Prospective application of a simplified risk score to prevent postoperative nausea and vomiting

[L'application prospective d'un score de risque simplifié pour prévenir les nausées et les vomissements postopératoires]

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Purpose: To compare the risk-adapted approach with ondansetron against ondansetron plus dexamethasone to prevent postoperative nausea and vomiting (PONV) in a randomized clinical trial.

Methods: 460 patients scheduled for elective surgery were enrolled in this prospective study and stratified according to a simplified risk score for PONV. Patients having no or one risk factor were considered at low risk (group L) and did not receive study medication. Those with two to four risk factors were considered high risk and were randomized to receive 4 mg ondansetron plus placebo (group H-O) or 4 mg ondansetron plus 8 mg dexamethasone (group H-OD). Incidence and intensity of PONV were observed for 24 hr after surgery. Data were analyzed with Fisher's exact or Student's t tests; $P < 0.05$ was considered statistically significant.

Results: The incidence of PONV was 9% in group L ($n = 87$), 31% in those receiving ondansetron (group H-O, $n = 185$), and 22% in those receiving both drugs (group H-OD, $n = 181$). The incidence of PONV was significantly smaller in both high-risk groups than predicted without treatment ($P < 0.001$). While the incidence of PONV failed statistical significance between the two intervention groups ($P = 0.08$), the mean number of episodes of PONV and the mean maximal intensity of each episode of PONV were lower in group H-OD ($P = 0.03$ and $P = 0.01$, respectively). Patients of group H-OD required less antiemetic rescue therapy ($P = 0.004$).

Conclusions: Ondansetron plus dexamethasone prevents PONV more effectively than ondansetron alone in patients at high risk for PONV.

Objectif : *Comparer l'approche adaptée au risque avec ondansétron ou avec ondansétron et dexaméthasone pour prévenir les nausées et vomissements postopératoires (NVPO) dans une étude clinique randomisée.*

Méthode : *L'étude prospective a porté sur 460 patients, devant subir une intervention chirurgicale réglée, qui ont été stratifiés selon un score de risque simplifié de NVPO. Les patients ont été considérés à faible risque (groupe F) s'ils n'avaient aucun ou un facteur de risque et n'ont pas reçu la médication à l'étude. S'ils avaient de deux à quatre facteurs de risque, on les considérait à haut risque et ils recevaient au hasard 4 mg d'ondansétron plus un placebo (groupe H-O) ou 4 mg d'ondansétron plus 8 mg de dexaméthasone (groupe H-OD). L'incidence et l'intensité des NVPO ont été observées pendant 24 h après l'opération. Les données ont été analysées par les tests exact de Fisher ou t de Student ; $P < 0,05$ était statistiquement significatif.*

Résultats : *L'incidence de NVPO a été de 9 % dans le groupe F ($n = 87$), 31 % avec l'ondansétron (groupe H-O, $n = 185$) et 22 % avec les deux médicaments (groupe H-OD, $n = 181$). L'incidence de NVPO a été significativement plus basse dans les deux groupes à haut risque que ce qui avait été prédit sans traitement ($P < 0,001$). Même si l'incidence de NVPO n'était pas statistiquement significative entre les deux groupes expérimentaux ($P = 0,08$), le nombre moyen d'épisodes de NVPO et l'intensité maximale moyenne de chacun ont été plus faibles dans le groupe H-OD ($P = 0,03$ et $P = 0,01$, respectivement). Les patients du groupe H-OD ont demandé moins d'antiémétiques de secours $P = 0,004$).*

Conclusion : *L'ondansétron plus la dexaméthasone préviennent les NVPO plus efficacement que l'ondansétron seul chez des patients à haut risque de NVPO.*

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THERE are inconsistent findings concerning the optimal approach to the management of postoperative nausea and vomiting (PONV) and disagreement as to whether prophylaxis of PONV should be the standard of care.[1–4] According to recently published consensus guidelines, routine prophylaxis is not justified. Instead, a strategy focusing on patients at high risk for PONV seems to be most appropriate and is, therefore, recommended.[5]

Antiemetic prophylaxis using ondansetron alone results in a relative reduction rate of PONV of about 30%.[6] Combining ondansetron with antiemetics that act through different receptors reduces the incidence further,[7–9] which seems also true when 5-HT_3 receptor antagonists are combined with dexamethasone.[10,11] However, a further reduction with the prophylactic combination of ondansetron plus dexamethasone compared to ondansetron alone has not been established convincingly. Previous studies comparing the antiemetic effect of ondansetron compared to ondansetron plus dexamethasone had the following limitations: first, patients were not stratified according to each patient's underlying risk for PONV. Second, in most of the studies little emphasis was placed on examining the intensity of symptoms, i.e., the main focus was placed on incidence only. Thus, the main objective of this study was to investigate whether the combination of ondansetron plus dexamethasone is superior to ondansetron alone in reducing both the incidence and the intensity of PONV in patients at high risk for this adverse event.

