

Comparison of the effects of dexmedetomidine-remifentanyl and propofol-remifentanyl combinations on postoperative cognitive functions in patients undergoing hysteroscopy: A randomized prospective study

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Abstract

Aim: In the present study, we aimed to compare Dexmedetomidine-Remifentanyl and Propofol-Remifentanyl combinations in terms of postoperative cognitive functions in hysteroscopy attempts.

Material and Methods: A total of 70 ASA I-II patients who were aged between 18 and 65 years were included in the study following the ethics committee approval. The patients were randomized into two groups (n=35), and standard routine monitoring were applied to them. The sedation depth was evaluated with Ramsey Sedation Score (RSS) before and after the sedation; and cognitive functions of the groups were evaluated with the Minimal Mental State Test (MMST).

Propofol 1 mg/kg bolus 25-100 µg/kg/min infusion was administered to Group PR, and Dexmedetomidine 1 µg/kg bolus 0.4-0.7 µg/kg/h infusion dose was administered to Group DR. Remifentanyl 0.25 µg/kg bolus 0.04 µg/kg/min infusion was administered to the groups, and the groups were followed to ensure RSS≥4.

Result: In cognitive functions, it was observed that there was significant regression in Group PR in postoperative period compared to the preoperative period (p<0.05). The hemodynamic parameters were lower in Group DR than in Group PR at 5th, 10th and 15th minutes following the hysteroscopy (p<0.05). The Modified Aldrete Score in Group DR were high, and pain scores were lower (p<0.05). Satisfaction with the surgeon, patient and anesthetist scores were higher in Group DR. No respiratory depression was observed (p<0.05).

Conclusion: We believe that administering Dexmedetomidine-Remifentanyl combination in sedation in hysteroscopy ensures better postoperative cognitive function, recovery conditions, analgesia, and patient and surgeon satisfaction compared to the Propofol-Remifentanyl combination.

Keywords: Hysteroscopy; sedation; dexmedetomidine; propofol; remifentanyl; cognitive functions.

INTRODUCTION

Hysteroscopy is the standard diagnostic and treatment modality for the diagnosis and treatment of endometrial pathologies and can be performed with local, regional, general anesthesia, or sedoanalgesia in the lithotomy position (1).

Local and regional anesthesia applications cause anxiety in patients due to patient positioning and the application area of these anesthetic techniques (2). If the patients are awake during hysteroscopy interventions, their sudden unexpected leg movements caused by

visual and auditory stimuli can impair the surgical vision and sterilization, thereby leading to tissue damage or perforation. Sedoanalgesia, as it leads to relatively better preservation of patient cooperation and physiological reflexes compared to general anesthesia, does not only increase the efficiency of the operation room and patient comfort, satisfaction, and safety but also provides faster recovery (3). Meaningfully, sedoanalgesia has emerged as an effective anesthetic technique preferred to general anesthesia in daily anesthetic practice (2).

Although hysteroscopy seems to be a minimally invasive procedure, it involves painful procedures such as cervical

Received: 08.04.2019 Accepted: 09.05.2019 Available online: 12.06.2019

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dilatation, polypectomy, and myomectomy. Today, hysteroscopy is used in obstetrics and gynecology practice predominantly for the evaluation of infertile women as well as functional and anatomical evaluation of uterine anomalies and for the diagnosis and treatment of abnormal uterine bleeding. Providing adequate anesthesia and analgesia during hysteroscopy is a crucial issue for anesthesiologists. A good anesthetic application can provide well-balanced hemodynamic stability by adequately suppressing the sympathetic response. As a result, since the patient and the physician are both comfortable throughout the sedation period during hysteroscopy, conscious sedation protocols increase the success rate of the procedure. Propofol is frequently used for conscious sedation in hysteroscopy; however, the use of dexmedetomidine, a new sedative agent, has not been sufficiently investigated (4).

Dexmedetomidine has recently emerged as an alternative to propofol and other sedative agents in conscious sedation applications. Dexmedetomidine is a fat-soluble imidazole derivative and a potent and highly selective α_2 -adrenoceptor agonist and provides sedation analgesia in which the patients can be awakened and can be cooperated with, without leading to respiratory depression. Moreover, as it does not cause respiratory depression during sedation and analgesia, dexmedetomidine is accepted as an appropriate drug for the interventions performed under local and regional anesthesia (5).

In this study, we aimed to compare the dexmedetomidine-remifentanyl and propofol-remifentanyl combinations used for conscious sedation during hysteroscopy in terms of postoperative cognitive functions, hemodynamic parameters, sedation, analgesia, recovery, and surgeon and patient satisfaction.


