Low incidence of the oculocardiac reflex and postoperative nausea and vomiting in adults undergoing strabismus surgery

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Purpose: To investigate the incidence of the oculocardiac reflex (OCR), and of postoperative nausea and vomiting (PONV) in adults undergoing strabismus surgery.

Methods: Adults (18–86 yr) undergoing inpatient strabismus surgery received 10 $\mu g \cdot kg^{-1}$ atropine and 10 $\mu g \cdot kg^{-1}$ alfentanil *iv* and were randomly allocated to: (A) 5 $mg \cdot kg^{-1}$ thiopentone *iv*, isoflurane/N_2O maintenance; (B) 3 $mg \cdot kg^{-1}$ propofol *iv*, propofol/N_2O maintenance (10–14 $mg \cdot kg^{-1} \cdot hr^{-1}$); © 3 $mg \cdot kg^{-1}$ propofol *iv*, propofol/air/O_2 maintenance (10–14 $mg \cdot kg^{-1} \cdot hr^{-1}$). Analyses were with the number-needed-to-treat/harm.

Results: In 97 adults the absolute risk of OCR (13–20%) and PONV (21–31% after 24 hr) was low, with no differences between groups. Number-needed-to-treat to prevent PONV with propofol with or without N_2O compared with thiopentone-isoflurane was 7 to 11. Number-needed-to-harm for one OCR with propofol compared with thiopentone-isoflurane was 17.

Conclusion: Adults undergoing strabismus surgery with prophylactic atropine had a low risk of OCR and PONV, independent of the anaesthetic technique used.

Objectif : Rechercher l'incidence du réflexe oculocardiaque (ROC) et des nausées et vomissements postopératoires (NVPO) chez les adultes opérés pour correction de strabisme.

Méthodes : Des adultes programmés pour une correction de strabisme ont reçu atropine 10 $\mu g \cdot kg^{-1}$ et alfentanil 10 $\mu g \cdot k^{-1}$ *iv* et ont été répartis au hasard pour recevoir : (A) thiopentone 5 mg *iv*, entretien isoflurane/N_2O ; (B) propofol 3 $mg \cdot kg^{-1}$ *iv*, entretien propofol/N_2O (10–14 $mg \cdot kg^{-1} \cdot h^{-1}$) ; (C) propofol 3 $mg \cdot kg^{-1} \cdot h^{-1}$ *iv*, entretien propofol/air/O_2 (10–14 $mg \cdot kg^{-1} \cdot h^{-1}$). La méthode du nombre de patients à traiter pour prévenir une complication a servi à l'analyse des résultats.

Résultats : Chez 97 adultes, le risque absolu de ROC (13–20%) et de NVPO (21–31% après 24 h) était faible et ne différait pas entre les groupes. Comparativement au thiopentone/isoflurane, avec le propofol avec ou sans N_2O, le nombre de patients traités pour prévenir un épisode de NVPO était de 7 à 11. Avec le propofol, ce nombre appliqué à un épisode de ROC comparativement au thiopentone-isoflurane était de 17.

Conclusion : Les adultes opérés pour strabisme qui recevaient préventivement de l'atropine avaient un risque faible de ROC et de NVPO indépendant de la technique anesthésique.

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CHILDREN undergoing strabismus surgery are at high risk of both intraoperative bradycardia due to the oculocardiac reflex (OCR) and postoperative nausea and vomiting (PONV). Surgery related factors (e.g., traction on extraocular muscles) and young age may be responsible for this outcome.[1-3] There are no data of the absolute risk of PONV in adults undergoing strabismus surgery. There are only limited data on the risk of the OCR in adults; it has been shown that the incidence of the OCR decreased with increasing doses of prophylactic anticholinergic drugs.[4]

The aim of this study was to compare, in a randomised controlled trial, the effect of three currently used anaesthetic techniques (thiopentone induction with isoflurane maintenance, propofol induction with propofol-nitrous oxide {N_2O} maintenance, and a total intravenous propofol-air/O_2 anaesthetic {TIVA}), on the incidence of OCR and PONV in adults undergoing strabismus surgery. As a measurement of clinical relevance of a difference between interventions we used the number-needed-to-treat method. The number-needed-to-treat is the reciprocal of the absolute risk reduction and indicates how many patients are need to be treated in order to prevent one complication.[5]

Methods

We studied adults, age 18 to 86 yr, ASA physical status 1 to 3, scheduled for elective strabismus surgery. This study was approved by the local Human Study Committee. Written information was provided to the patients who gave written informed consent.

