BJA

British Journal of Anaesthesia, 118 (6): 918–23 (2017)

doi: 10.1093/bja/aex099
Advance Access Publication Date: 15 May 2017
Paediatrics

Addition of droperidol to prophylactic ondansetron and dexamethasone in children at high risk for postoperative vomiting. A randomized, controlled, double-blind study

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Abstract

Background: The combination of dexamethasone (DEX), ondansetron (OND) and droperidol (DRO) is efficacious in preventing postoperative nausea and vomiting in adults, but has not been well assessed in children.
Methods: Children undergoing elective surgery under general anaesthesia and considered at high risk for postoperative vomiting (POV) were randomly assigned to receive a combination of DEX, OND and placebo (Group A) or a combination of DEX, OND and DRO (Group B). The primary outcome was the incidence of POV during the first 24 hours after surgery. We hypothesized that the addition of DRO to the standard antiemetic prophylaxis would provide a further 15% reduction in the residual risk for POV. The secondary outcome considered was any adverse event occurring during the study.
Results: One hundred and fifty-three children, aged three to 16 years, were randomized to Group A and 162 to Group B. The overall incidence of POV did not differ significantly between the two groups, with 16 patients in Group A (10.5%) and 18 in Group B (11.1%) presenting with one or more episodes of POV, $P=0.86$. Fewer patients presented with adverse events in Group A (2%) compared with Group B (8%), $P=0.01$. Drowsiness and headache were the principal adverse events reported.

Editorial decision: February 12, 2017; **Accepted:** March 22, 2017

Conclusions: The addition of DRO to a combination of OND and DEX did not decrease POV frequency below that obtained with the two-drug combination in children at high risk of POV, but increased the risk of drowsiness. The combination of DEX and OND should be recommended in children with a high risk of POV.
Clinical trial registration. NCT01739985.

Key words: postoperative nausea and vomiting, child, antiemetics

Editor's key points

- Postoperative vomiting is a common problem in children.
- Anti-emetics are most effective in children at high risk of postoperative vomiting.
- The authors studied the addition of droperidol to ondansetron and dexamethasone in a high risk group.
- Addition of droperidol did not decrease the incidence of vomiting, but did increase the incidence of drowsiness.

Postoperative nausea and vomiting (PONV) is a significant complication of general anaesthesia in paediatric patients, with an incidence of up to 70% in the absence of prophylactic antiemetic treatment.[1] With modern anaesthetic procedures, life-threatening postoperative complications have become rare. Postoperative care therefore now focuses on the management of pain or postoperative symptoms decreasing patient comfort. PONV was long considered a minor inconvenience of surgery. However, PONV is a source of anxiety for patients and causes considerable discomfort; for these reasons, PONV is the postoperative complication that patients and parents would most like to see resolved.[2] PONV is also the main reason for unplanned hospitalization in cases of day-hospital surgery. The overall incidence of postoperative vomiting (POV) is between 25% and 30% in the paediatric population, but the incidence of POV is much higher for some types of surgery and has been reported to reach 80% in some studies of strabismus surgery.[3] High-risk children may be identified through the calculation of risk scores of POV, such as the VPOP score.[4] This score ranges from 0 to 6 points (Table 1): children with a score of 0–1 are at low risk of POV, those with a score of 2–3 are at moderate risk, and those with a score of 4 or more are considered to be at high risk of POV. A very high incidence of POV (>50%) has been found in children with VPOP scores of 5 or more.