Methods

The study protocol was approved by the Ethics Committee of the Bavarian Medical Board (approval #01130). Written informed consent was obtained from each patient prior to study enrolment. The study was conducted in accordance with "good clinical practice" and all applicable regulatory requirements, including those originating from the Declaration of Helsinki.

Protocol

Patients aged 18 to 70 yr scheduled for an elective procedure under general anesthesia (hospital stay > 24 hr) were eligible for this study. Exclusion criteria were as follows: known allergy to any of the drugs used in this study, severe impairment of bowel motility, insulin-dependent diabetes mellitus, phenylketonuria, drug abuse, nausea or vomiting within 24 hr prior to study enrolment, antiemetic treatment within 24 hr prior to study enrolment, systemic treatment with steroids within 24 hr prior to study enrolment, pregnancy or breastfeeding, or participation in any other clinical investigation within 30 days prior to study enrolment.

After enrolment, study subjects were stratified into two study arms. The stratification was based upon a simplified risk score for PONV.[12] Risk factors used by this score are as follows: female gender, non-smoking status, history of PONV and/or motion sickness (MS), and postoperative administration of opioids. Studies have confirmed that the presence of zero, one, two, three, or four of these risk factors correspond to approximately 10, 20, 40, 60, and 80% risk for PONV, respectively.[13,14] Patients who had less than two risk factors were classified as being at "low risk" for PONV (study group L). Patients in this group were not given any prophylactic antiemetic. Patients with two or more risk factors were classified as being at "high risk" for PONV and were randomized into two groups. One high-risk group received ondansetron (study group H-O); the other received ondansetron and dexamethasone (study group H-OD).

The project statistician prepared a computer-generated randomization list. Dexamethasone or placebo were supplied in coded 2 mL-vials and were packed in individual boxes according to the randomization list. Boxes were numbered consecutively. Every patient enrolled in the study received the study medication with the lowest randomization number available. A set of sealed, numbered envelopes containing information on the content of trial medication boxes was also supplied to each investigator but was to be opened only in case of an emergency. Otherwise the randomization code was at no time revealed to the investigators.

Patients in the H-O group were given 4 mg ondansetron plus placebo; patients in the H-OD group received 4 mg ondansetron plus 8 mg dexamethasone. All study medication was given intravenously at induction of general anesthesia. GlaxoSmithKline, Germany, supplied the dexamethasone, placebo, and ondansetron.

In order to be consistent with daily clinical practice, no restrictions were made regarding the drugs to be used for premedication and during general anesthesia.

Measurements

All patients were monitored for the occurrence of any emetic symptoms and possible side effects of the treatment within the first 24 hr following emergence from general anesthesia (observation period). In accordance with recently published guidelines on how to conduct PONV studies, postoperative nausea (PON), postoperative vomiting (POV), and PONV were recorded by blinded investigators for three periods: 0–2 hr, 2–24

hr, and 0–24 hr after general anesthesia.[15] The intensity of PON, POV, and PONV was graded on a numeric rating scale (NRS; 0 = symptoms not present, 1 = mild symptoms, 2 = intermediate symptoms, 3 = strong symptoms).

The mean maximal intensity of PON, POV, and PONV was calculated as follows: sum of NRS values per group divided by the number of patients per group. As another measurement of the intensity of PON, POV, or PONV, the number of episodes of PON, POV, or PONV for each group was divided by the number of patients in that group to calculate the average number of PON, POV, or PONV episodes per group.

Any antiemetics given during the observation period at the discretion of the attending physicians (who were blinded to the administration of study medication) in response to nausea, vomiting, or patient request were recorded in order to compare the requirements for antiemetic rescue therapy between groups.

Other variables recorded for each patient included the following: age, sex, weight, height, ASA-classification, presence of any of the four risk factors for PONV mentioned above, concomitant medications, and any additional medications (such as opioids) given during the observation period.