One hour before surgery all patients received 7.5 mg midazolam *po*. On arrival in the anaesthetic room a peripheral venous line was inserted and all patients had the following standard monitoring equipment connected: ECG, oscillometer, pulse oximetry, and peripheral neurostimulator. Patients were preoxygenated and received 10 $\mu g \cdot kg^{-1}$ atropine *iv* and 10 $\mu g \cdot kg^{-1}$ alfentanil *iv*. The patients were then randomly assigned (sealed and numbered envelopes) to one of three groups: (A) induction with 5 $mg \cdot kg^{-1}$ thiopentone *iv* followed by maintenance with isoflurane 1–1.5% and a N_2O in O_2 mixture (60:40%); (B) induction with 3 $mg \cdot kg^{-1}$ propofol *iv* followed by a continuous intravenous infusion of propofol 10–14 $mg \cdot kg^{-1} \cdot hr^{-1}$ and N_2O/O_2 (60:40%); (C) induction with 3 $mg \cdot kg^{-1}$ propofol *iv* followed by a continuous intravenous infusion of propofol 10–14 $mg \cdot kg^{-1} \cdot hr^{-1}$ and O_2 in air (TIVA). In all groups 0.1 $mg \cdot kg^{-1}$ vecuronium *iv* was given to facilitate tracheal intubation and lungs were ventilated using intermittent positive-pressure ventilation to keep end-tidal carbon dioxide between 32 and 45 mmHg. During surgery 5 $\mu g \cdot kg^{-1}$ alfentanil *iv* were given as necessary to keep blood pressure and heart rate within 20% of preinduction values. Neuromuscular blockade was maintained with supplementary doses of vecuronium.

The horizontal component of convergent or divergent squint was corrected with the classical recession-tucking operation. In cases of convergent strabismus with an additional variable angle a retroequatorial myopexy according to the Cuppers technique modified by Polenghi was combined with the recession-tucking operation. A vertical component was corrected by surgery on the oblique muscles.

A significant OCR was defined as an acute decrease in heart rate of 20% associated with traction on an eye muscle. Treatment of OCR consisted of relief of traction. If the heart rate still did not return to baseline values, additional atropine, 10 $\mu g \cdot kg^{-1}$ *iv*, were administered.

At the end of surgery gastric contents were aspirated with a single lumen orogastric tube (one attempt) and neuromuscular blockade was reversed with 10 $\mu g \cdot kg^{-1}$ atropine and 20 $\mu g \cdot kg^{-1}$ neostigmine *iv*. Patients stayed in the recovery room for one hour and were then discharged to the ward. Patients' eyes were not covered in the postoperative period and they were allowed to drink upon request. Postoperative observations were made by nurses who were not aware of the intraoperative group assignment. All episodes of postoperative nausea and vomiting (including retching) and time of their occurrence were recorded. Antiemetic rescue treatment consisted of metoclopramide. Pain was treated with paracetamol and nonsteroidal anti-inflammatory drugs, or, if necessary, with morphine. Patients were discharged home the day after surgery. Telephone contact was made to determine the incidence of PONV from discharge until 48 hr after surgery.

Demographic and surgical data were compared among groups by one-way analysis of variance and Student's test. Statistical significance and clinical relevance of differences between anaesthetic techniques were evaluated using odds ratio and number-needed-to-treat.[6] Odds ratio estimates were calculated with 95% confidence intervals (95% CI).[7] Point estimates and 95% CI of the number-needed-to-treat were calculated.[8] The cumulative incidence of postoperative nausea and vomiting was analysed for an early period (within six hours of surgery) and a late period (within 24 hr). The early period was chosen to represent the maximum time an outpatient would spend in a day case unit. The late period represented the time patients spent in hospital. Antiemetic efficacy was defined as absence of nausea or vomiting. A statistically significant improvement of one anaesthetic over another was assumed when the

lower 95% confidence limit of the odds ratio was >1. The number-needed-to-treat then indicated how many patients had to be exposed to this anaesthetic in order to prevent PONV in one of them, who would have vomited or would have been nauseated with the control anaesthetic. The same method was applied to analyse dichotomous OCR data but with presence of the bradycardic event as an endpoint. The corresponding number-needed-to-harm indicated how many patients had to be exposed to a particular anaesthetic technique in order to provoke at least one OCR in one of them, who would not have had a bradycardic reaction with control.

Results

One hundred and five adults were randomised. Eight patients were excluded from analysis. Two were operated on by a surgeon who was not involved in this trial, postoperative data were missing in four, and two patients were operated on as outpatients.

The final analysis, therefore, involved 97 adults. There was no difference in patient characteristics (Table I) or surgical data (Table II). All patients were operated upon by one of two staff surgeons equally distributed among the study groups.