In this population, prophylactic antiemetic administration should significantly decrease the incidence of POV, because antiemetic drugs seem to be particularly effective for prophylaxis in patients with a moderate to high risk of POV.[5] In these patients, POV can be prevented by treatment with various antiemetics, including setron,[6 7] corticosteroids[8] and droperidol,[4 5 8] with differing success rates and adverse effects.[9] Apfel and colleagues[10] showed that increasing the number of antiemetic drugs administered could reduce the incidence of PONV in adults. However, even with the use of a combination of two antiemetic agents, the residual incidence of PONV remained high (about 30%) in patients at high risk.[11–13] One study assessed the prophylactic antiemetic efficacy of a combination of three agents (ondansetron, dexamethasone and metoclopramide) in children.[14] However, the complex design of the study, including the use of different doses of the different antiemetic agents, and methodological biases made it impossible to firmly conclude whether the combination of three antiemetic drugs was superior to a combination of two antiemetic agents.[14]

We therefore carried out this multicentre, randomized, double-blind, placebo-controlled clinical trial to compare the efficacy of a combination of three drugs (ondansetron, dexamethasone and droperidol) with a combination of two drugs (ondansetron and dexamethasone) for reducing the incidence of POV in paediatric patients at high risk of POV. Nausea is difficult to assess in young children. We therefore limited this study to the evaluation of postoperative vomiting (POV).

Table 1 VPOP score.[4] VPOP score varies from 0 to 6 points. The incidences of postoperative vomiting (POV) are 5%, 6%, 13%, 21%, 36%, 48% and 52% for VPOP scores of 0 to 6, respectively. *Predisposition to POV: personal history of POV or motion sickness or familial history of POV. †Types of surgery associated with a high risk of POV: tympanoplasty, tonsillectomy and strabismus surgery. ‡Multiple doses of opioids: injection either during induction or maintenance of anaesthesia or in the post-operative period

Risk factor	Points
Age	
≤3 years	0
>3 and <6 years or >13 years	1
≥6 and ≤13 years	2
Predisposition to POV*	
No	0
Yes	1
Duration of anaesthesia >45 min	
No	0
Yes	1
High-risk surgery†	
Tonsillectomy	
Tympanoplasty	1
Strabismus surgery	
Others	0
Multiple doses of opioids‡	
No	0
Yes	1
Total	0–6

Methods

This multicentre study was conducted at 14 university hospitals from December 2010 to April 2013. The Institutional Review Board (Comité de Protection des Personnes Ile-de-France 3) approved this study (Number 2009-017293-20), and written informed consent was obtained from the parents. Patients between the ages of three and 16 years, scheduled for elective surgery under general anaesthesia and with a VPOP score ≥4

were included.[4] The exclusion criteria were antiemetic treatment during the 24 hours preceding surgery, allergy to a study drug, postoperative sedation and ventilation, preoperative corticosteroid administration, long QT (QT interval: interval from the beginning of the QRS complex to the end of the T wave) syndrome and parental refusal.

Children were allowed no solid food during the six hours preceding surgery, but were permitted clear fluids until two hours before the induction of anaesthesia. All patients received oral hydroxyzine (1 mg kg^{-1}), one hour before surgery, for premedication. Children were prospectively randomized to one of the two treatment groups with online Cleanweb software. All children received ondansetron (100 μg kg^{-1}) and dexamethasone (125 μg kg^{-1}) intravenously immediately after the induction of anaesthesia. Thirty minutes before the end of surgery, the Group A patients received normal saline (placebo) intravenously whereas the Group B patients received i.v. droperidol (50 μg kg^{-1}). The study drugs were prepared in identical 10 ml syringes and administered in equal volumes (10 ml) of normal saline, such that the investigators and observers were blind to the drug given. The test drug sets, labelled for blind administration, were prepared by the pharmacy staff at each institution. Anaesthesia was induced with sevoflurane in 100% oxygen or in a mixture of 1:1 mixture of air and oxygen administered via a facemask or with intravenous propofol, at the discretion of the anaesthesiologist responsible for patient management. Patients received opioids for analgesia and a myorelaxant, as necessary. Anaesthesia was maintained with sevoflurane in a 1:1 mixture of air and oxygen. The administration of nitrous oxide was not permitted during the induction or maintenance of anaesthesia. Intravenous fluids were administered at a rate of 10 ml kg^{-1} h^{-1} during the first hour. The infusion rate subsequently reduced according to the 4–2–1 rule.[15] All the children were monitored continuously throughout surgery, by electrocardiography, non-invasive blood pressure (NIBP) determinations, pulsed oximetry (SpO_2) and end-tidal carbon dioxide ($EtCO_2$) determinations. At the end of surgery, all the patients were woken up, extubated and transported to the recovery room (RR). All episodes of postoperative vomiting and the times at which they occurred were recorded during the patient's stay in the RR and in the surgical ward, during the first 24 hours after surgery. Rescue treatment with ondansetron (100 μg kg^{-1}) was permitted for patients with postoperative vomiting. All complications occurring over the 24 h study period were recorded.

