

# Methylprednisolone vs. dexamethasone in the prevention of post-operative nausea and vomiting : a prospective, randomised, double-blind, placebo-controlled trial

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**Abstract :** Dexamethasone and methylprednisolone have been proven effective in the prevention of nausea after chemotherapy. Dexamethasone has been proven effective in the prophylaxis of late PONV. Literature about methylprednisolone in PONV prophylaxis is rare. We randomized 118 patients in a double blind way to receive either dexamethasone 8 mg, methylprednisolone 40 mg or placebo as prophylactic agent.

Duration of anaesthesia was significantly longer and significantly more sufentanil was used in the methylprednisolone group. Despite these 2 risk factors, methylprednisolone was significantly better than placebo in the prevention of late nausea, retching and PONV. There was a beneficial clinical effect of dexamethasone in this population, although not significant. A possible explanation lies in the fact that monotherapy is mostly insufficient in a population at risk like ours.

This study confirms that steroids are mostly effective in the prevention of late PONV, less effective in early PONV.

**Key words :** Postoperative nausea and vomiting ; dexamethasone ; methylprednisolone.

Postoperative nausea and vomiting (PONV) still has an overall incidence of 20 to 30% (3, 5, 9, 16, 25). The incidence can increase up to 70% in high risk patients (2).

PONV is one of the most unpleasant complications of anaesthesia (15, 19). It can lead to prolonged post anaesthesia care unit stay, unanticipated admissions in ambulatory surgery and medical complications (10, 11, 23).

Anaesthesia-, surgery- and patient related risk factors have been identified in the aetiology of PONV. Simplified risk scores for PONV have been developed by APFEL *et al.* (2), SINCLAIR *et al.* (24). Risk factors according to APFEL *et al.* are female gender, history of PONV or motion sickness, opioids and non smoking status.

Both dexamethasone and methylprednisolone have been proven effective in the prevention of chemotherapy-induced emesis (14, 17, 18). Dexa-

methasone in the prevention of PONV has been extensively studied (4, 13). Literature about the effectiveness of methylprednisolone in this matter is rare (7, 21).

The mechanism of the anti-emetic effect of steroids is unclear. Several mechanisms of action in chemotherapy-induced emesis were proposed in literature. Possible mechanisms for the anti-emetic effects of steroids may be prostaglandin antagonism (20), an anti-inflammatory effect which leads to serotonin inhibition in the gut (8), release of endorphins with mood elevation, stimulation of appetite or other beneficial effects (12). Corticosteroids may also reduce levels of serotonin in neural tissue (26) and may potentate the effect of other anti-emetics by sensitizing their pharmacological receptors (22).

In this trial we want to compare the effectiveness of methylprednisolone and dexamethasone vs. placebo in the prevention of PONV.

## METHODS

After approval from our institutional ethics committee and written informed consent of all subjects, we included 118 surgical in-patients. Inclusion criteria were female gender, adult age, elective abdominal or gynaecological surgery and informed consent of all subjects. Exclusion criteria were pregnancy or lactation, the intake of anti-emetic drugs within 24 hours preceding the surgery and emergency procedures.

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Patients were randomized in three groups by a computer generated list : the dexamethasone group, the methylprednisolone group and the placebo group. Alprazolam 0.25 mg was given orally 2 hours before surgery for premedication. A standard general anaesthesia was performed. Anaesthesia was induced with sufentanil 0.3  $\mu\text{g.kg}^{-1}$ , propofol 2  $\text{mg.kg}^{-1}$ , and atracurium 0.5  $\text{mg.kg}^{-1}$ . Anaesthesia was maintained with 1 MAC of desflurane and additional doses of sufentanil and atracurium as needed. Pre-emptive analgesia with ketorolac 0.5  $\text{mg.kg}^{-1}$  intravenously was given immediately after induction. Intravenous paracetamol 15  $\text{mg.kg}^{-1}$  was given 20 minutes before the end of surgery. Prophylactic anti-emetic drugs were given according to the randomisation in a double blind matter. All patients were given a 10 ml intravenous solution at the induction of anaesthesia. The dexamethasone group received 8 mg of dexamethasone in saline, the methylprednisolone group 40 mg methylprednisolone in saline and the placebo group normal saline respectively.

Postoperative analgesia consisted of paracetamol 15  $\text{mg.kg}^{-1}$  (maximally 1 g) intravenously per 6 hours, ketorolac 0.25  $\text{mg.kg}^{-1}$  IV per 8 hours (for maximally 48 hours) and piritramide 0.25  $\text{mg.kg}^{-1}$  intramuscularly if needed according to the patient and an experienced ward nurse.

Primary endpoint is to compare dexamethasone and methylprednisolone to placebo for the prevention of PONV.