The incidence of OCR was generally low (13–22%), affected patients showed one or two bradycardic episodes, and treatment with atropine was rarely necessary (Table IIIa). There was no difference in the incidence of the OCR between the propofol-N_2O and the TIVA group. The risk of an OCR with propofol compared with thiopentone-isoflurane was of primary interest because of the known additional risk with propofol in children undergoing strabismus surgery.[9] We, therefore, compared the combined propofol OCR data with OCR data from the thiopentone-isoflurane group. The number-needed-to-harm point estimate for one OCR with combined propofol data compared with thiopentone-isoflurane was about 17 (Table IIIb).

There was a tendency towards a lower incidence of PONV with propofol with and without N_2O compared with thiopentone-isoflurane (Table IVa). However, PONV event rates with either group were low, and no propofol group was statistically different from thiopentone-isoflurane. The number-needed-to-treat point estimates suggested that about 10 patients would have to be treated with either propofol technique in order to prevent PONV in one of them who would have vomited or being nauseated with thiopentone-isoflurane (Table IVb).

Postoperative morphine was given to two adults (none of them had PONV). Episodes of PONV between the 24th and 48th hours (after discharge) were reported in about 10% of patients, independent of anaesthetic technique (Table IVa). The latest episode of vomiting was reported after 40 hr. Several patients reported nausea up to the 48th hour. There was no difference between the delay until the first tolerated oral intake between groups. There was no spontaneous report of intraoperative awareness.

TABLE I Demographic data

	Isoflurane+ N_2O *32*	*Propofol+ N_2O* *29*	*Propofol+ air/O_2* *36*
Sex (male/female): n	13/19	10/19	14/22
Age (yr):	39 ± 17	36 ± 17	37 ± 12
History of PONV: n (%)	3 (9)	8 (28)	2 (6)
History of motion sickness: n (%)	6 (19)	7 (24)	6 (17)

Mean ± SD

TABLE II Surgical data

n	*Isoflurane+ N_2O* *32*	*Propofol+ N_2O* *29*	*Propofol+ air/O_2* *36*
Minutes of surgery:	52 ± 19	50 ± 15	48 ± 18
Alfentanil dose (μg/kg):	26 ± 10	20 ± 7	23 ± 9
Total number of muscles operated on: median (range)	2 (1–4)	2 (1–3)	2 (1–4)
Bilateral surgery: n (%)	9 (28)	10 (34)	6 (17)
Classical recession-tucking: n (%)	28 (88)	23 (79)	31 (86)
Myopexy: n (%)	9 (28)	8 (28)	10 (28)

Mean ± SD

TABLE III Oculocardiac reflex (OCR)

a. Absolute risk, number of episodes, and treatment

n	*Isoflurane+ N_2O* 32	*Propofol+ N_2O* 29	*Propofol+ air/O_2* 36
OCR: n (%)	4 (13)	4 (14)	8 (22)
Episodes of OCR: median (range)	1 (1–2)	1 (1)	1 (1–2)
Treatment of OCR: n (%)	2 (6)	0	4 (11)

b. Number-needed-to-harm to produce an OCR in one patient with propofol compared with thiopentone-isoflurane

	OR (95% CI)	*NNH (95% CI)*
Propofol* *vs* thiopentone-isoflurane	1.5 (0.5–4.8)	16.8 (4.8-∞)

OCR = oculocardiac reflex = decrease in heart rate > 20% during traction on extraocular muscles. Patients received 10 $\mu g \cdot kg^{-1}$ atropine *iv* at induction.

OR = odds ratio; NNH = number-needed-to-harm; CI = confidence interval;

∞ = infinity (negative value, indicating absence of a difference between groups)

* combined propofol-N_2O and TIVA groups

TABLE IV Postoperative nausea and vomiting

a. Absolute risk, number of episodes, nausea and vomiting after 24 hr, rescue medication, and first oral intake

n	*Isoflurane+ N_2O* 32	*Propofol+ N_2O* 29	*Propofol+ air/O_2* 36
Early nausea: n (%)	8 (25)	5 (17)	5 (14)
Early vomiting: n (%)	7 (22)	3 (10)	3 (8)
Late nausea: n (%)	10 (31)	6 (21)	8 (22)
Late vomiting: n (%)	8 (25)	3 (10)	6 (17)
Episodes of vomiting: median (range)	1 (1–3)	2 (1–3)	1 (1–2)
> 1 episode of vomiting: n (%)	5 (16)	2 (7)	1 (3)
PONV 24–48 hr: n (%)	4 (13)	2 (7)	4 (11)
Antiemetic rescue medication: n (%)	5 (16)	1 (4)	2 (6)
First tolerated oral intake (hr):	6.2 ± 2	5.7 ± 4.4	5.2 ± 3.1

b. Number-needed-to-treat to prevent postoperative nausea and vomiting with propofol compared with thiopentone-isoflurane

