The effects of dexamethasone and metoclopramide on early and late postoperative nausea and vomiting in women undergoing myomectomy under spinal anaesthesia

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Abstract

Background: Post-operative nausea and vomiting (PONV); early or late, has detrimental effects on surgical patients such as surgical wound disruption, esophageal tear and delayed discharge from the post anesthetic care unit. This study evaluated the effects of dexamethasone-metoclopramide (DM) in the prevention of early and late PONV in women undergoing myomectomy under subarachnoid block.

Materials and Methods: Following approval from the Research and Ethics Committee of the Hospital, informed consent was obtained from each prospective patient. Patients were randomly allocated to either the DM group, metoclopramide only (MO) group or dexamethasone only (DO) group using the computer-generated random numbers in sealed envelopes. Immediately after the induction of spinal anesthesia, the DM group received intravenous (i.v.) dexamethasone 8 mg and metoclopramide 10 mg, the MO group received metoclopramide 10 mg i.v and the DO group received dexamethasone 8 mg i.v. The incidence of early and late PONV formed the primary outcome.

Results: A total of 90 patients, with aged range between 21-64 years were studied. Dexamethasone alone group had the highest incidence of 40% for early but no for late PONV (P = 0.003) Metoclopramide alone group had an incidence of 29.97% for early PONV and 26.6% for late PONV. There was reduced incidence of both early and late PONV in the DM group, but of lesser magnitude than DO or MO respectively.

Conclusion: Dexamethasone protects against the incidence of late PONV with a minimal effect on early PONV. The combination of dexamethasone and metoclopramide had comparable effect on both and of better magnitude than metoclopramide alone.

Key words: Antiemetic, myomectomy, spinal anaesthesia

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Introduction

Post-operative nausea and vomiting (PONV) is a commonly reported complication following surgery and anesthesia.[1] Its incidence varies from the type of surgical procedure to the type of anesthetic technique employed. The incidence of PONV following gynecological surgery has been reported to be 75-93%.[3] For surgery under general anesthesia (GA), the incidence of PONV ranges between 25% and 40% respectively.[1]

PONV may be classified into early and late PONV. White et al.[1] classified PONV into early PONV (0-24 h) and
late PONV (24-72 h).\textsuperscript{11} Using Apfel’s simplified risk scoring system,\textsuperscript{12} they found that it was predictive of emetic symptoms within 24 h. However, there was no correlation between the scoring system and late PONV.

Velickovic and Kalezic also found different risk factors for early and late PONV.\textsuperscript{14} However, they classified PONV into early PONV as 0-2 h and late PONV as 2-24 h post-surgery. Previous history of PONV and parathyroid surgery were predictive for early PONV while female gender was more predictive for late PONV in their study.

Volatile anesthetics were the leading cause of early PONV in a study conducted by Apfel et al.\textsuperscript{5} Other factors like childhood and the use of post-operative opioids were the main predictors of late PONV in their study. From the above findings, it can be deduced that different risk factors accounted for early and late PONV. A source of concern however is the different classification for early and late PONV used in these studies.

PONV following spinal anesthesia is related to spinal-induced hypotension, which increases the incidence of PONV.\textsuperscript{6} Hypotension (systolic blood pressure [SBP] <80 mmHg), blocks higher than T5 and the addition of vasoconstrictors to local anesthetic for spinal anesthesia have also been found to increase the incidence of nausea and vomiting during spinal anesthesia.\textsuperscript{21}

Dexamethasone is a safe, efficacious\textsuperscript{8,9} and cost-effective anti-emetic when compared with other conventional anti-emetic drugs such as metoclopramide or ondansetron. It is effective against PONV resulting from a wide variety of surgeries such as tonsillectomy, thyroidectomy, abdominal hysterectomy, gynecological laparoscopy and laparoscopic cholecystectomy.\textsuperscript{10} In addition, it has been used in combination therapy with both serotonin 5-hydroxytryptamine antagonists and droperidol and was shown to increase the anti-emetic efficacy of these drugs when given for prophylaxis against PONV.\textsuperscript{21}

Nevertheless, the differential effect of dexamethasone on early and late PONV remains to be determined in women undergoing gynecological surgeries under spinal anesthesia. This study therefore aimed to evaluate the effect of dexamethasone in the prevention of early and late PONV in this group of patient.

Ethical approval
Approval for the conduct of the study was obtained from the hospital’s Ethics Committee. A written informed consent was obtained from every prospective patient enlisted for the study.