MATERIAL and METHODS

After obtaining an approval from the local ethics committee (Date: November 21, 2017; No: 08), the patients planned for elective hysteroscopy were included in the study. Each patient underwent preoperative evaluation at the Anesthesiology and Reanimation polyclinic at least one day prior to the study. A total of 82 patients planned for hysteroscopy were evaluated. Of these, 12 patients were excluded from the study since they were aged below 18 years or over 65 years, failed to provide a written or oral consent, had serious cardiac, renal, hepatic or respiratory diseases and allergic responses to the agents used in the treatment, or psychomotor dysfunction. As a result, a total of 70 patients aged 18-65 years with an ASA score of I-II were included in the study and were randomized into two groups with 35 patients each. Informed written and oral consents were obtained from each patient or from their parents/guardians. Both the patients and the physicians evaluating the patients were blinded to the study groups. Demographic characteristics of the patients were recorded. Prior to the procedure, the patients were placed on the operation table and standard routine monitoring including Electrocardiography (ECG) monitoring, peripheral oxygen

saturation (SpO_2), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) was performed for each patient in the supine position.

The sedation depth before and after sedation was evaluated with The Ramsey Sedation Score (RSS) and the cognitive functions of the groups were evaluated with the Mini-Mental State Examination (MMSE) (Figure 1).

STANDARDIZED MINI-MENTAL STATE EXAMINATION (SMMSE)

QUESTION	TIME ALLOWED	SCORE
1 a. What year is this?	30 seconds	/1
b. Which season is this?	30 seconds	/1
c. What month is this?	30 seconds	/1
d. What is today's date?	30 seconds	/1
e. What day of the week is this?	30 seconds	/1
2 a. What country are we in?	30 seconds	/1
b. What province are we in?	30 seconds	/1
c. What city/town are we in?	30 seconds	/1
d. IN HOME - What is the street address of this house? IN FACILITY - What is the name of this building?	30 seconds	/1
e. IN HOME - What room are we in? IN FACILITY - What floor are we on?	30 seconds	/1
3 SAY: I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes. Say the following words slowly at 1-second intervals - ball/ car/ man	30 seconds	/3
4 Spell the word WORLD. Now spell it backwards.	30 seconds	/5
5 Now what were the three objects I asked you to remember?	30 seconds	/3
6 SHOW wristwatch. ASK: What is this called?	30 seconds	/1
7 SHOW pencil. ASK: What is this called?	30 seconds	/1
8 SAY: I would like you to repeat this phrase after me: No ifs, ands or buts.	30 seconds	/1
9 SAY: Read the words on the page and then do what it says. Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	30 seconds	/1
10 HAND the person a pencil and paper. SAY: Write any complete sentence on that piece of paper. (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/1
11 PLACE design, eraser and pencil in front of the person. SAY: Copy this design please.	1 minute	/1
		
Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.		
12 ASK the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. SAY: Take this paper in your right/left hand (whichever is non-dominant), fold the paper in half once with both hands and put the paper down on the floor. Score 1 point for each instruction executed correctly.	30 seconds	/1
Takes paper correctly in hand		/1
Folds it in half		/1
Puts it on the floor		/1
TOTAL TEST SCORE		/30

Note: This tool is provided for use in British Columbia with permission by Dr. William Molloy. This questionnaire should not be further modified or reproduced without the written consent of Dr. D. William Molloy.

Provided by the Alzheimer's Drug Therapy Initiative for physician use.

Figure 1. Standardized Mini Mental State Examination

Prior to the surgery, vascular access was established using a 20-gauge cannula inserted into the right or left antecubital vein, followed by intravenous administration of 1000 ml saline solution (0.9% NaCl). Each patient was pre-medicated with midazolam 0.025 mg kg^{-1} (Demizolam®, Dem, Turkey).

The patients were randomized by sealed tender and divided into two groups as Propofol- Remifentanyl (PR) (n=35) and Dexmedetomidine-Remifentanyl (DR) group (n=35). In the PR group, propofol (1% Propofol® Fresenius Kabi, Turkey) $1 \mu\text{g/kg}$ was administered, followed by the infusion of 25-100 $\mu\text{g/kg/min}$. In the DR group, dexmedetomidine (Precedex® Abbott, Istanbul, Turkey) $1 \mu\text{g/kg/10 min}$ bolus was administered, followed by the infusion of 0.4 to 0.7 $\mu\text{g/kg/h}$. Subsequently, in both groups, remifentanyl (Ultiva®, GlaxoSmithKline, Belgium) $0.25 \mu\text{g/kg}$ bolus was administered, followed by the infusion of 0.04 $\mu\text{g/kg/min}$. Each patient was given O_2 with a nasal cannula at a flow rate of 4-6 L min^{-1} throughout the procedure. Care was taken to maintain the RSS value at ≥ 4 . When the RSS value

was <4, an additional dose of 0.5 mg/kg of propofol or 0.2 µg/kg of dexmedetomidine was administered.