Data analysis

Our primary goal was to compare the efficacy of prophylactic ondansetron alone vs ondansetron plus dexamethasone in patients at high risk for PONV. For ethical reasons no placebo group was included. Instead, observed incidences were compared to expected incidences based upon a risk score.[12] In order to support the assumption that the risk score is applicable to this setting, a comparison of expected and observed incidences in patients at low risk for PONV was performed.

Primary endpoints were the incidence (number of patients) and the intensity (mean maximal intensity and mean number of emetic episodes) of PON, POV, and PONV. The secondary endpoint was the safety and tolerability of the treatment.

Sample size estimation was performed in accordance with the results of a recently published multicentre study that also used a risk-adapted approach.[16] In that study, the incidence of PONV was 43% in patients at high risk for PONV after having received 4 mg ondansetron. At 172 patients per group, there is an 80% chance to detect an absolute risk reduction of 15 percentage points (e.g., from 43% to 28%) in the high risk groups (H-O and H-OD) using a two-sided Fisher's exact test with a type I error of 0.05. In addition, 80 low risk patients were enrolled in order to show that the observed and expected incidences of PONV were similar. Allowing for early dropouts, a total of 440 patients needed to be enrolled.

All data analysis was carried out on an intention-to-treat (ITT) basis according to a pre-established analysis plan. Unless otherwise mentioned, data are presented as means (± SD) for continuous variables or absolute and relative frequencies (lower and upper limits of 95% confidence interval) for discrete variables. Student's t test was used to compare continuous variables. Fisher's exact test (two-sided) was used to compare incidences of target parameters. Statistical significance was defined as $P < 0.05$.

Results

Patients were enrolled from November 2001 to July 2002. Due to logistical reasons, the number of patients enrolled in the study exceeded the number originally planned for enrolment. In total, 460 patients were enrolled. Four subjects were excluded from both safety and efficacy analyses because they underwent neither surgery nor general anesthesia. Of the remaining 456 patients, three patients were excluded from the ITT analysis because of major protocol violations: one patient had two risk factors and qualified for the high-risk group; by mistake he was classified as "low risk" and thus did not receive study treatment. One patient was classified as "high risk" but did not receive study treatment. Lastly, one patient was treated intraoperatively with prednisolone and thereafter was not monitored for PONV by the investigator. Thus, 453 patients were analyzed for efficacy.

Subjects in the H-O group had similar patient characteristics and variables known to affect PONV to subjects in the H-OD group (Table I). A comparison of group L to group H-O and H-OD in this respect was conducted in accordance with the design of the study.

Efficacy analysis

Data presented below on the incidence and intensity of PON, POV, and PONV refer to the entire 24-hr observation period. A detailed breakdown of the incidence for each time period (0–2 hr and 0–24 hr) is shown in Table II and the intensity of symptoms for each time period is shown in Figures 1 and 2.

The incidence of PON did not differ in the two high-risk groups (20% in H-O *vs* 15% in H-OD; $P = 0.27$, Table II). Likewise, the mean number of episodes of nausea per patient was similar in the high-risk groups and (0.34 in H-O *vs* 0.28 in H-OD; $P = 0.444$, Figure 1). The average maximal intensity of the episodes of nausea was significantly greater in those only receiving ondansetron (0.56 in H-O) compared

TABLE I Patient characteristics and variables related to PONV

	L	*H-O*	*H-OD*	*P**
n	*87*	*185*	*181*	-
Age (yr)	42 (± 15.0)	47 (± 13.8)	45 (± 14.5)	0.11
Weight (kg)	78 (± 14.6)	74 (± 15.7)	72 (± 15.4)	0.37
Height (cm)	176 (± 8.4)	168 (± 8.3)	168 (± 8.3)	0.86
Female patients (%; *n*)	22; 19	82; 151	83; 151	0.68
Non-smokers (%; *n*)	14; 12	78; 145	72; 131	0.23
History of PONV (%; *n*)	5; 4	45; 76	55; 84	0.34
History of MS (%; *n*)	3; 3	28; 51	24; 44	0.55
Hx. of PONV and/or MS (%; *n*)	7; 6	54; 100	59; 107	0.34
Postoperative opioids (%; *n*)	45; 39	84; 156	81; 146	0.41
Risk factors	0.9 (± 0.4)	3 (± 0.8)	2.9 (± 0.8)	0.54
Duration of anesthesia (hr)	1.7 (± 0.8)	1.9 (± 1.3)	1.9 (± 1.2)	0.84
Risk of PONV (%)	19 (± 4)	59 (± 16)	58 (± 15)	0.58
IVA (%; *n*)	10; 9	7; 13	8; 14	0.84
TIVA (%; *n*)	9; 8	15; 28	18; 32	0.57
IA (%; *n*)	81; 70	78; 144	74; 135	0.54

