A balanced anesthesia with dexmedetomidine decreases postoperative nausea and vomiting after laparoscopic surgery

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ABSTRACT

الأهداف: تقييم تأثير إضافة عقار ديكسميدوتدين بطريقة تخدير متوازنة على الغثيان و القيء ما بعد العمليات الجراحية النسائية التنظيرية.

الطريقة: أجريت دراسة استطلاعية عشوائية في مستشفى الجامعة الأردنية – عمان – الأردن خلال الفترة ما بين ديسمبر 2008 و فبراير 2009. تم تقسيم 81 مريضة في فترة الخصوبة تتراوح أعمارهن من 48-17 عام طبقاً للجمعية الأمريكية للتخدير (ASA) ممن كان مقرر لهم عملية جراحية تنظيرية تحت التخدير العام إلى مجموعتين. تلقت مجموعة D و العدد n=42 تلقوا تسريباً وريدياً من عقار ديكسميدوتدين، بينما تلقت مجموعة (P) و العدد (n=39) محلول صوديوم كلوريد 0.9% مع التخدير العام. وقد سجلت حالات حدوث الغثيان و القيء بعد العملية مبكراً حتى 24 ساعة و الحاجة لإعطاء أدوية مضادة للقيء.

النتائج: لقد انخفضت نسبة حدوث القيء والغثيان بعد العملية بشكل ملحوظ في المجموعة D و العدد 13 من أصل 42 مريضة بنسبة 31% مقارنة بالمجموعة P و العدد 23 من أصل 39 بنسبة 59%، إلا أن نسبة حدوث الغثيان واستخدام أدوية مضادة للقيء قد اختلفت بشكل ملحوظ. وقد لوحظ انخفاض ملحوظ في الاستخدام الكلي لسيفلورين و الفنتانيل في المجموعة D أيضا.

خاتمة: إن إضافة ديكسميدوتدين لأدوية التخدير الأخرى يؤدي إلى تخدير أكثر توازنا وإلى انخفاض ملحوظ في نسبة حدوث الغثيان والقيء بعد العمليات الجراحية التنظيرية النسائية.

Objectives: To evaluate the effect of adding dexmedetomidine to a balanced anesthetic technique on postoperative nausea and vomiting after laparoscopic gynecological surgeries.

Methods: A prospective double-blind randomized study was designed at Jordan University Hospital, Amman, Jordan between December 2008 and February 2009. Eighty-one female patients in their child-bearing age (17-48 years); American Society of Anesthesiologists (ASA) clinical status I, who were scheduled for elective diagnostic laparoscopic surgeries under general anesthesia were divided into 2 groups. Group D (n=42) received dexmedetomidine infusion, while group P (n=39) received 0.9% sodium chloride infusion along with the balanced anesthesia. The incidence of early (up to 24 hours) postoperative nausea, vomiting, nausea and vomiting, and the need for postoperative rescue anti-emetic medications were recorded.

Results: The total incidence of postoperative nausea and vomiting decreased significantly in group D; 13 out of 42 patients (31%), compared to group P; 23 out of 39 patients (59%), vomiting alone did not significantly change, the incidence of postoperative nausea, and the use of rescue anti-emetic medications were significantly different. A significant drop in overall consumption of fentanyl and sevoflurane was also noted in group D.

Conclusion: Combining dexmedetomidine to other anesthetic agents, results in more balanced anesthesia and a significant drop in the incidence of postoperative nausea and vomiting after laparoscopic gynecological surgeries.

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Balanced anesthesia is a technique of general anesthesia based on the concept of administering a mixture of small amounts of several anesthetic agents. It summates the advantages, but not the disadvantages of the individual components of the anesthetic mixture. The combination of a volatile anesthetic with a short-acting opioid, balanced anesthesia represents a big step towards an ideal anesthetic.[1] Nausea and vomiting are of the unpleasant, distressing, and exhausting postoperative disadvantages and common in patients undergoing laparoscopic surgeries that are difficult to prevent even with balanced anesthesia techniques. The incidence of post-gynecological laparoscopic surgeries, nausea, and vomiting ranges from 60-75%.[2] Dexmedetomidine is a highly selective alpha-2-adrenoreceptor agonist that is approved as an intravenous sedative and a co-analgesic drug. Although its main use was in the intensive care units,[3] recently the drug is gaining more popularity for a more painful surgical procedure.[4,5] Gubert et al[5] demonstrated that continuous intravenous dexmedetomidine administration during abdominal surgeries, provided an effective postoperative analgesia, and reduced the postoperative morphine requirements without increasing the side effects. Nausea and vomiting were of the studied side effects, which were reduced. Our aim in this study is to test the effect of adding dexmedetomidine to a balanced anesthetic technique, on postoperative nausea and vomiting (PONV) after laparoscopic gynecological surgeries.