Study design
A prospective, randomized, double-blind controlled trial of dexamethasone alone, dexamethasone-metoclopramide (DM) versus metoclopramide alone as anti-emetics in women undergoing myomectomy under spinal anesthesia. Each eligible patient was randomly assigned to either of the three groups using computer-generated random numbers in sealed envelopes.

A pre-hoc power analysis indicated 26 patients per group were required to detect a 50% in the incidence of PONV. Allowing for subjects lost to protocol violations and drop outs, we recruited 90 patients in all.

Study population
American Society of Anesthesiologists (ASA) 1 or 2 female patients with age ranges between 21 and 64 years who were scheduled for myomectomy under spinal anesthesia were recruited for the study.

Exclusion criteria
previous history of PONV, motion sickness or use of anti-emetics or steroid therapy, gastro-intestinal disease, psychiatric illness and substance abuse.

Study protocol
The study medications (DM) were prepared in identical, equal volume 5 ml syringes and labeled by the investigator who also administered the drugs. An independent person who had no knowledge of study drugs observed each patient for PONV.

Anesthetic management
Pre-anesthetic review was done for all eligible patients in the ward the night before surgery. Routine investigations including full blood count, electrolyte, urea and creatinine, urinalysis were all requested for and done. The patients were then classified appropriately based on the ASA physical status into either ASA 1 or 2. They were all fasted overnight from 2200 h to time of procedure. All the patients received oral diazepam 10 mg the night before surgery and an hour prior to induction of anesthesia as per departmental protocol.

Baseline vital signs namely pulse rate (PR), blood pressure, respiratory rate, arterial saturation of oxygen \(\text{SpO}_2\) were taken and recorded using a multi-parameter monitor (Dash 4000 G.E) before induction of spinal anesthesia in the operating room. Intravenous (i.v) access was secured

Patients and Methods

Study area
University of Benin Teaching Hospital, Benin City at the Obstetrics and Gynecology Department of the hospital.
with a 16 G cannula and 0.9% saline infused at a rate of 10 ml/kg for preloading the circulation. Spinal anesthesia was induced in the sitting position under strict aseptic technique with skin preparation with 0.5% chlorhexidine and methylated spirit and sterile fenestrated draping. The L3/L4 inter-space was located and the skin was infiltrated with 2 ml of 2% lidocaine. A 25 G Quincke spinal needle was inserted at the L3/L4 inter-space and after confirmation of correct placement with free flow of cerebrospinal fluid, a hyperbaric solution of 0.5% bupivacaine 15 mg (3 ml) was injected into the subarachnoid space. Immediately, the patient was re-positioned supine with the head and shoulder supported with a pillow to prevent excessive rostral spread of the anesthetic. The level of sensory block was tested using the gentle pin-prick method and recorded. Thereafter, the blood pressure was monitored every minute for 5 min and every 5 min until the end of procedure were obtained.

Immediately following the induction of spinal anesthesia, the dexamethasone only (DO) group received 8 mg dexamethasone i.v, the DM group received i.v. dexamethasone 8 mg and i.v. metoclopramide 10 mg and the metoclopramide only (MO) alone group received 10 mg i.v. metoclopramide.

Intra-operative vital signs were monitored at regular intervals (5-10 min) using the Dash 4000 G.E multi-parameter monitor as well as any incidence of nausea and vomiting. For the purpose of this study, duration of anesthesia was defined as the period between the establishment of spinal anesthesia and discharge from the recovery room. The incidence of PONV was monitored for the first 3 h from the beginning of surgery and during the stay in the recovery room (early PONV) and the next 24 h in the ward (late PONV). Duration of surgery was between 60 and 90 min Vital signs, PR, blood pressure, SpO2 were continually monitored every 10 min in the recovery room until discharge to the ward (45 ± 15 min). Vital signs monitoring was continued in the ward until the end of 1st 24 h after surgery by the ward nurses and recorded. Patients were also questioned about incidence and severity of PONV in the ward by the investigator during the post-operative visits. Incidence of PONV taken as nausea, vomiting and nausea together and vomiting in the three groups was noted and recorded. Severity of PONV was graded as 0 = No nausea or vomiting, 1 = Nausea, no vomiting, 2 = Vomiting once and 3 = Two or more episodes of vomiting. Any intra-operative nausea or vomiting was treated with a dose of i.v. metoclopramide 10 mg.