L = low-risk group; H-O = high-risk group receiving ondansetron; H-OD = high-risk group receiving ondansetron and dexamethasone. **P*-value is for comparison between H-O and H-OD groups. Data presented as means ± SD or absolute and relative frequencies, where applicable. PONV = postoperative nausea and vomiting; MS = motion sickness; Postoperative opioids = patients in whom the administration of postoperative opioids was planned; Risk of PONV = estimated risk of PONV according to a validated score.[12] IVA = intravenous anesthesia in combination with nitrous oxide; TIVA = total intravenous anesthesia; IA = inhalational anesthesia.

TABLE II Incidences of PON, POV and PONV

	L	*H-O*	*H-OD*	*P**
n	*87*	*185*	*181*	-
PON 0-24 hr	8 (3.3 - 15.9)	19.5 (14 - 25.9)	14.9 (10.1 - 21)	0.270
PON 0-2 hr	5.7 (1.9 - 12.9)	10.8 (6.7 - 16.2)	9.4 (5.6 - 14.6)	0.730
PON 2-24 hr	5.7 (1.9 - 12.9)	7 (5.9 - 14.9)	8.3 (4.7 - 13.3)	0.716
POV 0-24 hr	1.1 (0 - 6.2)	11.4 (7.2 - 16.8)	7.2 (3.9 - 12)	0.208
POV 0-2 hr	1.1 (0 - 6.2)	4.9 (2.2 - 9)	4.4 (1.9 - 8.5)	1
POV 2-24 hr	1.1 (0 - 6.2)	10.3 (6.3 - 15.6)	3.9 (1.6 - 7.8)	0.024
PONV 0-24 hr	9.2 (4.1 - 17.3)	30.8 (24.2 - 38)	22.1 (16.3 - 28.9)	0.075
PONV 0-2 hr	6.9 (2.6 - 14.4)	15.7 (10.8 - 21.7)	13.8 (9.1 - 19.7)	0.66
PONV 2-24 hr	6.9 (2.6 - 14.4)	20 (14.5 - 26.5)	12.2 (7.8 - 17.8)	0.047

L = low-risk group; H-O = high-risk group receiving ondansetron; H-OD = high-risk group receiving ondansetron and dexamethasone. PONV = postoperative nausea and vomiting; PON = postoperative nausea; POV = postoperative vomiting; **P*-value is for comparison between H-O and H-OD groups. Data presented as relative frequencies and, in parenthesis, the upper and lower limits of the 95% confidence interval.

to patients receiving ondansetron and dexamethasone (0.33 in H-OD; $P = 0.022$, Figure 2).

The incidence of POV was similar in the two high-risk groups as well (11% in H-O *vs* 7% in H-OD; $P = 0.208$, Table II). Patients in the H-O group had significantly more emetic episodes per patient than did patients in the H-OD group (0.35 *vs* 0.16, respectively; $P = 0.004$, Figure 1). The mean maximal intensity of emetic episodes was also significantly greater in the H-O group than in the H-OD group (0.56 *vs* 0.25, respectively; $P = 0.002$, Figure 2).

The incidence of PONV did not differ significantly in the H-O and H-OD groups (31% *vs* 22%, respectively; $P = 0.075$, Table II). The average number of PONV episodes per patient was greater in group H-O than in group H-OD (0.69 *vs* 0.44; $P = 0.034$, Figure 1). Patients who received ondansetron and dexamethasone had a significantly lower average maximal intensity of their episodes (0.45 in H-OD) than those who received only ondansetron (0.74 in H-O; $P = 0.011$, Figure 2).

