Dexmedetomidine as a substitute for remifentanil in ambulatory gynecologic laparoscopic surgery

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ABSTRACT

الأهداف: مقارنة عقار ديكسميديتوميدين مع عقار ريميفنتانيل بناء على الجراحة النسائية الإسعافية باستعمال منظار البطن، مع الأخذ بعين الاعتبار تأثيراتها على الإدراك، ووقت الخروج من المستشفى، الغثيان–التقيؤ والحاجة إلى مسكنات بعد العملية الجراحية.

الطريقة: تم تقسيم 60 مريضة تبلغ أعمارهن مابين 20–40 عاماً، واللواتي يخضعن لعملية جراحية نسائية عشوائية إلى مجموعتين. وقد أجريت هذه الدراسة في جامعة هاسيتيب بكلية الطب – غرف العمليات – أنقرة – تركيا، خلال عام 2004م، كدراسة تطلعية وعشوائية ومجهولة الطرفين. تلقت مجموعة ريميفنتانيل (مجموعة R) ومجموعة ديكسميديتوميدين (مجموعة D) جرعة مقدارها 1µg/kg خلال 10 دقائق، تلتها جرعة مقدارها 0.2µg/kg/minute خلال دقيقة قبل العملية الجراحية من تسريب عقار ريميفنتانيل بمقدار 0.4µg/kg/hour من عقار ديكسميديتوميدين. تم تسجيل قياسات حركات الدم، وقت الفطام، الإدراك للأشخاص والمكان، الوقت، الغثيان والتقيؤ، الألم، احتياج المسكنات في المنزل، الرضى مع التخدير.

النتائج: كانت البيانات السكانية، حركيات الدم، نقاط الألم ووقت الخروج من المستشفى متشابهة في لكلتا المجموعتين. كان وقت نزع (الفطام) الأنبوب، إدراك الأشخاص من حول المريض، المكان، والوقت أقصر لدى (المجموعة R). كان الغثيان والتقيؤ بعد العملية الجراحية، والاحتياج المسكنات في المنزل أقل في مجموعة ديكسميديتوميدين (مجموعة D).

خاتمة: تثبت هذه الدراسة أن تسريب عقار ديكسميديتوميدين يسبب شفاء بطيء نسبياً مع انخفاض في الغثيان والتقيؤ بعد العملية الجراحة، والاحتياجات للمسكن، وحركيات الدم المشابهة، مقارنتاً مع مجموعة ريميفنتانيل (مجموعة R)، في عمليات تنظير البطن الإسعافية. وربما قد يكون بديلاً ريميفنتانيل في التخدير ألإسعافي.

Objectives: To compare dexmedetomidine with remifentanil in desflurane based ambulatory gynecologic laparoscopic surgery, in respect to its effects on orientation, discharge time, nausea-vomiting, and postoperative analgesic need.

Methods: Sixty 20-40 year old ASA I-II patients undergoing gynecologic laparoscopic surgery were randomized into 2 groups. This study was performed in the operating theaters of the Hacettepe University Faculty of Medicine, Hacettepe, Turkey in 2004 as a prospective, randomized, and double blinded study. The remifentanil group (group R), and dexmedetomidine group (group D) received a bolus of 1µg/kg over 10 minutes, followed by 0.2µg/kg/minute peroperative infusion of remifentanil, and 0.4 µg/kg/hour of dexmedetomidine. Hemodynamic parameters, time to extubation, and to orientation to person, place, and date, postoperative nausea, vomiting, pain, analgesic requirement at home, and satisfaction with anesthesia were recorded.

Results: Demographic, hemodynamic data, postoperative pain scores, and discharge time were similar in both groups. Time to extubation, to orientation to person, to place and date were shorter in group R. Postoperative nausea, vomiting, and analgesic requirements at home were less in group D.

Conclusion: This study demonstrated that dexmedetomidine infusion causes a relatively slow recovery with reduced postoperative nausea, vomiting, and analgesic requirements, and similar hemodynamics compared to remifentanil in ambulatory laparoscopic surgeries. It may be an alternative to remifentanil in ambulatory anesthesia.

