

Overall (0–24 h) PON was reported in 6 studies with a RR of 1.24 (0.98–1.59; P = 0.08) (Fig. 1) (11,20,22–25). Overall POV (0–24 h) was reported in 8 studies with coadministration of atropine or glycopyrrolate with a RR of 0.91 (0.70–1.18; P = 0.48) (Fig. 2) (11,20,22–25,27,28). Thus, neostigmine was not associated with a significant increase in PON or POV in any of the above-mentioned analyses.
Table 1. Characteristics of Analyzed Studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Score (random, blind, dropouts)</th>
<th>N</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boeke et al., 1994 (20)</td>
<td>(1, 0, 1)</td>
<td>79</td>
<td>Vecuronium; neostigmine 1.5 mg and atropine vs. no treatment</td>
<td>PON, POV in day care; first and second day nausea, vomiting</td>
<td>Early: day care stage</td>
</tr>
<tr>
<td>Ding et al., 1994 (21)</td>
<td>(1, 0, 1)</td>
<td>69</td>
<td>Succinylcholine + mivacurium + no reversal vs. mivacurium + mivacurium + no reversal vs. mivacurium + mivacurium + neostigmine 2.5 mg and glycopyrrolate 0.5 mg</td>
<td>PON and POV in 0–1 h; 2–3 h; 3–9 h; 9–15 h; 15–21 h; 21–27 h total (0–27 h)</td>
<td>Early: PACU stay</td>
</tr>
<tr>
<td>Hovorka et al., 1997 (22)</td>
<td>(1, 2, 1)</td>
<td>160</td>
<td>Mivacurium; Neostigmine 2.0 mg and glycopyrrolate vs. placebo</td>
<td>PON and VO in PACU; 24 h PON, POV</td>
<td>Early: 0–3 h</td>
</tr>
<tr>
<td>Janhunen and Tammisto, 1972 (28)</td>
<td>(0 to 1, 0, 0)</td>
<td>81</td>
<td>Tubocurarine; Neostigmine 2.0 mg + atropine 1.0 mg vs. No reversal</td>
<td>POV (0–24 h) Only included standard vs. no reversal patients</td>
<td>Early: PACU and Phase II stage</td>
</tr>
<tr>
<td>Joshi et al., 1999 (23)</td>
<td>(2, 2, 0)</td>
<td>100</td>
<td>Mivacurium vs. rocuronium; Residual block reversal with neostigmine 2.5 mg + glycopyrrolate 0.5 mg</td>
<td>PACU, Phase II, 24 h PON and POV</td>
<td>Early: PACU and Phase II stage</td>
</tr>
<tr>
<td>King et al., 1988 (24)</td>
<td>(1, 0, 0)</td>
<td>38</td>
<td>Tubocurarine; Neostigmine 2.5 mg vs. placebo</td>
<td>PON, POV in 24 h</td>
<td></td>
</tr>
<tr>
<td>Lovstad et al., 2001 (25)</td>
<td>(2, 2, 1)</td>
<td>90</td>
<td>Mivacurium; Neostigmine 2.5 mg + glycopyrrolate 0.5 mg vs. placebo</td>
<td>0–6 h; 6–24 h; 0–24 h PON, PON; Satisfaction score</td>
<td>Pretreated with Ondansetron Only PONV, no PON, POV data Recount data after got original data</td>
</tr>
<tr>
<td>Nelskyla et al., 1998 (12)</td>
<td>(2, 2, 1)</td>
<td>100</td>
<td>Mivacurium; Neostigmine 2.0 mg + glycopyrrolate 0.4 mg vs. No treatment</td>
<td>PON, POV in PACU, ward, on the way home, at home, 24 h</td>
<td></td>
</tr>
<tr>
<td>Walsh et al., 1988 (26)</td>
<td>(2, 0, 1)</td>
<td>120</td>
<td>Pancuronium; Neostigmine (60 μg/kg) + atropine (20 μg/kg) vs. No treatment</td>
<td>Early POV</td>
<td></td>
</tr>
<tr>
<td>Wacha et al., 1995 (27)</td>
<td>(1, 2, 0)</td>
<td>113</td>
<td>Mivacurium; Placebo vs. Edrophonium (1 mg/kg) + atropine (10 μg/kg) vs. Neostigmine (70 μg/kg) + Glycopyrrolate (10 μg/kg)</td>
<td>Early POV, POV in 24 h</td>
<td></td>
</tr>
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</table>

PACU = postanesthesia care unit; PON = postoperative nausea; POV = postoperative vomiting.