The primary outcome was the incidence of any emetic episodes (retching or vomiting) during the first 24 hours following surgery. The secondary outcome was the incidence of any adverse effect.

Statistics

Statistical analysis was performed with *ad hoc* routines implemented in R software (http://www.R-project.org; accessed 26 April 2017). The sample size required was calculated assuming an incidence of POV of 30% in the ondansetron/dexamethasone/placebo group. We calculated the sample size required to provide 90% power (with a two-sided α risk of 0.05) for the detection of an absolute risk reduction in POV incidence of 15% in Group B. This calculation yielded a planned sample size for this study of 322 randomized patients. The data are presented as proportions for categorical data and as median and inter-quartile range (IQR) for quantitative data. Quantitative variables were compared in non-parametric Wilcoxon tests and proportions were compared in Fisher's exact tests or χ^2 tests, as appropriate.

In order to rule out any issues regarding the power of the study, a Bayesian analysis has been performed afterwards using Winbugs program.[16] This analysis aimed to derive the probability that the addition of droperidol would actually reduce the incidence of POV given the observed data. The prior probability for success ($P_{success}$) in each arm was modelled following a beta distribution with shape parameters $\alpha=1$ and $\beta=1$. This uniform distribution was chosen because it corresponds to a non-informative prior that is not based on a formulation of subjective prior beliefs and have minimal influence on the inference. A binomial distribution with parameters n=total number of patients and $P=P_{success}$ was used to model the likelihood function for the observed sample.

Potential risk factors for vomiting in our population were then determined. Univariate analyses were performed for each independent variable, followed by a multivariate logistic regression analysis. The assumption of a linear relationship between all numerical predictors and the outcome was assessed with a spline function implemented in the mgcv package.[17] All variables with a P-value <0.2 were then selected for inclusion in the multivariate logistic regression analysis. We considered P-values <0.05 to be statistically significant for all analyses unless otherwise stated. All comparisons were based on two-tailed tests.

Results

We included 315 children in this study (Fig. 1). There was no significant difference between the two groups in terms of patient characteristics and clinical data (Table 2). Thirty-four patients presented POV during the first 24 h after surgery: 16 patients in Group A and 18 patients in Group B ($P=0.86$). The overall incidence of POV was not significantly different between the two groups: 10.5% in Group A *vs* 11.1% in Group B ($P=0.86$). According to the Bayesian analysis the probability that droperidol is actually beneficial for POV prevention given the observed data was estimated to be <10%. Furthermore, the probability that addition of droperidol would provide an absolute risk reduction in POV incidence of 15% was also computed and estimated to be <1%.

No centre effect was observed in this study (P-value=0.32).

The drugs used during the induction and maintenance of anaesthesia in both groups are presented in Table 3. No significant difference was observed between the two groups in terms of the types of drug (propofol, sevoflurane and opioids) received during the induction or maintenance of anaesthesia (Table 3).

The overall incidence of postoperative complications differed significantly between the two groups: three adverse effects (2.0%) were reported in Group A *vs* 13 (8.0%) in Group B ($P=0.01$). Drowsiness and headache were the principal adverse effects reported (Table 4). Two early repeat interventions, one for wound infection and one for bleeding, were noted in Group B. However, the drugs administered were not considered to be responsible for the need for repeat surgery in the reviews of these two cases. No extrapyramidal symptoms or cardiac events were observed.