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Day-case surgery has developed in the last decade due to improvements in both surgical and anesthesia techniques. Anesthetics, neuromuscular blockers, analgesics, and sympatholytics with a rapid onset and short effect have been introduced, and monitoring techniques have improved. Undesired effects observed with recovery in ambulatory anesthesia have decreased.[1] Recovery and discharge time is long in case of deep anesthesia, which is used to decrease metabolic response to surgical stress.[2] Titration of the dose of analgesic and hypnotic components has a great advantage in decreasing recovery time.[3] Many opioids, sedative hypnotics, analgesics, sympatholytics, and other drugs were used to suppress autonomic responses and provide faster recovery, but the most suitable technique to be used in day case anesthesia is still controversial.[4,5] Remifentanil is an opioid widely used for ambulatory anesthesia. Since it has a rapid onset and short duration of action, it facilitates the control of the depth of anesthesia.[3] However, nausea, vomiting, and respiratory depression in the postoperative period may limit its use.[4] Dexmedetomidine, an α-2 agonist, is a new drug used for sedation, amnesia, and analgesia either in perioperative settings or in the intensive care units.[6] It is easy to titrate its effect and both drugs are used by continuous infusion.[7] Although dexmedetomidine may be an anesthetic in its own right, there have been no studies on the use of dexmedetomidine as a sole substitute for remifentanil in ambulatory anesthesia based on desflurane.[6,8] The magnitude of the analgesic effect of dexmedetomidine is smaller than that observed with remifentanil, which is consistent with the clinical notion that the analgesic property of an α-2 agonists is not as effective as that of opioids. However, it exhibits a qualitatively different analgesic effect as shown by a decrease in the pain response slope.[9,10] In light of these findings, we aimed to investigate dexmedetomidine due to its analgesic property as a substitute for remifentanil in anesthesia maintenance. Its effects on hemodynamic parameters, time to eye opening, postoperative orientation, nausea-vomiting, analgesic need, and satisfaction in ambulatory gynecologic laparoscopic surgery were studied.

Methods. After ethics committee approval and informed consent, 60, 20-40-year old ASA I-II patients, scheduled to undergo elective ambulatory gynecologic laparoscopic surgery were included in this prospective, randomized, and double-blinded study. Exclusion criteria were ASA class ≥III, emergency operations, chronic use of opioid analgesics, alcohol, drug addiction, or smoking, allergy to any of the study drugs, a body mass index (BMI) of ≥30 kg/m^2. One of the anesthetists participating into the study randomized patients to one of 2 study groups, using a computer-generated random number table. Study drugs (dexmedetomidine and remifentanil) were prepared by a nurse without any mark on the syringe. The same nurse who knew the study protocol adjusted the perfusor dose, and the perfusor's syringe and screen were covered to enable double blindness throughout the operation, and no change of the dose was allowed. The anesthetist blinded to the drug continued with the anesthesia process and recorded the study parameters. On arrival to the operating theater, heart rate (HR), noninvasive blood pressure, and pulse oximeter monitoring were applied, and the hemodynamic parameters were evaluated throughout the operation. A S/5 M-BIS module (Datex-Ohmeda, Madison, WI) was used to measure bispectral index value (BIS). Patients were not premedicated. In the operating room, a 20-gauge venous cannula was inserted, and 0.9% saline solution was administered. Anesthesia was induced with 2 mg/kg propofol. Vecuronium bromide (0.1 mg/kg) was used to facilitate tracheal intubation. The patients in group D received 1 μg/kg IV dexmedetomidine bolus dose in 10 minutes, and an infusion of 0.4 μg/kg/hr. The patients in group R received 1 μg/kg IV remifentanil in 10 minutes, and an infusion of 0.2 μg/kg/min. Bolus doses were administered by the same nurse. The remifentanil dose (0.2 μg/kg/minute) was selected based on previous studies to produce adequate analgesia.[11] Study drug infusion was started after the anesthesia induction. Anesthesia was maintained with mean end tidal 6% desflurane in 50% O_2-50% air mixture in both groups. The BIS value was kept around 45-55 by adjusting the desflurane concentration up and down, and if this is not enough, by adding propofol (20 mg). No intraoperative narcotics were used in both groups. The hemodynamic parameters were recorded before induction, after endotracheal intubation, at skin incision, at the placement of trochars, and after extubation. Residual neuromuscular block was antagonized with 0.01 mg/kg atropine and 0.05 mg/kg neostigmine. The infused drug and desflurane were discontinued after the completion of surgical suturing. The patient was transferred from the recovery room when the fast tracking criteria score was greater than 12 (*__Appendix 1__).[12] Time to eye opening on verbal command ('open your eyes'), to extubation, to orientation to person, to orientation to place and date, and to discharge were assessed. Postoperative emesis and pain were evaluated with a 100 mm visual analogue scale

*The full text including Appendix is available in PDF format on Saudi Medical Journal website (www.smj.org.sa)

(0; no emesis, 100; worst possible emesis). If VAS_{emesis} was greater than 40 mm, 4 mg of IV ondansetron was administered, 15 minutes later if VAS_{emesis} persisted to be over 40 mm, a further dose of 4 mg of IV ondansetron was given, and the same dose was repeated after 15 minutes if still necessary. If VAS_{pain} were higher than 40 mm, 30-40 μg/kg of IV morphine sulphate was administered and was repeated with 15 minute intervals if required. The patients were discharged home with Aldrete scores greater than 9.[12] Oral paracetamol was prescribed to the patients and the dose of paracetamol required, and time of first analgesia at home was questioned by phone call at the 24th postoperative hour. Postoperative pain was evaluated with a 4-point scale [none (0), mild (1), moderate (2), severe (3)]. Satisfaction with anesthesia was questioned using a 3 point scale [unsatisfactory (1), satisfying (2), and excellent (3)].