Table 2. Early and Delayed Postoperative Nausea and Vomiting with Neostigmine Versus Control; Results of the Meta-analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Anticholinergics</th>
<th>Number of studies</th>
<th>Number of participants</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early nausea (0–6 h)</td>
<td>Atropine and Glycopyrrolate</td>
<td>6</td>
<td>584</td>
<td>1.24 (0.86–1.80)</td>
</tr>
<tr>
<td></td>
<td>Atropine</td>
<td>1</td>
<td>79</td>
<td>0.67 (0.36–1.26)</td>
</tr>
<tr>
<td></td>
<td>Glycopyrrolate</td>
<td>5</td>
<td>505</td>
<td>1.39 (0.97–1.99)</td>
</tr>
<tr>
<td>Early vomiting (0–6 h)</td>
<td>Atropine and Glycopyrrolate</td>
<td>8</td>
<td>768</td>
<td>1.05 (0.72–1.55)</td>
</tr>
<tr>
<td></td>
<td>Atropine</td>
<td>2</td>
<td>199</td>
<td>0.75 (0.52–1.08)</td>
</tr>
<tr>
<td></td>
<td>Glycopyrrolate</td>
<td>6</td>
<td>568</td>
<td>1.35 (0.88–2.06)</td>
</tr>
<tr>
<td>Delayed nausea (6–24 h)</td>
<td>Glycopyrrolate</td>
<td>4</td>
<td>337</td>
<td>1.09 (0.76–1.57)</td>
</tr>
<tr>
<td>Delayed vomiting (6–24 h)</td>
<td>Glycopyrrolate</td>
<td>4</td>
<td>337</td>
<td>1.01 (0.58–1.78)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

We performed multiple logistic regression analysis of overall POV on 9 studies with 800 patients (Table 3) (11,12,20,22–25,27,28). The average dose of neostigmine when given with glycopyrrolate was 3.02 mg/70 kg; the average dose when given with atropine was 2.59 mg/70 kg. We used the coefficients in Table 3 to calculate the odds ratio for a combination of interventions by “odds ratio = e^(dose*a+β)” where “e” is the natural logarithm (2.71), “dose” is the neostigmine dose in mg, “a” is the coefficient for the neostigmine (ln 1.32 = 0.278), and “β” is the coefficient for the concomitant anticholinergic drug, −0.73 (ln 0.482) for glycopyrrolate or −1.14 (ln 0.32) for atropine. Thus, patients who received an average of 3.02 mg neostigmine and glycopyrrolate had an odds ratio for developing POV of 1.11 (= e^(3.02*0.278–0.73)) whereas those receiving an average of 2.59 mg neostigmine with atropine had an odds ratio of 0.66 (= e^(2.59*0.278–1.14)). For comparison, the effect of the center, i.e., where the study was conducted, had odds ratios ranging from 0.12 to 5.24. Thus, logistic regression analysis suggested that neostigmine does not significantly increase overall POV.

Two studies described inadequate muscle strength in their control groups: One patient was excluded from a 40-patient control group because of failure to
regain muscle strength (20), and 2 of 50 control patients were excluded from the efficacy analysis of another study because they needed muscle reversal for muscle weakness (19). There were no other reports of other side effects in patients given neostigmine or in the control patients.
Tramer and Fuchs-Buder also identified a dose-dependent relationship between neostigmine and PONV, which we were unable to confirm. A closer look at their Figure 2 reveals that the label of the Y-axis should probably be risk reduction rather than number-needed-to-treat, as published. But even then, the “1” at the top of the dotted line should be “0” and values for the 1.5-mg neostigmine were less than with no antagonism. This would represent a negative effect at small dose and would be inconsistent with a classical pharmacological dose-response relationship. Furthermore, as dose cannot be considered as a covariate in RevMan, we subjected the data to logistic regression analysis, which showed that the dose of neostigmine did not exert a statistically significant effect on the rate of PONV. Furthermore, center effects (i.e., where the study was performed) were an order of magnitude larger than the dose dependence, suggesting that the nonsignificant effect of neostigmine dose is considerably smaller than other influences.