Methods. The study protocol was approved by the Scientific Committee of the Faculty of Medicine, University of Jordan and the Ethical Committee of Jordan University Hospital, Amman, Jordan. Informed written consent were obtained from each patient. Eighty-four female patients, American Society of Anesthesiologists (ASA) physical status I undergoing general anesthesia for elective diagnostic laparoscopic gynecological procedure at the Jordan University Hospital, between December 2008 and February 2009 were enrolled in a randomized, double-blinded controlled study. Patients with a history of PONV, motion sickness, major systemic disease (morbid obesity, diabetes mellitus, or hypertension) and those who received anti-emetic or cortisone within 48 hours before surgery were excluded from the study. Pregnant, breast-feeding ladies, and patients with gastrointestinal, hepatic, renal, mental or psychiatric illnesses were also excluded. The anesthetic technique was standardized. All patients received diazepam 5 mg 2 hours preoperatively. Induction of anesthesia was achieved with intravenous propofol 2 mg/kg and fentanyl 1 μg/kg. Tracheal intubation was facilitated with 0.6 mg/kg of intravenous rocuronium. The anesthesia was maintained with 0.5-2% (end tidal concentration) sevoflurane in 50% air and 50% oxygen along with dexmedetomidine continuous infusion in Group D, or with a continuous infusion of 0.9% sodium chloride (NaCl) in Group P (placebo) instead. The dexmedetomidine in Group D was supplied in 2 ml ampoules of 100 μg/ml concentrations (Precidex®) (Hospira, Inc. Lake Forest, Illinois, USA), which was diluted with NaCl 0.9% to yield a total volume of 100 ml and a total concentration of 2 μg/ml. No bolus dose of dexmedetomidine was given, and the infusion was started after anesthesia induction at 0.5 μg/kg/hour. Another 100 ml total volume of NaCl, 0.9% was infused to Group P at the same starting rate. The patient randomization was achieved by using the sealed envelope technique and was prepared by an independent person not involved in the study.

Routine monitoring consisted of electrocardiography, peripheral oxygen saturation (SpO_2), non-invasive blood pressure, and capnography. All patients were also monitored by bispectral index monitor (BIS) view (Aspect Medical System Inc, Norwood, MA, USA) to assess depth of anesthesia. Bispectral index monitor readings between 50 and 60 were considered to be associated with adequate depth of anesthesia. Inadequate depth of anesthesia was treated incrementally raising the sevoflurane end-tidal concentration by 0.5% until the BIS reading drop back <60. On the other hand, BIS readings <50 were managed by dropping the sevoflurane end-tidal concentration by 0.5%. The aim also was to maintain arterial blood pressure within 80-120 mm Hg of the baseline values. Mean arterial pressure increases up to ≥20% above the baseline, with adequate BIS readings (50-60), was treated by administering a 1 μg/kg intravenous bolus of fentanyl, while an arterial blood pressure drop of >20% below the baseline was treated with reduction of the end-tidal sevoflurane concentration by 0.5% if the BIS readings were >50, or a 3 mg of ephedrine if the BIS readings were between 50 and 60. The mean sevoflurane end-tidal concentration and the total fentanyl dosage administrations in both groups were calculated and compared.

The dexmedetomidine or NaCl infusions were terminated at the end of surgery, and the patients were extubated when they were adherent to the extubation criteria, and after receiving the neuromuscular blocked reversal, which consisted of a combination of 40 μg/kg neostigmine and 15 μg/kg atropine. A total volume of one liter of Ringers lactate was infused to all patients intraoperatively, and no anti-emetic medications were given to any patient. All patients were transferred to the recovery room, where they were monitored, received oxygen supplementation with a simple face mask, and were kept for 2 hours. The pain intensity was assessed using an 11-point visual analogue scale (VAS), on