Statistical analysis. Data were analyzed using SPSS (Statistical Package for Social Sciences) 10.0 for Windows software package. Kolmogorov-Smirnov test was used for analyzing distribution of data. Data with a normal distribution were compared with t-test, and data without normal distribution was compared with Mann Whitney U test. Hemodynamic data were analyzed with repeated measures analysis of variance. A *p*-value less than 0.05 was considered to be statistically significant. Sample size was decided according to previous studies. Retrograde power analysis was performed when considering 'extubation time', it was 93.9% with an a error of 5%. When time to orientation, to person was considered, the power of the study was 83.7%.

Results. There were no differences in respect to demographical parameters (age, weight, height, BMI, gender, and ASA status) (**Table 1**). Duration of anesthesia and operation were similar in both groups (**Table 2**). Intraoperative HR and systolic blood pressure values of the groups were not statistically different throughout the operation. No patient had intraoperative or postoperative bradycardia (HR <45 beats/minute), or hypotension in either groups. Time to eye opening was similar in both groups (p=0.06). Time to extubation, to orientation to person, and to orientation to place and date was shorter in the remifentanil group compared with dexmedetomidine group (**Table 3**). There were no differences in respect to discharge time between the groups (p=0.06). Incidence of emesis and vomiting was higher in the remifentanil group compared with the dexmedetomidine group. The patients in the remifentanil group required more antiemetic at

Table 1 - Demographic data (mean±SD).

Demographic data	Group Remifentanil (n=30)	Group Dexmedetomidine (n=30)
Age (years)	34 ± 8	34 ± 7
Weight (kg)	64 ± 14	66 ± 12
Height (cm)	156 ± 25	163 ± 6
ASA I/II	21 / 9	22 / 8

Table 2 - Intraoperative parameters (mean±SD).

Parameters	Group Remifentanil (n=30)	Group Dexmedetomidine (n=30)
Anesthesia duration (min.)	45 ± 23	44 ± 23
Operation duration (min.)	38 ± 22	35 ± 22
BIS minimum	39 ± 6	36 ± 6
BIS maximum	57 ± 7	51 ± 6
Total intravenous fluids (ml)	604 ± 187	525 ± 150

BIS - bispectral index value

Table 3 - Recovery data (mean±SD).

Recovery Data	Group Remifentanil (n=30)	Group Dexmedetomidine (n=30)
Time to eye opening (minutes)	3.5 ± 1.1	4.1 ± 1.4
Extubation time (minutes)	6.1 ± 1.6*	7.3 ± 1.3
Orientation to person (minutes)	9.1 ± 2.3*	10.5 ± 1.8
Orientation to place and date (minutes)	16.1 ± 6.3*	21.2 ± 11.7
Discharge time (minutes)	200.3 ± 39.5	224.5 ± 49.2

*p<0.05 considered statistically significant

Table 4 - Pain and postoperative side effects.

Postoperative side effects	Group Remifentanil (n=30)	Group Dexmedetomidine (n=30)
Pain (VAS, cm)	3.1 ± 2.9	2.8 ± 3.5
Emesis (VAS, cm)	1.7 ± 2.7*	0.2 ± 0.5
Vomiting (no. of patients)	8*	0
Rescue antiemetics (no. of patients)	6*	0
Rescue analgesics (no. of patients)	11	9
Time to first analgesic at home (hours)	4.3 ± 3.6	4.6 ± 3.2
Analgesics required at home (no. of doses required)		
0	2	10*
1	10	13
2	15	6*
3	2	1
4	1	0
Satisfaction with recovery		
Unsatisfactory (1)	0	0
Satisfying (2)	27	24
Excellent (3)	3	6
Satisfaction with anesthesia		
Unsatisfactory (1)	0	0
Satisfying (2)	25	27
Excellent (3)	5	3

VAS - Visual analogue scale, *p<0.05 considered statistically significant

the hospital, and more analgesics at home (p=0.04). Postoperative pain scores were similar in both groups (p=0.07). Eleven patients in the remifentanil group, and 9 patients in the dexmedetomidine group received rescue analgesic (morphine) once in the post anesthesia care unit (PACU) (p=0.07). Patient satisfaction with anesthesia was found to be satisfying in both groups, and it was not statistically different within groups (**Table 4**).