Incidence of hypotension (defined as a decrease in blood pressure of more than 20-30% below baseline values) were managed by increasing the flow rate of 0.9% saline at 7-10 ml/kg. Where this was not adequate, incremental doses of i.v ephedrine in 3 mg aliquots to a total dose of range of 15-30 mg was administered titrated to effect for each patient.

Data collection
Pre-coded and pre-tested structured-interview type questionnaires were used both pre-operatively and post-operatively to obtain relevant socio-demographic data: Age, weight, height, educational status, occupation. History of types of medication, past medical and surgical history was obtained from each patient.

Nausea and vomiting was assessed thus:

Early PONV: Any incidence of PONV 0-3 h of anesthesia and surgery. This was the period starting from the intra-operative period to the recovery and till discharge from the post anesthetic care unit.

Late PONV: Incidence of PONV 4-24 h post-operatively. Patients were observed for nausea and vomiting in the ward for the first the 24 h post-operatively by the ward nurses who were informed about the study and by the investigator.

Statistical analysis
Data collected were entered into a proforma and subjected to statistical analysis using the Statistical Package for the Social Sciences version 16.0. SPSS (Microsoft Corporation @ 2001). Two-simple independent Student’s t-test (2-tailed) and ANOVA were used to analyze continuous patient’s variables such as age, weight, duration of surgery/anesthesia. Chi-square and Fisher’s exact test were appropriated for discreet variables like symptoms of PONV. A P level <0.05 was taken as being significant.

Results
A total of 90 patients ASA I or II, representing 51.1% and 48.9% respectively were enrolled for the study, n = 30 for each of the three groups namely dexamethasone alone groups, metoclopramide alone and combined DM group [Table 1].

All patients in the three groups had comparable socio-demographic characteristics and clinical profiles except for the mean age [Table 1]. The mean age for the three groups, DM, MO, DO were 39.8 ± 6.4, 37.8 ± 7.9 and 35.2 ± 4.2 respectively. Patients in the DM group had a higher mean age than the other two groups and this is significant (P = 0.023). The body mass index for the three groups was similar (28.7 ± 5.6, 29.1 ± 4.3 and 29.7 ± 7.7 respectively).

Table 2 shows the intra-operative clinical variables of the study population. The baseline mean PR in beats/min of the three groups (the combined DM group, metoclopramide group, the dexamethasone group were 85.6 ± 13.5, 89.8 ± 12.7 and 85.5 ± 16.9 respectively (P = 0.294).
The mean SBP and diastolic blood pressure showed statistical significance ($P = 0.002$). Patients who received metoclopramide alone group had a mean higher blood pressure (140/85 ± 17/10 mmHg) than the ones in the other two groups, dexamethasone 130/78 ± 13.89/12.41 mmHg and DM 131/76 ± 12.12/9.745 mmHg.

The average total i.v. fluid given for the three groups was similar. An average of 3.2 ± 0.7 L of fluid was given to the patients in the combined DM group while 3.2 ± 0.8 L and 3.3 ± 0.7 L was given to the DM groups respectively ($P = 0.903$). The estimated blood loss (EBL) for the three groups was also not statistically significant. For the combined DM group, the average EBL was 483.3 ± 215.9 ml while for the DM groups were 506 ± 206.7 ml and 491.7 ± 218.6 ml respectively ($P = 0.912$).

The incidence of early and late PONV in the dexamethasone is as shown in Table 3. 40 had early PONV while none had late PONV. Although the incidence of early PONV in the dexamethasone alone group was higher than the other two groups, however its superior efficacy in the prevention of late PONV was clearly demonstrated by preventing late PONV ($P = 0.003$).

On the incidence of PONV among the three patient groups, DM group [Figures 1 and 2] had the least incidence of both early and late PONV, (3) 10% and (2) 6.7% respectively. Metoclopramide alone group had an incidence of (9) 29.9% for early PONV and (8) 26.6% for late PONV while the DO group had an incidence of (12) 40% for early PONV. The overall incidence of early and late PONV in this study was similar, i.e. 33.3% and 33.3% respectively. All the cases of PONV in the combined group were mild while 10% and 20% had moderate and severe PONV respectively in the metoclopramide group. The reverse was the case in the dexamethasone group as 20% had moderate and 10% had severe PONV [Table 4].

Table 5 shows the side effect profile of the study drugs. Similar number of patients in the study had mild degree of sedation (sedation score 1). However 4 patients in the MO had a sedation score of 2 compared with 1 patient in the DM group who had sedation score of 2 and none in the DO group.