Nausea was defined as a subjective unpleasant feeling of having to vomit and was scored with a numeric scale of 0 to 10, 0 being no nausea, 10 the worst imaginable form of nausea. Retching was defined as a vomiting movement, without vomiting. It was scored as absent or present (0 or 1). Vomiting was defined as the expulsion of stomach-contents. The number of vomiting episodes was scored. A patient was considered having PONV if one or more of these criteria were scored above 0.

Secondary endpoints are the incidence of early (first 2 hours) and late (2 to 24 hour post-operatively) PONV ; the use of rescue medication (alizapride 50 mg or ondansetron 4 mg) and the early and late pain scores (visual analogue scale).

If normally distributed, results of continuous data were expressed as means (with SDs) and analyzed with Student's *t* test. Variables that did not show normal distribution were expressed as medians (with interquartile ranges) and compared with the Mann-Whitney *U* test. Categorical data were analyzed with Fisher's exact test. *P* values of < 0.05 were considered statistically significant.

## RESULTS

We included 118 female patients in this trial. There were no significant differences between our 3 groups with regard to age, type of surgery, body mass index (BMI), history of PONV, smoking status, use of  $\text{N}_2\text{O}$  or use of clonidine (Table I). Duration of anaesthesia was significantly longer in the methylprednisolone group in comparison with placebo (*p* 0.044). Significantly more sufentanil was used in the methylprednisolone group in comparison with placebo (*p* 0.032). Neither the use of sufentanil nor the duration of anaesthesia was significantly different between the two steroid groups.

PONV was seen in 34% (95% CI 20-51%) of patients treated with dexamethasone, 20% (95% CI 9-36%) treated with methylprednisolone and 43% (95% CI 27-59%) treated with placebo (Table II). The incidence of PONV was significantly lower in the methylprednisolone group compared to placebo (*p* 0.019). The relative risk reduction for PONV for dexamethasone is 20% (95% CI -41-55%), the number needed to treat is 12 (95% CI 3- $\infty$  %). The relative risk reduction for PONV for methylprednisolone is 53% (95% CI 5-77%), the number needed to treat is 4 (95% CI 2-31). This difference between dexamethasone and methylprednisolone was not significant. The use of rescue medication for PONV was not significantly different between groups (Table I).

In our trial we could not demonstrate any significant difference between groups for early nausea, retching, vomiting nor early PONV.

Early PONV was seen in 18% (95% CI 8-34%) treated with dexamethasone, 10% (95% CI 3-24%) treated with methylprednisolone and 18% (95% CI 7-33%) treated with placebo respectively.

Late PONV was seen in 29% (95% CI 15-46%) patients treated with dexamethasone, 15% (95% CI 6-30%) treated with methylprednisolone and 35% (95% CI 21-52%) treated with placebo respectively. Methylprednisolone was significantly better in the prevention of late PONV than placebo (*p* 0.045). There was a positive trend for dexamethasone, although not significant. The relative risk reduction for late PONV for dexamethasone is 17% (95% CI -57-57%), the number needed to treat is 17 (95% CI 4- $\infty$  ). The relative risk reduction for late PONV for methylprednisolone is 57% (95% CI 40-82%), the number needed to treat is 5 (95% CI 3-97). This difference between methylprednisolone and dexamethasone was not significant.

Methylprednisolone was significantly better in the prevention of late nausea (methylprednisolone :

Table I  
Demographic data

	Dexamethasone (n = 38)	Methylprednisolone (n = 40)	Placebo (n = 40)
Age (yr)	45.03 (16.07)	45.35 (15.23)	47.28 (16.58)
Gynaecology <sup>a</sup>	27 (71.05)	30 (75.00)	28 (70.00)
Abdominal <sup>a</sup>	11 (28.95)	10 (25.00)	12 (30.00)
Laparoscopy <sup>a</sup>	23 (60.53)	11 (27.50)	24 (60.00)
Body Mass Index (kg.m <sup>2</sup> )*	28.05 (10.50)	25.20 (6.21)	25.80 (7.45)
Tabacco <sup>a</sup>	5 (13.15)	13 (32.50)	5 (12.50)
History PONV <sup>a</sup>	4 (10.53)	3 (7.50)	4 (10.00)
Duration surgery (min.)*	91.0 (36.47)	102.5(72.5)	85.0 (43.75)
Duration anaesthesia (min.)*	112.5 (37.50)	127.5 (87.50) <sup>b</sup>	105.0 (43.70)
Sufentanil (µg)*	26.51 (7.72)	27.94 (10.34) <sup>b</sup>	23.94 (6.79)
N <sub>2</sub> O <sup>a</sup>	14 (37.84)	11 (27.50)	12 (30.00)
Piritramide (mg)	10 (20)	10 (20)	10 (20)
Alizapride (mg)	0 (50)	0 (0)	0 (50)

All data are presented as mean (SD), unless \* not normally distributed, thus presented as median (interquartile range) ; <sup>a</sup> number of patients (% of total) ; <sup>b</sup> p < 0.05 versus placebo.