A further limitation of the previous meta-analysis is that it did not include atropine or glycopyrrolate as potential confounders; instead, the authors argued that the choice of the anticholinergic partner drug does not affect PONV. Our logistic regression analysis revealed that atropine was associated with a statistically significant decreased risk for POV whereas glycopyrrolate was not. This result is supported by the study from Chhibber et al. (11) in which atropine was associated with significantly less POV when compared directly with glycopyrrolate. Thus, it could be hypothesized that atropine is a better antiemetic than glycopyrrolate because of its central anticholinergic effects. As patients given atropine received about 0.5 mg less neostigmine than those given glycopyrrolate, only a multivariate analysis could correct for those confounders. Ignoring the different antiemetic
effects of the anticholinergic partner drugs may thus have contributed to the appearance of a dose-response relationship for neostigmine in the previous meta-analysis. However, because there is only one true head-to-head comparison of atropine versus glycopyrrolate (12), these results should be interpreted with some caution.

It is possible that the rate of PONV is dependent on the ratio between neostigmine and the coadministered anticholinergic drug. However, the ratio of neostigmine to glycopyrrolate was 5:1 in almost all of the studies included in our meta-analysis, and we only had 2 studies in which atropine was the anticholinergic. This consistency in the ratio of neostigmine to glycopyrrolate precluded introducing this factor into the multiple regression analysis (collinearity problem).

There were only three cases of residual muscle weakness noted in the control groups. Among the 10 studies we used for efficacy analysis, only 1 of 933 patients was reported to have residual muscle relaxation requiring treatment (0.1%). Although this infrequent incidence of residual paralysis suggests that antagonism of neuromuscular block may not be necessary, numerous complications have been reported when patients are inadequately antagonized (29).

Search strategies of systematic reviews are designed to locate all relevant studies pertinent to the question. To achieve the highest level of evidence, meta-analyses provide an objective approach to quantify the effects of all data available from trials. It is, therefore, conceivable that the point estimates from meta-analyses have more external validity than single studies. However, the best approach to weighing the relative impact of studies remains in dispute. For example, we used the standard inverse standard error to weight the studies, although this approach can lend too much weight to small studies (30,31). Point estimates regarding the effectiveness should, therefore, be interpreted with some caution. Another problem of meta-analyses is the heterogeneity of reported end-points (e.g., PON and POV) and when they are measured (early, delayed, or overall period). A consequence is that, as in our analysis, point estimates for different outcomes are not necessarily derived from the same trials. Thus, although analysis of the early postoperative period suggests that neostigmine might increase early PON but not early POV, such interpretations should be viewed with a high degree of skepticism.

Our meta-analysis failed to demonstrate that neostigmine leads to a clinically important increase in the risk of PONV. This might be a result of the limited number of patients available for analysis. For example, the incidences of overall PON for the neostigmine and the control groups were 41% and 33%, respectively, so that the average group size of 280 patients only provided a 43% power to detect this absolute difference of 8% (which would be of limited clinical importance in any case). Thus, only a large, well-designed, randomized controlled trial can fully resolve this issue (32). Such a trial should also address whether there is a dose-response relationship between neostigmine and PONV and the effect of atropine versus glycopyrrolate, possibly by using a factorial design, which has been proven to be a powerful tool (6,33,34). Defining a clinically important decrease in PONV of approximately 25% for the omission of neostigmine would require at least 372 patients if an incidence of 60% were to be studied, 524 patients for an incidence of 50%, and 744 for 40% (13).

In conclusion, our meta-analysis suggested that neostigmine does not increase the risk of POV in the early, delayed, or overall postoperative period and that there is insufficient evidence to conclude that neostigmine leads to a clinically important increase in the risk of PON. Thus, concerns about the effect of neostigmine on PONV should probably not influence the clinician’s decision to antagonize neuromuscular block.

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References