Similarly, almost equal number of patients (10, 12, 12) in the three groups respectively had mild hypotension (BP <20% of baseline). 12 in both the MO and DO groups while 10 had mild hypotension in the DM group. More patients (8) in the MO group had moderate hypotension (BP <25% of baseline ($P = 0.337$). No patient in the three groups had any episode of severe hypotension to necessitate the use of a vasopressor.

### Table 1: Socio demographic profile of study groups

<table>
<thead>
<tr>
<th>Patients’ parameters</th>
<th>Dexamethasone+Metoclopramide (D-M)</th>
<th>Metoclopramide (MO)</th>
<th>Dexamethasone (DO)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.8±6.4</td>
<td>37.8±7.9</td>
<td>35.2±4.2</td>
<td>0.023</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.6±12.8</td>
<td>74.6±12.3</td>
<td>78.4±19.1</td>
<td>0.530</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.6±0.4</td>
<td>1.6±0.5</td>
<td>0.6±0.3</td>
<td>0.080</td>
</tr>
<tr>
<td>BMI = weight/(height)$^2$</td>
<td>28.7±5.6</td>
<td>29.1±4.2</td>
<td>29.7±7.8</td>
<td>0.791</td>
</tr>
<tr>
<td>ASA I/II 14/16</td>
<td>16/14</td>
<td>16/14</td>
<td>16/14</td>
<td></td>
</tr>
</tbody>
</table>

BMI = Body mass index, ASA = American society of anesthesiologists

### Table 2: Intra-operative clinical variables

<table>
<thead>
<tr>
<th>Patients’ clinical variables</th>
<th>Dexamethasone+Metoclopramide (M-D)</th>
<th>Metoclopramide (MO)</th>
<th>Dexamethasone (DO)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline vital signs</td>
<td>85.6±13.5</td>
<td>89.8±12.7</td>
<td>85.5±16.9</td>
<td>0.294</td>
</tr>
<tr>
<td>PR (b/min)</td>
<td>131.0±12.1</td>
<td>140.1±17.8</td>
<td>130.0±13.9</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>76.0±9.7</td>
<td>85.5±10.8</td>
<td>78.3±12.4</td>
<td>0.002</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>98.9±11.1</td>
<td>98.2±1.8</td>
<td>98.5±1.7</td>
<td>0.262</td>
</tr>
<tr>
<td>Level of sensory block</td>
<td>T4 0</td>
<td>16</td>
<td>06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T6 04</td>
<td>05</td>
<td>03</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>T8 11</td>
<td>05</td>
<td>07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T10 15</td>
<td>04</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Total IVF (L)</td>
<td>3.2±0.7</td>
<td>3.2±0.8</td>
<td>3.3±0.8</td>
<td>0.903</td>
</tr>
<tr>
<td>Ext. Blood Loss (ml)</td>
<td>483.3±215.9</td>
<td>506.7±206.7</td>
<td>491.7±218.6</td>
<td>0.912</td>
</tr>
</tbody>
</table>

PR = Pulse rate, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, SPO2 = Arterial saturation of oxygen
None of the patients in the MO group complained of itching. However, five patients (16.7%) in the DO group and three (10%) in the DM group had episodes of itching which did not require treatment. None of the patients in the MO and DM group had any incidence of jerking movement.

**Discussion**

The incidence of early (0-3 h) and late PONV (4-24 h) varied significantly between the three study groups. The dexamethasone alone group had the highest incidence of early PONV while the combined DM group had the least incidence of early PONV. The combined group had the least severe PONV, followed by the dexamethasone alone group while the metoclopramide alone group had the most severe.

This finding agrees with a similar study that has demonstrated the efficacy of dexamethasone in the prevention of late PONV. Dexamethasone is known to act by reducing inflammatory edema and altering central and peripheral responsiveness to pro-emetic compounds such as anesthetics and analgesics. It has been established that the effects of steroids are more pronounced in late or delayed vomiting than early vomiting. This is due to delayed onset of action and longer duration of action. This fact has been used in combination therapy in the prevention of PONV. Entezariasl et al. in their study found that the incidence of nausea with metoclopramide combined with dexamethasone was 8% versus 44% with placebo and the incidence of vomiting was 0% versus 20% with placebo. They concluded that although prophylactic injection of 10 mg metoclopramide or 8 mg dexamethasone separately