which 0 indicated no pain and 10 indicated the worst pain imaginable. Pain scale above 3; according to the VAS, was treated initially with 1 gm of intravenous paracetamol (Perfalgan®, Bristol-Myers Squibb Pharmaceuticals Ltd, Middlesex, UK), and if the VAS persisted above 3 after 30 minutes, a bolus dose of 2 mg of morphine was administered and the patients were excluded from the study. All patients continued on postoperative intravenous paracetamol (Perfalgan®) in the postoperative period every 6 hours as the protocol of postoperative analgesia at our institute. Nausea, vomiting and the need for the rescue anti-emetic drugs were assessed before discharge to the ward and after 24 hour on the ward (or until the patient was discharged; if she was discharged before completing the 24 hours) by a trained anesthesia resident not involved in the study, and blinded to the patient's group. Nausea was defined as a feeling of the urge to vomit. Vomiting was defined as expulsion of the stomach contents through the mouth or retching. The medication charts were reviewed after interviewing the patients for the rescue anti-emetic medication needed until the moment of discharge or until 24 hours postoperatively.

Several studies have found the average post-laparoscopic surgery, nausea, and vomiting incidence under general anesthesia is in the range of 60-70% (namely, without any intervention or anti-emetic). A sample size of 39 patients in each group was determined to be adequate or demonstrating a power to detect 50% reduction in the incidence of PONV from 65-32.5%, with an alpha error of 0.05, and a beta error of 0.85.

Statistical analysis was carried out using Stat graphics Centurion XV version 15.1.02 (Statpoint Inc, USA). Values were expressed as either means and standard deviations or number of observations and percentages. Each of the following variables (age, weight, duration of anesthesia, duration of surgery, and duration of gas insufflation) was studied and compared between the 2 groups using the t-test to compare means. As for variables: nausea alone, vomiting alone, and combined nausea and vomiting; the chi square test was used to compare between the 2 groups. The 95% confidence interval are given for the main outcomes. A p value of 0.05 or less was considered significant.

Results. Eighty-four female patients completed the study; 3 patients received morphine in the recovery room for postoperative analgesia, and were excluded from the study protocol. Data from the remaining 81 (42 patients in group D, and 39 patient in group P) were analyzed. There were no significant statistical differences regarding patient age, weight or ASA clinical status (**Table 1**) between the 2 groups. The 2 groups also had a non-significant difference in the duration of anesthesia

Table 1 - Patient characteristics.

Patient characteristics	Group P (placebo)	Group D (Dexmedetomidine)	*P*-value
Age	32.03 ± 1.2	31.02 ± 1.1	Not significant
Weight	72.4 ± 2.5	66.9 ± 2.7	Not significant
ASA	I	I	Not significant
Duration of anesthesia (min)	43.9 ± 2.3	50.7 ± 3.4	Not significant
Duration of surgery (min)	28.4 ± 2.2	30.5 ± 3.1	Not significant
Duration of gas insufflation (min)	21.6 ± 1.7	19.55 ± 1.9	Not significant
Fentanyl administration (μg)	145.86 ± 57.1	112.8 ± 51.3	0.007
End-tidal sevoflurane (%)	1.27 ± 0.6	1.05 ± 0.41	0.05

Data presented as mean ± standard deviation or median, ASA - American Society of Anesthesiologists

Table 2 - Incidence of postoperative nausea and vomiting, and the rescue antiemetic drugs during 24 hours postoperatively.

Incidence	Group P (placebo)		Group D (Dexmedetomidine)		*P*-value
Nausea	15	(38.5)	8	(19.0)	0.05
Vomiting	8	(20.5)	5	(11.9)	NS
Nausea and vomiting	23	(59.0)	13	(31.0)	0.04
Rescue antiemetic	8	(20.5)	2	(4.8)	0.04

Data are expressed as number of observations and percentages.

or surgery and gas insufflations. The overall incidence of nausea and vomiting along with the need for rescue anti-emetic medications during the entire 24 hours study period are shown in **Table 2**.

Postoperative nausea occurred significantly less in group D than in group P, and although the difference in the postoperative vomiting was not significant in the 2 groups.

The postoperative need for rescue anti-emetic medications were significantly less in Group D. Results also show (**Table 1**) that there was a significant difference in the overall fentanyl and end-tidal sevoflurane administration between the 2 groups. Patients in group D required less total fentanyl than those in group P.