The results of a secondary analysis to identify the potential risk factors for POV in our population are presented in Table 5. The multivariate analysis identified age and duration of anaesthesia as the only independent risk factors for POV. The administration of propofol had no significant effect on the risk of POV in our population. However, the rates of propofol administration differed significantly ($P<10^{-4}$) between patients of different age groups: 30% in patients aged three to six years, 67% in patients aged six to 12 years, and 98% in patients aged 13 years and over. However, age was not an independent risk factor for POV in the

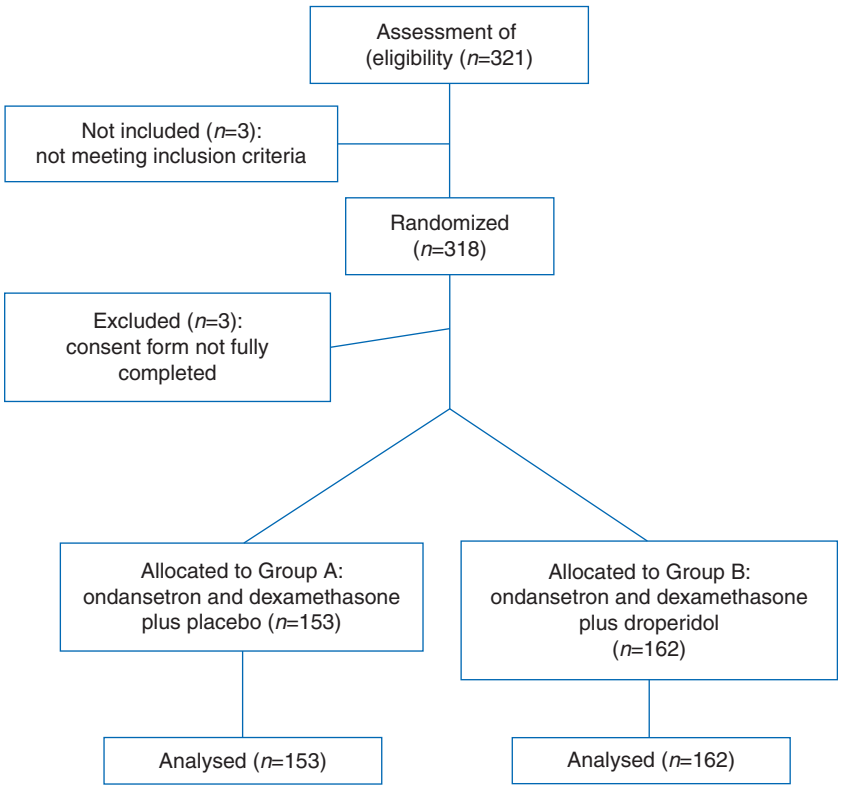

Fig 1 Flow chart.

subgroup of patients not receiving propofol. There was a linear relationship between the duration of anaesthesia and the risk of POV. Every 10 minute increase in the duration of anaesthesia was associated with an 11% increase in the risk of POV.

Discussion

The principal finding of this study is that the addition of droperidol to a prophylactic mixture of two antiemetic drugs, ondansetron and dexamethasone, does not reduce the incidence of POV in children at high risk. However, the addition of droperidol to the combination increased the incidence of postoperative adverse events (i.e. drowsiness).