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Dexamethasone+Metoclopramide (%)</th>
<th>Metoclopramide (%)</th>
<th>Dexamethasone (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>18 (60)</td>
<td>16 (53.3)</td>
<td>20 (66.7)</td>
<td>0.222</td>
</tr>
<tr>
<td>1</td>
<td>11 (36.7)</td>
<td>10 (33.3)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>04 (13.3)</td>
<td>04 (13.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>16 (53.3)</td>
<td>10 (33.3)</td>
<td>15 (50)</td>
<td>0.337</td>
</tr>
<tr>
<td>Mild</td>
<td>10 (33.3)</td>
<td>12 (40)</td>
<td>12 (40)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>04 (13.3)</td>
<td>08 (26.7)</td>
<td>03 (10)</td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>03 (10)</td>
<td>0</td>
<td>05 (16.7)</td>
<td>0.074</td>
</tr>
<tr>
<td>No</td>
<td>27 (90)</td>
<td>30 (100)</td>
<td>25 (83.3)</td>
<td></td>
</tr>
</tbody>
</table>
can decrease the incidence of PONV, the combined use of these drugs has a more marked and significant effect. This is because while metoclopramide protects against early PONV, dexamethasone acts late for the prevention of late PONV.

Different risk factors have been found to account for the incidence of early and late PONV. Earlier studies revealed that previous history of PONV, Apfel scoring scale, parathyroid surgery and volatile anesthetics accounted more for early PONV. On the other hand, female gender, parathyroid surgery, age (childhood) and the use of opioid for post-operative analgesia were responsible for developing late PONV. As a result of this finding, different anti-emetics may be more affective for early and late PONV.

Dexamethasone had the least effect on sedation from this study. This will prove beneficial when sedation is undesirable in patients undergoing surgery under spinal anesthesia. In a report compiled by the Food and Drug Administration, out of 50,257 patients who had side effects while receiving dexamethasone, 168 (0.33%) had sedation. This was found to be duration, sex and age related. Patients on dexamethasone for 1-6 months had the highest incidence of sedation (48.8%). More males (62.4%) than females (37.6%) and the elderly (>60 years) had more incidence of sedation (48%). A single use of dexamethasone as was administered in this study would not predispose to sedation. Furthermore, the study population in this study was of the female gender aged 21-60 years.

Sign et al. in their study found that i.v dexamethasone given for prophylaxis and treatment of PONV may cause perineal pain and pruritus of variable intensity in the awake patients. They found that more females were affected than their male counterpart. They further suggested that the pain/pruritus could be reduced or abolished by diluting dexamethasone in 50 ml of fluid given over 5-10 min. Another way suggested by their study to achieve this is by giving the drug after induction of anesthesia. In our study, the incidence of pruritus in the dexamethasone alone group was higher than the other two study drugs. This could be due to the gender (female) of the study population and the attenuating effect of metoclopramide in the combined group.

Mild hypotension was seen in all the three study groups in the intra-operative period. Hypotension is a known complication of spinal anesthesia and the fact that similar trends were observed in all the three groups meant that it was not primarily due to any of the study medications. Pusch et al. demonstrated that a maximum decrease in SBP >35% during induction of anesthesia is associated with an increased incidence of PONV after gynecological surgery during general anesthesia. However, the authors did not explain whether the blood pressure decrease triggered PONV or PONV symptoms influenced hemodynamic variables. They nonetheless suggested that the initial hemodynamic instability during the induction of anesthesia may play a role in the development of PONV. The degree of hypotension observed in this study could be attributed to the spinal anesthesia given to all the patients. Furthermore, because the hypotension in this study was mild, its role in the development of PONV could be negligible.

Post-operative pain has been recognized as one of the predisposing factors to PONV alongside anesthetic technique. However, all the patient groups in the study had a similar surgical procedure under the same anesthetic technique. This served to reduce the impact of post-operative pain on the incidence of PONV. Despite this fact, i.v. administration of dexamethasone had been found to enhance the analgesic effect of intrathecal pethidine and reduced the incidence of PONV. By so doing, dexamethasone could have also contributed in reducing the impact of post-operative pain on the incidence of late PONV in these patients.

A limitation to the interpretation of our results is the non-inclusion of control group. For clinical equipoise, it was not necessary to offer a placebo when the standard of care in the center is the use of metoclopramide. Nonetheless, the demonstration of the effect of dexamethasone on late PONV underscores the strength of this study irrespective of the observable limitations.

Conclusion

Dexamethasone protects against the incidence of late PONV without any effect on early PONV. Metoclopramide on the other hand has comparable effect on both.

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