Discussion. The etiology of PONV after laparoscopic surgery is not fully understood, and still a major drawback of this type of surgery. Multiple factors are associated with an increased incidence of PONV, including patient, anesthetic, and surgical factors.[6] Albeit, many anti-emetic drugs are currently prescribed, such as serotonin subtype 3 antagonists,[7,8] and other low-cost anti-emetic medications such as anticholinergics, antihistaminics, and dopamine receptor antagonists,[9] the incidence is still relatively high and no universal prophylaxis can completely prevent these side effects.[10] Although anesthesia techniques, such as total intravenous anesthesia when combined with multimodal anti-emetic management was superior to the use of balanced anesthesia technique in preventing PONV when combined with the same multimodal anti-emetic medications,[11] however, it seems to be the fact that sufficient evidence regarding this issue has not been accumulated yet.[12] Currently, the anesthesiologist has the possibility to choose his preferred anesthetic technique based on the patient's individual needs, the surgery performed, and the side effects each technique may have, it is clear that the balanced anesthesia technique using the relatively new anesthetic agents such as sevoflurane is more common in our daily practice. In this study, we wanted to apply the regimen that is used more routinely in our country. Our primary endpoint in this study was namely, to evaluate the effect of adding dexmedetomidine to a balanced anesthesia technique on the incidence of PONV after diagnostic gynecological laparoscopic surgery. Gurbt et al's[5] found that the intraoperative infusion of dexmedetomidine significantly reduced the PONV as well as the perioperative analgesic requirements in patients undergoing total abdominal hysterectomy surgery, and receiving postoperative morphine infusion via patient controlled analgesia (PCA). No explanations of this finding were discussed. The findings in our study were similar to Gurbet et al[5] study, and showed that the intravenous infusion of dexmedetomidine significantly reduced the PONV, as well as the requirements of postoperative rescue anti-emetic medications, in a surgery, which even carries a higher incidence of PONV, which is laparoscopic surgery. Three possible explanations for this finding are possible. The first of them is the significant drop in the requirement of each component of the balanced anesthetic mixture used. The findings in this study demonstrated that the sevoflurane end-tidal concentration and the fentanyl administration dropped significantly in the group of patients who received dexmedetomidine as an adjuvant. This is in accordance with a previous study by Yildiz et al[13] who found that in elective minor surgeries, a preoperative administration of a single dose of dexmedetomidine reduced the requirements of fentanyl and sevoflurane, both of which emetogenecity.[14] Secondly, dexmedetomidine is an alpha-2 adrenoreceptor agonist. This drug has an action on the locus coeruleus, which is a major noradrenergic cell group located in thepontine brain stem, and appears to have regulatory effects on extracellular dopamine.[15] The alpha-2 adrenoreceptor agonist of dexmeditomodine, which resembles that of clonidine, decreases the noradrenergic activity as a result of binding to alpha-2 presynaptic inhibitory adrenoreceptors in the locus coeruleus, an inhibition that possibly results in an anti-emetic effect. Thirdly, it is well known that the gastrointestinal distention stimulates vagal visceral afferents, this in turn activates the vomiting center and induces nausea and vomiting. By increasing sympathetic outflow and decreasing parasympathetic outflow from the central nervous system, dexmedetomidine may exert its effect by increasing the gastric emptying and the gastrointestinal motility, which possibly has an important effect in decreasing nausea and vomiting. Similar anti-emetic results were also observed when clonidine was used. In Rosa-e-Silva et al's[16] non-placebo controlled study, they reported a substantial decrease in nausea and vomiting in 6 diabetic patients with gastroparesis treated with oral clonidine. Park et al[17] also showed less frequent nausea and vomiting, and a fewer requirements of anti-emetics in patients undergoing major knee surgery, who received oral clonidine 1.5 hours before surgery and at 12 and 24 hours after the initial dose.

A limitation of this study was possibly not identifying all the predictive factors of PONV in the 2 groups. Although, predictive factors were not measured, we believe that both groups basically had the same risk according to Apfel score,[18] since we excluded patients with previous history of PONV or motion sickness. All our patients were non-smokers, all of them were females, and we excluded those who needed postoperative opioids.

In conclusion, the use of dexmedetomidine as part of a balanced anesthesia technique reduces the incidence of post-laparoscopic surgery nausea and vomiting, either directly, or by decreasing the overall consumption of anesthetic drugs, which are known for their emetogenic effect. Controlled studies comparing the uses of anti-emetic medication versus optimized balanced anesthesia techniques using different doses of dexmedetomidine are needed.

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