The vital parameters of the patients recorded at the operation table before drug administration were accepted as the baseline values and the subsequent values were recorded every 5 min before and after the administration of loading dose. The recovery score was measured with the Modified Aldrete Scoring (MAS) and the time until MAS 10 was achieved was recorded for each patient (Table 1). Pain assessment was performed using the Wong-Baker FACES Pain Rating Scale (WBS) (Figure 2). The anesthesiologist, surgeon, and patient satisfaction levels were assessed using a 10-point scale (0: Not satisfied at all, 10: Fully satisfied) (6,7).

Statistical Analysis

In the power analysis, the sample size was determined to be n=31 according to equation n by accepting the primary variable of interest as MMSE and assuming the average score of the test as 20 and the standard deviation as (π) 4, based on an effect size (d) of 1.4, an α score of 0.05, and a power value of 80%. To ensure the reliability of the analysis, 35 patients were included in each group.

maximum values for continuous variables and as frequencies and percentages for categorical variables. Repeated Measures analysis of variance (ANOVA) was used to compare the group means in terms of continuous variables. Following the Repeated Measures ANOVA, Duncan's test was performed to determine different groups. The Chi-square test was used to determine the relationship between the groups and the categorical variables. A p value of <0.05 was considered significant.

RESULTS

No significant difference was found between the two groups in terms of age, height, body weight, ASA risk classification and the duration of hysteroscopy procedure (p>0.05) (Table 2). No change was found between the pre- and post-operative MMSE scores in the DR group, whereas a significant decrease was observed in postoperative scores in the PR group compared to preoperative scores (p<0.05) (Table 3).

In terms of SpO₂ values, the value at min 5 after induction was significantly higher in the DR group compared to the PR group (p<0.05) (Figure 3).

Table 1. Modified aldrete scores		
Modified Aldrete Scoring		
Activity	Four limbs (four limbs are moving)	2
	Two limbs (two limbs are moving)	1
Respiration	No movement	0
	Dyspnea, surface respiration	1
	Apnea and congestion	0
Circulation	Blood pressure is different from preoperative values by ± 20 mmHg	2
	Blood pressure is different from preoperative values by ± 20-50 mmHg	1
	Difference more than 50 mmHg	0
Consciousness	Full awake, oriented	2
	Responding to calls	1
Color	No response	0
	Pink	2
	Paleness and darkness	1
	Cyanotic	0

Table 2. Demographic data of cases			
	Group DR (n=35) (Mean±SD)	Group PR (n=35) (Mean±SD)	p
Height (cm)	161.26±6.21	161.74±5.05	0.73
Weight (kg)	71.63±14.35	74.89±11.02	0.29
Age (years)	40.00±10.84	36.23±8.85	0.11
ASA	1.57±0.52	1.48±0.52	0.47
Hysteroscopy time (min)	12.71±4.43	13.71±5.05	0.38

Table 3. Comparison of Preop and Postop Minimal Mental State Tests of Groups			
	Group DR (n=35) (Mean±SD)	Group PR (n=35) (Mean±SD)	p
Preop-MMDT	26.86±4.13	25.34±4.30	0.13
Postop-MMDT	25.89±3.01	21.74±5.54	0.01



Figure 2. Wong-Baker FACES Pain Rating Scale (WBS)

Data were analyzed using SPSS for Windows version 21.0 (Armonk, NY: IBM Corp.). Descriptive were expressed as mean, standard deviation (SD), and minimum and

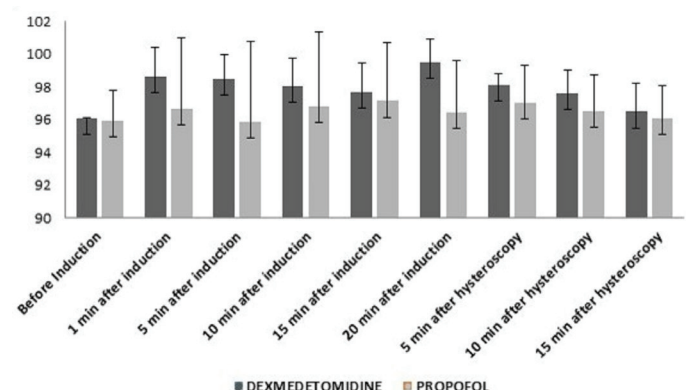


Figure 3. Average peripheral O₂ saturation values by groups,

In the DR group, the HR, BPD, DBP and MBP values at min 5, 10, and 15 after hysteroscopy were lower than those in the PR group ($p < 0.05$). Figure 3 presents the MBP values. In terms of MBP, the values at min 5, 10, and 15 after hysteroscopy were significantly lower in the DR group compared to the PR group ($p < 0.05$) (Figure 4).