Table II  
Incidence of PONV

	Dexamethasone (n = 38)	Methylprednisolone (n = 40)	Placebo (n = 40)	p value methylprednisolone vs. placebo
Early nausea	7 (18, 8-34)	4 (10, 3-24)	7 (18, 7-33)	0.289
Early retch	5 (13, 4-12)	1 (3, 0-13)	5 (13, 4-27)	0.1
Early vomiting	4 (11, 3-25)	2 (5, 1-17)	6 (15, 6-30)	0.132
Early PONV	7 (18, 8-34)	4 (10, 3-24)	7 (18, 7-33)	0.259
Late nausea	11 (29, 15-46)	5 (13, 4-27)	14 (35, 21-52)	0.017
Late retch	8 (21, 10-37)	3 (8, 2-20)	11 (28, 15-44)	0.018
Late vomiting	5 (13, 4-12)	3 (8, 2-20)	8 (20, 9-36)	0.096
Late PONV	11 (29, 15-46)	6 (15, 6-30)	14 (35, 21-52)	0.045

All data are presented as number of patients (% of total, 95% CI).

13% (95% CI 4-27%) vs. placebo : 35% (95% CI 21-52%) ; p 0.017) and late retching (methylprednisolone : 8% (95% CI 2-20%) vs. placebo : 28% (95% CI 15-44%) ; p 0.018). Methylprednisolone seemed better in the prevention of late nausea than dexamethasone (methylprednisolone : 13% (95% CI 4-27%) vs. dexamethasone : 29% (95% CI 15-46)). This difference is not significant. There was no significant difference in late vomiting between groups.

In our trial we could not demonstrate a significant difference in the use of rescue medication and postoperative opioids. There was also no difference in postoperative pain scores (visual analogue scale) (Table I). In each group 10 mg (SD 20) of piritramide was given per patient (Table I).

Median duration of surgery (minutes) was significantly longer in patients suffering from early PONV (115 vs. 85 ; p 0.0013), as well as in patients suffering from late PONV (90 vs. 85 ; p 0.044) in comparison with those without (Table IV). There was no significant difference for late nausea alone.

Duration of surgery was significantly longer in all patients suffering from PONV in comparison with those without PONV (90 (+/- 44) vs. 75 (+/- 55) minutes, p 0.0024) (Table III).

The use of N<sub>2</sub>O was not significantly different between the 3 groups studied. The use of N<sub>2</sub>O was higher in patients suffering from PONV (19/42 (45%, 95% CI 30-61%) vs. 23/88 (26%, 95% CI 17-37%). This difference was not significant. The type of surgery was of no significant influence on the occurrence of PONV (Table III). Furthermore more laparoscopic procedures were performed in patients with no PONV. The number of gynaecological, abdominal and laparoscopic procedures respectively was not significantly different between the 3 groups studied.

## DISCUSSION

Methylprednisolone was better than placebo in the prevention of late nausea, retching and PONV,

Table III  
PONV versus non PONV

	PONV (n = 42)	No PONV (n = 88)
Age (yr)	49,57 (13,70)	44,05 (16,11)
Gynaecology (patients) <sup>a</sup>	33 (79)	58 (66)
Abdominal (patients) <sup>a</sup>	9 (21)	30 (34)
Laparoscopy (patients) <sup>a</sup>	21 (50)	63 (72)
Body Mass Index (kg.m-2)*	27,04 (8,92)	25,62 (9,78)
Tobacco (patients) <sup>a</sup>	7 (17)	19 (22)
History PONV (patients) <sup>a</sup>	6 (14)	9 (10)
Duration surgery (min.)*	90 (44,00)	75,00 (55,00) <sup>b</sup>
Duration anaesthesia (min.)*	123 (63,75)	105 (45,00) <sup>b</sup>
Sufentanil (microg)*	26,43 (8,77)	23,94 (6,79)
N2O (patients) <sup>a</sup>	19 (45,24)	23 (26,14)
Piritramide (mg)	10 (20)	10 (20)
Alizaprid (mg)	50 (100)	0 (0)

All data are presented as mean (SD), unless \* presented as median (interquartile range) ; <sup>a</sup> number of patients (% of total) ; <sup>b</sup> p < 0.05.