Very few trials have assessed the relative benefits of prophylactic combinations of antiemetics in children. In adult patients, a prospective study evaluating the efficacy of a combination of several antiemetics for the prevention of PONV showed that the addition of droperidol to ondansetron and dexamethasone decreased the incidence of PONV from 28% to 22% (corresponding to a 22% decrease in relative risk).[10] In contrast, we found that the addition of droperidol to ondansetron and dexamethasone was of no benefit in our paediatric study population. However, we also found that the incidence of POV was surprisingly low after the prophylactic administration of two antiemetics, despite the inclusion of children at high risk of POV in this study. Incidences of POV of 36–70% have been reported in children at high risk, in the absence of antiemetic prophylaxis.[1 4] Our results are consistent with those of Gunter and colleagues[14] showing no greater efficacy of a mixture of three antiemetic drugs than of a mixture of two antiemetic drugs for preventing POV in children. However, the residual incidence of POV in the presence of antiemetic prophylaxis was 38% in this previous study whereas we observed a much lower residual incidence (about 10%). In the study by Gunter and colleagues,[14] children were randomized to one of 15 combinations of ondansetron (0–60 μg kg^{-1}), metoclopramide (0–400 μg kg^{-1}) and dexamethasone (0–500 μg kg^{-1}). Differences in anaesthetic techniques (induction with nitrous oxide/oxygen and sevoflurane followed by maintenance with halothane in air/oxygen), doses and the choice of antiemetic drugs administered (droperidol rather than metoclopramide) could account, at least in part, for the greater antiemetic efficacy observed in our study. Given the low observed vomiting rate, the calculated sample size may have been misspecified in order to detect an absolute risk reduction in POV incidence of 15%. An additional Bayesian analysis was then applied. This analysis aimed to estimate the posterior distribution of observed effects when the sampling size may not allow to conclude. Given the observed data, the probability that addition of droperidol would provide an absolute risk reduction in POV incidence of 15% was estimated to be <1%. Usually if the predictive probability is below a pre-specified level, generally less than 20%, a recommendation to stop the trial has to be made for futility.[18]

More than half the patients in our study received propofol during anaesthesia induction, and almost 20% received propofol

Table 2 Patient characteristics and clinical data for the patients included in Group A (dexamethasone and ondansetron) and Group B (dexamethasone, ondansetron and droperidol). There was no significant difference in demographic characteristics between the two groups. Data are median (inter-quartile range) or number of cases (%). POV, postoperative vomiting

	Group A	Group B
Age	9 (7–11)	9 (7–12)
Body weight	30 (24–40)	32 (22–45)
Sex ratio (male/female)	70/83	85/77
ASA physical status		
I	114 (74.5)	119 (73.5)
II	37 (24.2)	39 (24.1)
III	2 (1.3)	4 (2.4)
Duration of anaesthesia (min)	154 (100–205)	143 (103–200)
POV history	84 (55)	83 (51)
VPOP score		
4	72 (47)	75 (46)
5	60 (39)	68 (42)
6	21 (14)	19 (12)
Type of surgery		
Abdominal	7 (5)	18 (11)
Orthopaedics	43 (28)	38 (23)
Urology	8 (5)	11 (7)
Ear–nose–throat	79 (52)	75 (46)
Ophthalmology	1 (0.5)	2 (1)
Facial surgery	5 (3)	5 (3)
Other	10 (6.5)	13 (8)

Table 3 Drugs used during the induction and maintenance of anaesthesia in Group A (dexamethasone and ondansetron) and Group B (dexamethasone, ondansetron and droperidol). There was no significant difference between the two groups. Data presented are the number of cases (%)

	Group A (n=153)	Group B (n=162)	P-value
Induction of anaesthesia			
Propofol	100 (65)	92 (57)	0.16
Sevoflurane	97 (63)	101 (62)	0.91
Opioids	143 (94)	150 (93)	1.0
Maintenance of anaesthesia			
Propofol	29 (19)	18 (11)	0.06
Sevoflurane	105 (69)	119 (74)	0.37
Opioids	121 (79)	121 (75)	0.42

Table 4 Postoperative adverse events in Group A (dexamethasone and ondansetron) and in Group B (dexamethasone, ondansetron and droperidol). Data presented are the number of cases (%)

	Group A	Group B	P-value
Drowsiness	2 (1.3)	10 (6.2)	0.03
Headache	1 (0.7)	1 (0.7)	1.0
Surgical wound infection	0 (0)	1 (0.6)	1.0
Surgical revision for bleeding	0 (0)	1 (0.6)	1.0
Total	3	13	0.01

Table 5 Results of the multivariate analysis identifying independent risk factors for postoperative vomiting. OR (95% CI): odds ratio with its 95% confidence interval. Group A: dexamethasone and ondansetron; Group B: dexamethasone, ondansetron and droperidol. *Each 10 minute increase in the duration of anaesthesia was associated with an 11% increase in the risk of POV