Discussion. In this study, we demonstrated that intraoperative use of dexmedetomidine caused relatively longer time of orientation but less nausea, vomiting, and requirement for analgesics at home compared to remifentanil. The main goal of ambulatory anesthesia is to minimize discharge time by decreasing recovery time and complications, and thereby reducing costs.[4] The hemodynamic variables during the surgical procedure were within the clinically satisfactory limits in both dexmedetomidine and remifentanil groups. Several studies have shown that HR decreases after dexmedetomidine injection, which may or may not be associated with a transient increase in mean blood pressure.[13-16] The decrease in HR is dose-dependent and is probably due to baroreflex activation, and slow infusion of dexmedetomidine tends to minimize this. In the present study, no patient had bradycardia or hypotension. Remifentanil was proven to decrease recovery time when used with isoflurane in arthroscopic surgery.[17] Nonetheless, α_2 adrenoreceptor agonists may prolong post anesthesia orientation time when associated with other anesthetics.[13,18] Bulow et al,[19] found that dexmedetomidine revealed a more prolonged recovery time for some parameters such as orientation and extubation times. Their study, in which they investigated the opioid sparing effect of dexmedetomidine compared to remifentanil, did not find any differences in PACU discharge times between the groups. In our study, extubation, and orientation times were prolonged in the dexmedetomidine group when compared with the remifentanil group. However, there was no difference in discharge time from the hospital between the groups. Remifentanil was shown to enable faster extubation but more postoperative pain with similar postoperative nausea and vomiting ratios compared to fentanyl in pediatric outpatient tonsillectomy and adenoidectomies.[20] Similarly, in our study, remifentanil group's postoperative pain scores and analgesic needs were higher. This may be in part due to the hyperalgesic effects of remifentanil, experimental evidence suggests that short-term infusion of potent opioids may lead to hyperalgesia on withdrawal of the opioid.[21,22] Due to its short duration of action, a greater requirement for postoperative analgesics should be expected.[23] In a study, remifentanil was used in laparoscopies, and additional intraoperative long-acting opioids were suggested.[24] The administration of α_2-agonists decreases the perioperative opioid requirement, which would enable adequate analgesia with fewer opioid-related side effects (for example, respiratory depression, and nausea).[25,26] Gurbet et al[26] demonstrated that a perioperative dexmedetomidine infusion of 0.5 mg/kg/minute reduced perioperative analgesic consumption in abdominal surgeries. Also, Arain and Ebert[25] reported that patients who had received dexmedetomidine during surgery had significantly smaller need for morphine sulphate throughout the recovery period, which was similar to our study results. In the study of Beers et al,[27] the VAS_{emesis} scores and antiemetic requirements were higher with remifentanil when compared to fentanyl with similar VAS_{pain} scores, vomiting ratios, analgesic requirements in the recovery room, and patient satisfaction. A recent study investigating the effects of dexmedetomidine on postoperative shivering, nausea-vomiting, and analgesic need show that dexmedetomidine reduced postoperative shivering incidence, antiemetic, and analgesic need.[28] Similarly, postoperative antiemetic need in the dexmedetomidine group was lower in our study. Remifentanil infusion combined with sevoflurane or desflurane increases postoperative emesis without increasing complications.[29] The BIS was developed from a database of EEG segments, which correlated well with the hypnotic and sedation level in volunteers given increasing and decreasing doses of several anesthetics.[30] No awareness has been described with a BIS less than 50.[31] The BIS values measured after the induction were similar in both groups.

The limitation of the study is that awareness and recall of intraoperative events were not investigated in our study. Another point to focus is that the cost of both drug infusions was not calculated, which is an important end point of ambulatory anesthesia, this may be subject to further studies.

In conclusion, dexmedetomidine was shown to provide adequate perioperative hemodynamic stability while decreasing postoperative nausea-vomiting and the need for antiemetics and analgesics, but a relatively long recovery time without prolonging discharge time, it may be an alternative to remifentanil in ambulatory anesthesia.

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Appendix 1 - The frequency distribution of the causes of burns in patients.

Level of consciousness	Score
Awake and oriented	2
Arousable with minimal stimulation	1
Responsive only to tactile stimulation	0
Physical activity	
Able to move all extremities on command	2
Some weakness in movement of extremities	1
Unable to voluntarily move extremities	0
Hemodynamic stability	
Blood pressure <15% of baseline MAP value	2
Blood pressure 15%–30% of baseline MAP value	1
Blood pressure >30% below baseline MAP value	0
Respiratory stability	
Able to breathe deeply	2
Tachypnea with good cough	1
Dyspneic with weak cough	0
Oxygen saturation status	
Maintains value >90% on room air	2
Requires supplemental oxygen (nasal prongs)	1
Saturation <90% with supplemental oxygen	0
Postoperative pain assessment	
None or mild discomfort	2
Moderate to severe pain controlled with IV analgesic	1
Persistent severe pain	0
Postoperative emetic symptoms	
None or mild nausea with no active vomiting	2
Transient vomiting or retching	1
Persistent moderate to severe nausea and vomiting	0
Total score	**14**