Table IV  
Duration of surgery (minutes)

	YES	NO	p
Early nausea	115,00 (62,50)	85,00 (53,75)	0,0013
Early retch	110,00 (57,50)	87,00 (55,00)	0,016
Early vomit	115,00 (70,00)	85,00 (55,00)	0,0035
Early PONV	115,00 (62,50)	85,00 (53,75)	0,0013
Late nausea	90,00 (41,50)	85,00 (55,00)	0,08
Late retch	100,00 (47,00)	85,00 (55,00)	0,011
Late vomit	105,00 (57,50)	86,00 (55,00)	0,01
Late PONV	90,00 (44,75)	85,00 (55,00)	0,044

All data are presented as median (interquartile range), except for p.

despite longer duration of anaesthesia and the use of more sufentanil in the methylprednisolone group. There was no difference in the prevention of early PONV.

Henzi suggested that dexamethasone might be particularly effective in the prevention of late PONV (13). Mokhtar ELHAKIM *et al.* also found that the effect of dexamethasone (0.5 mg/kg, with a maximum of 8 mg) on PONV was more pronounced in the late postoperative phase (6). ROMUNDSTAD *et al.* found that methylprednisolone 125 mg was more effective than placebo in the prevention of PONV. No distinction was made between early and late PONV (21).

Methylprednisolone (NNT 5) seems better than dexamethasone (NNT 17) in the prevention of late PONV. Further studies are needed to prove if methylprednisolone is significantly better than dexamethasone in the prevention of PONV.

We could not demonstrate a significant beneficial effect of dexamethasone vs. placebo in this population.

We found an incidence of PONV of 43% (95% CI 27-59%) in the placebo group vs. 34% (95% CI 20-51%) in the dexamethasone group. This results in a relative risk reduction of 21% (95% CI minus 41-55%), which is consistent with a 26% risk reduction as found by APFEL *et al.*, although not statistically significant in our population (1).

A possible explanation for not finding a significant beneficial effect for dexamethasone could be that our population is a population at risk according to risk scores of APFEL (2) and SINCLAIR (24). All patients were of female gender, opioids were used pre- and postoperatively and most of the patients were non-smokers (80%). In a population at risk a combination of anti emetic drugs is recommended (11). The combination of dexamethasone with a serotonin receptor antagonist is more effective than dexamethasone or a serotonin antagonist alone in all patients (13).

If dexamethasone in combination with a serotonin antagonist is better than either of the two alone, would methylprednisolone in combination with a serotonin antagonist be better than methylprednisolone or a serotonin antagonist alone? Further studies on this subject should be performed.

In literature the incidence of PONV is estimated to be approximately 30% (3, 5, 9, 16, 25) (up to 70% in high risk patients). The incidence of PONV in our placebo group was 43% (95% CI 27-59%). Our population is a population at risk according to risk scores of APFEL (2) and SINCLAIR (24). All patients were of female gender, opioids were used pre- and postoperative and most of the patients were non-smokers (80%, 95% CI 72-87%).

In the majority of reports on dexamethasone in the prevention of PONV, 8 mg of dexamethasone was used (4, 13, 17), although APFEL *et al.* proved 4 mg of dexamethasone to be as effective as higher doses (1). The dose equivalent for the anti-inflammatory effect of dexamethasone 8 mg is 40 mg of methylprednisolone. We used 8 mg of dexamethasone in comparison with 40 mg of methylprednisolone to rule out a difference in potency for the prevention of PONV. Methylprednisolone was used in much higher doses in the other trials that found a beneficial effect on PONV. In a recent report ROMUNDSTAD *et al.* found that methylprednisolone 125 mg is more effective in the prevention of PONV than placebo (21). FILLINGER *et al.* found in their report on the inflammatory response to cardiac surgery, that patients who received methylprednisolone (15 mg/kg 1 hour prior to surgery and 0.3 mg/kg/6 hours, 4 times postoperatively) had a

significant reduction in the incidence of PONV on the first postoperative day (7).

As stated above, the effect of methylprednisolone was more pronounced on late PONV. Postoperative opioids however were of no influence on the incidence of PONV in this population. We could not demonstrate any significant difference in postoperative pain scores, nor in the use of piritramide between groups.

In our population the duration of surgery and anaesthesia were risk factors for the occurrence of early nausea, retch, vomiting, PONV and late retch, vomiting and PONV. The duration of anaesthesia was longer in methylprednisolone vs. placebo. There were no further differences in duration between groups. Duration of surgery and anaesthesia is a risk factor according to SINCLAIR (24), but not according to APFEL (2).

The use of N2O was a risk factor for PONV in our population. Nitrous oxide increases postoperative vomiting according to HABIB *et al.* (11). There was no significant difference in the use of N2O between groups.

## CONCLUSION

We confirm that steroids are most effective in the prevention of late PONV, less effective in early PONV. We showed a positive trend for dexamethasone (17) vs. placebo with a NNT of 12 to prevent late PONV, although not statistically significant. Methylprednisolone (5) is significantly better than placebo with a NNT of 4 to prevent late PONV. The difference between dexamethasone and methylprednisolone is not significant in our study.

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