Rescue medication

During the entire observation period (0–24 hr), fewer patients in the H-OD group compared to the H-O group received rescue antiemetics (12% *vs* 23%; $P =$

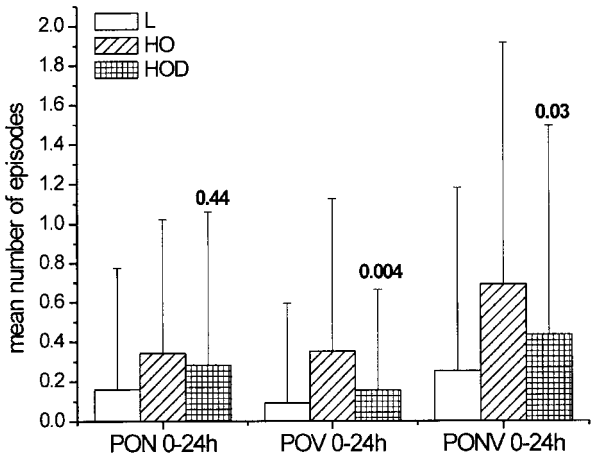

FIGURE 1 Episodes of postoperative nausea, postoperative vomiting and postoperative nausea and vomiting in the low-risk group (L), high risk group receiving ondansetron (H-O), and high-risk group receiving ondansetron and dexamethasone (H-OD). Data presented as mean ± SD. *P*-values of comparison between H-O and H-OD are given for each outcome.

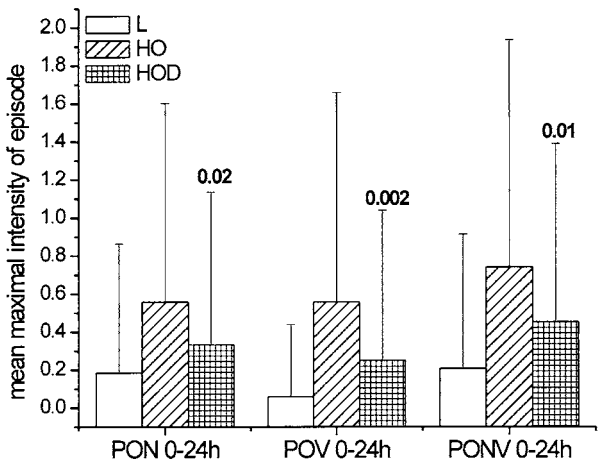

FIGURE 2 Maximal intensity of episodes of postoperative nausea, postoperative vomiting and postoperative nausea and vomiting in the low-risk group (L), high-risk group receiving ondansetron (H-O), and high-risk group receiving ondansetron and dexamethasone (H-OD). Data presented as mean ± SD. *P*-values of comparison between H-O and H-OD are given for each outcome.

0.004, Table III). A detailed breakdown of the requirements for antiemetics during the different observation periods is given in Table III.

Predicted PONV incidence vs actual PONV incidence

The incidence of PONV in the low-risk patients (group L; Table IV) was similar to the predicted value ($P = 0.084$). The incidence of PONV in both high-risk groups (H-O and H-OD) was significantly less than predicted according to the patients' underlying risks ($P < 0.001$, Table IV).

Safety analysis

No serious adverse events occurred in any of the study groups. The most frequent postoperative (non-serious) adverse events were hypotension, shivering, hypertension, bradycardia, and hemorrhage. Twenty-one patients (23.6%) in group L had a total of 22 adverse events; 35 (18.9%) patients in group H-O had a total of 46; and 31 (17%) in group H-OD had a total of 35. An increase in the number of adverse events with treatment was not detected. In summary, there were no significant safety problems related to the study drugs.

Discussion

We found that patients at high risk of developing PONV who received either ondansetron alone or ondansetron plus dexamethasone had a significantly reduced incidence of PONV within the first 24 hr after surgery, compared to the predicted incidence of PONV in these patients. Our results therefore confirm that ondansetron is efficacious in patients at high risk for PONV.[6] Moreover, we showed that the combination of ondansetron plus dexamethasone is superior to ondansetron alone in reducing PONV. Our findings have now been confirmed by the recent results of a large multicentre trial which indicates that antiemetics with different mechanisms act independently, i.e., the joint benefit from a combination of interventions can easily be estimated from the known benefits of the individual interventions.[16] The study reported here is novel in the respect that a risk assessment scale has been prospectively implemented into practice.