Endpoint and Comparison	OR (95% CI)	NNT (95% CI)
Prevention of early nausea		
Propofol-N_2O *vs* thiopentone-isoflurane	1.6 (0.5–5.3)	12.9 (3.6-∞)
TIVA *vs* thiopentone-isoflurane	2.0 (0.6–6.8)	9.0 (3.3-∞)
Prevention of early vomiting		
Propofol-N_2O *vs* thiopentone-isoflurane	2.3 (0.6–8.8)	8.7 (3.4-∞)
TIVA *vs* thiopentone-isoflurane	2.9 (0.8–11)	7.4 (3.3-∞)
Prevention of late nausea		
Propofol-N_2O *vs* thiopentone-isoflurane	1.7 (0.6–5.3)	9.5 (3.1-∞)
TIVA *vs* thiopentone-isoflurane	1.6 (0.5–4.6)	11.1 (3.3-∞)
Prevention of late vomiting		
Propofol-N_2O *vs* thiopentone-isoflurane	2.7 (0.7–9.7)	6.8 (3.0-∞)
TIVA *vs* thiopentone-isoflurane	1.7 (0.5–5.3)	12.0 (3.6-∞)

TIVA = Propofol-air/O_2; OR = odds ratio; NNT = number-needed-to-treat; CI = confidence interval; early nausea/vomiting = within 6 hr after surgery; late PONV = within 24 hr after surgery; vomiting included retching; ∞ = infinity (negative value, indicating absence of a difference among groups).

Mean ± SD

Discussion

The aim of this randomised controlled trial was to evaluate, in adults undergoing strabismus surgery, both the underlying risk of OCR and PONV, and the effect of three currently used anaesthetic techniques on these complications. In paediatric strabismus surgery OCR and PONV are among the most common surgery- and anaesthesia-related complications. In these adults, however, the absolute risk of both OCR and PONV was low with all anaesthetics. The cumulative incidence of PONV with thiopentone-isoflurane was only about 30% after 24 hr. This low event rate without antiemetic prophylaxis may be one reason why propofol with or without N_2O did not show any difference compared with thiopentone-isoflurane. These results suggest that it is not worthwhile to consider any antiemetic prophylaxis in this setting. This is particularly important because effective antiemetic treatment of established PONV is available.[10]

It may be argued that this study had insufficient power to detect a difference between propofol and thiopentone-isoflurane, and that, therefore, more patients need to be randomised. The number-needed-to-treat point estimates for prevention of PONV with propofol compared with thiopentone-isoflurane were about 10. An increased number of analysed patients (i.e., an increase in the power of this study) would almost certainly bring the lower and upper 95% confidence limits of the number-needed-to-treat closer together. Eventually the upper limit would become positive (and correspondingly the lower confidence limit of the odds ratio would be >1), indicating a difference between propofol and thiopentone-isoflurane. However, it has to be assumed that the number-needed-to-treat point estimate would then still be close to 10, indicating that about 10 patients have to undergo a propofol anaesthetic to prevent nausea or vomiting in one of them who would have vomited or being nauseated had he received a thiopentone-isoflurane anaesthetic. Not every clinician might consider this reduction in risk as a clinically relevant antiemetic effect.

A propofol-TIVA regimen has been suggested for its supposed very low emetogenic potency.[2] There was no obvious difference between propofol-N_2O and propofol-TIVA either. This most likely reflects the relationship between the low underlying risk of vomiting with N_2O in this trial, indicated by the low event rate in the propofol-N_2O group, and efficacy in decreasing the incidence of vomiting in omitting N_2O. If nobody is going to vomit with N_2O there is nothing to gain by omitting it.[11]

Bradycardic reactions due to the OCR were rare in these adults who received prophylactic atropine. There is strong evidence that propofol dramatically increases the risk of OCR in paediatric strabismus surgery compared with inhalational anaesthetics despite prophylactic anticholinergics.[9] Our data suggest that this is not the case in adults.

The difference between the absolute risk of OCR and PONV in adults undergoing strabismus surgery and the well documented risk of both these complications in children undergoing the same procedure is obvious. In the absence of direct comparisons, however, explanations must be speculative. We do not know if these differences are real age effects. There is experimental evidence suggesting that less relative bradycardia is observed in response to vasovagal manoeuvres with increasing age.[12] Children are generally thought to be at higher risk of PONV than adults, although there is no good evidence to support this view. In an uncontrolled series of patients from a plastic surgery ward, post-hoc subgroup analyses suggested that children were at higher risk for PONV than adults.[13] If there is a difference in the likelihood of PONV between younger and older patients it may be directly age-related or due to children specific surgical settings which entail a higher risk for PONV (such as ENT surgery, dental surgery and squint repair[14,15]) compared with adults.

In summary, our data suggest that propofol with prophylactic atropine may be used safely in adults undergoing strabismus surgery. With thiopentone-isoflurane or propofol with or without N_2O the risk of OCR and PONV was low and no differences were found between groups.

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