	OR (95% CI)	P-value
Age group		
3–6 years	1 (reference)	
6–12 years	0.35 (0.13–0.94)	0.03
>13 years	0.31 (0.05–1.87)	0.20
Duration of anaesthesia (/10 min)*	1.11 (1.06–1.17)	$<10^{-4}$
Group B *vs* Group A	0.95 (0.42–2.16)	0.91
Sex (female *vs* male)	0.56 (0.24–1.29)	0.17
Propofol during anaesthesia induction	0.95 (0.37–2.44)	0.92

for the maintenance of anaesthesia. The low overall incidence of POV may therefore be accounted for by the use of propofol. We did not prohibit the use of propofol in this study because we observed no antiemetic effect of propofol administration in children in a previous study (the VPOP Study).[4] Propofol use was similar in the two groups in this study. Thus, we cannot definitively rule out an effect of propofol administration on our results.

Another possible explanation for the observed low incidence of POV in this study would be a patient selection bias. Indeed, almost half the patients had a VPOP score of 4 (46.6%) whereas only 13% of the included patients had a VPOP score of 6. In the VPOP study, we considered patients with a VPOP score of 4 to be at high risk of POV, but their risk of POV was only 36%, potentially accounting, at least in part, for the relatively low incidence of POV in this study.

We chose to administer a dose of droperidol 50 μg kg^{-1}, because, according to the results of a meta-analysis, droperidol has a dose-dependent effect in the prevention of POV in children.[19] The most effective dose for reducing POV was 75 μg kg^{-1}, but this dose was also associated with a significantly higher incidence of adverse effects.[19] The authors therefore concluded that the recommended dose for droperidol in children should be 50 μg kg^{-1}, to obtain the best benefit-to-risk-ratio, optimizing efficacy (antiemetic effect) and safety (side effects).[19]

The higher incidence of drowsiness reported in this study is consistent with the results of another study in which the authors observed a dose-dependent increase in drowsiness or sedation in children given droperidol, with reported incidences of 2.4–18.1%.[20] In this previous study, droperidol was added directly to the morphine used for patient-controlled analgesia. It is not, therefore, possible to compare the doses of droperidol received by the patients directly with those used in our study, in which patients received a single bolus dose of droperidol 50 μg kg^{-1}. However, this small dose of droperidol seemed to be sufficient to induce sedation or drowsiness. In another study in which lower doses of droperidol (10 μg kg^{-1}) were injected for the treatment of persistent POV in children, the authors reported a high frequency of sedation (27%).[21] Droperidol should therefore be used with caution in children, particularly in outpatients.

In this study, we identified only two independent risk factors for POV: duration of anaesthesia and patient age. No other variable (POV history, use of opioids, type of surgery) was identified as an independent risk factor in this study, possibly because of its

design, with the inclusion of patients at high risk of POV (VPOP score of 4, 5 or 6), resulting in such variables being too frequent in our population of patients to be identified as risk factors.

Conclusion

In this study, the addition of droperidol to a prophylactic combination of ondansetron and dexamethasone did not decrease POV frequency below that obtained with the two-drug combination in children at high risk of POV, but increased the risk of drowsiness. It would therefore seem inadvisable to use droperidol routinely in association with ondansetron and dexamethasone for preventing POV in children.

Acknowledgements

Special acknowledgements to the collaborators in VPOP2 group: Véronique Chanderis, Jérôme Duret, Aurélien Legrand, Olivier Paut, Christophe Dadure.

Declaration of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from French Ministry of Social Affairs, Health and Women's Rights for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

This study was sponsored by the French Ministry of Social Affairs, Health and Women's Rights.

Authors' contributions

Study design, data analysis and writing up of the first draft of the paper: N.B.
Patient recruitment, data collection and writing up of the first draft of the paper: C.F., O.J., M.-L.G., J.J., C.S., C.E.-D., J.-M.D., F.B., E.G.
Study design (materials and methods), data analysis (statistical analysis) and writing up of the first draft of the paper: N.B.
Study design, data analysis and writing up of the first draft of the paper: J.-M.T., G.A.O.

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Handling editor: A. R. Absalom