However, while the incidences of PON, POV, and PONV in group H-OD patients were consistently less compared with those of group H-O, only the differences for POV and PONV during the two to 24-hr period were statistically significant (Table II). On the other hand, the average number of POV and PONV episodes was significantly smaller in the group receiving both drugs (Figure 1) and average maximal intensities of PON, POV, and PONV episodes were significantly smaller (Figure 2). There was also a decreased need for rescue treatment during the zero to 24-hr observation period in patients receiving both drugs (Table III). Despite the lack of statistically sig-

TABLE III Antiemetic rescue treatment

0-24 hr, n	*L* *8*	*H-O* *43*	*H-OD* *21*	*P**
0-24 hr, %	9.2 (4.1 - 17.3)	23.2 (17.4 - 30)	11.6 (7.3 - 17)	0.004
0-2 hr, *n*	5	25	10	
0-2 hr, %	5.7 (1.9 - 12.9)	13.5 (8.9 - 19.3)	5.5 (2.7 - 9.9)	0.012
2-24 hr, *n*	4	25	15	
2-24 hr, %	4.7 (1.3 - 11.5)	13.7 (9 - 19.5)	8.3 (4.7 - 13.3)	0.131

L = low-risk group, H-O = high-risk group receiving ondansetron, H-OD = high-risk group receiving ondansetron and dexamethasone. **P*-value is for comparison between H-O and H-OD groups. Data presented as absolute frequencies and percent of group total (upper and lower limits of the 95% confidence interval).

TABLE IV Predicted and actual PONV incidence

n	*L* *87*	*H-O* *185*	*H-OD* *181*
Predicted incidence n (%)	17 (19)	109 (59)	105 (58)
Actual incidence n (%)	8 (9.2)	57 (30.2)	40 (22.1)
Difference % (95% CI)	10.3 (-0.2 - 20.9)	28.1 (18.1 - 37.3)	35.9 (26.1 - 44.7)
P	0.08	< 0.001	< 0.001

L = group L, H-O = group H-O, H-OD = group H-OD; PONV = postoperative nausea and vomiting; CI = confidence interval; *P* = *P*-value from Fisher's exact test.

nificant differences between groups H-OD and H-O in some comparisons, we maintain that the results of this study show that the combination of ondansetron plus dexamethasone is superior to ondansetron alone in preventing PONV in patients at high risk for this adverse event.

As mentioned above, the superiority of the combination of ondansetron and dexamethasone compared to monotherapy was not as clear-cut as expected from previously published meta-analyses on dexamethasone.[10,11]This may have been caused by an insufficient sample size. The anticipated power of our study was probably reduced because we allowed the use of a propofol-based anesthetic technique, which is known to decrease the overall incidence of PONV.[6,17] Therefore, it is reasonable to assume that the baseline risk in groups H-O and H-OD was approximately 5% less than expected, which lowered the power to show a significant difference with our sample size estimation. This may, in part, explain why the incidence of PONV in group H-O was only 31%, compared to 43% in a comparable study.[16]

Dexamethasone's efficacy to prevent PON was shown to be the same as its efficacy to prevent POV [number needed-to-treat of 4.3].[10] In contrast, a meta-analysis claims that ondansetron is more efficacious in preventing POV than PON.[6] Therefore, it may be that the combination of ondansetron plus dexamethasone is less efficacious in preventing PON than POV. However, our study design does not address this question given that we did not include a placebo group.

The patients receiving both antiemetics had the same degree and number of adverse effects, as did those receiving only ondansetron. Thus, results of this study do not provide any evidence for the assumption that the addition of dexamethasone to ondansetron compared to ondansetron alone increases the risk for adverse events.

A limitation of our study is that we did not have a high-risk group that received placebo. While it may be argued that the level of evidence is lower when a score is used as a 'virtual placebo group' for comparison as opposed to a 'true placebo group,' we feel this is a valid experimental design for several reasons. First, the simplified risk score[12] has been validated.[13,14] Second, as interventions are already known to be effective for PONV, it is not ethically justified to deny high-risk patients prophylactic antiemetic treatment.[18] Finally, this design does not affect the validity of the results from the randomization of patients to treatment with ondansetron alone or ondansetron plus dexamethasone.

Taken together, the results of this study indicate the superiority of ondansetron plus dexamethasone over ondansetron alone in the prevention of PONV in patients at high risk for this condition. Moreover, it is important to note that the reduction of PONV in both study groups was achieved by implementing a validated risk score prospectively. Since prophylaxis of PONV is recommended in patients at moderate to high risk for PONV, the combination of ondansetron

plus dexamethasone certainly represents a useful component within the framework of a multimodal approach in the management of PONV.

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