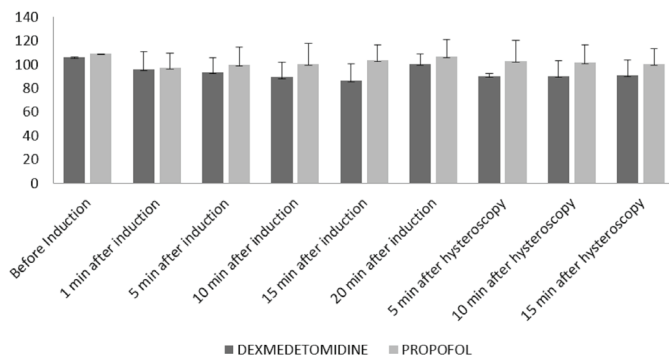


Figure 4. Mean arterial pressure (MAP) values of the groups

No significant difference was found between the groups in terms of RSS values ($p > 0.05$) (Table 4). In the DR group, the MAS scores were significantly higher and the WBS scores were significantly lower than those in the PR group ($p < 0.05$) (Table 4). The surgeon, patient, and anesthesiologist satisfaction values were found to be significantly higher in the DR group than in the PR group ($p < 0.05$) (Table 4).

Table 4. Comparison of RSS, FPS and MAS and satisfaction state of groups

	Group DR (n=35) (Mean±SD)	Group PR (n=35) (Mean ± SD)	p
Ramsey sedation scale	4.23±0.43	4.57±0.61	0.08
Face Pain Scale	0.14±0.36	2.71±1.64	0.01
Modified Aldrete scoring (time elapsed till 10)	9.60±0.69	8.63±0.69	0.01
Surgeon satisfaction (0: not at all satisfied, 10: Fully satisfied)	9.80±0.47	7.09±1.88	0.01
Patient Satisfaction (0: not at all satisfied, 10: Fully satisfied)	9.86±0.38	7.34±1.81	0.01
Anesthesiologist satisfaction (0: not at all satisfied, 10: Fully satisfied)	9.74±0.51	6.94±1.94	0.01

No desaturation and respiratory depression were observed in the DR group and no bradycardia was observed in the PR group. However, bradycardia occurred in 3 patients in the DR group and desaturation occurred in 13 patients and respiratory depression occurred in 8 patients in the PR group.

DISCUSSION

In this study, we found that the administration of dexmedetomidine 1 µg/kg/10 min bolus followed by the infusion of 0.4-0.7 µg/kg/h resulted in lower effects on

the cognitive functions and provided a shorter recovery period. We also found that the dexmedetomidine-remifentanyl (DR) group had more favorable outcomes in terms of surgeon and patient satisfaction compared to the propofol-remifentanyl (PR) group.

In our study, as there were no inactive metabolites in propofol and dexmedetomidine at the doses administered and as the drugs caused no re-sedation in any patient, the patients remained conscious enough to communicate, adequate sedation that sustained the surgical comfort of the patients was achieved, and shorter recovery was achieved.

Pain in hysteroscopy is a condition that makes the patients extremely uncomfortable and complicates the access to the uterine cavity (6). Moreover, this pain has also been reported to cause vasovagal syncope in 0.21-30% of the patients (7). Therefore, pain control is of paramount importance in hysteroscopy as it is a short procedure. In our patients, we used remifentanyl in our patients for pain control.

Hysteroscopy is a short endoscopic procedure that can be applied by local, regional, general anesthesia, sedoanalgesia or Monitored Anesthesia Care (MAC) in the lithotomy position. However, when performed with local anesthesia, the patients may feel anxious and may not be able to tolerate it due to patient positioning (8). For these reasons, we did not prefer local or regional anesthesia in our patients.

Different doses of dexmedetomidine have been proposed in the studies reporting on sedation for local and regional anesthesia. Arain et al. (9) administered an initial dexmedetomidine dose of 1 µg/kg⁻¹/10 min for intraoperative sedation and subsequently administered an infusion dose of 0.4 µg kg⁻¹h⁻¹ for anesthetic maintenance. Mc Cutcheon et al. (10) administered an initial dexmedetomidine dose of 0.5 µg/kg⁻¹/5 min in patients undergoing carotid endarterectomy under regional anesthesia and subsequently administered an infusion dose of 0.2 µg/ kg⁻¹/h⁻¹ for anesthetic maintenance. Balci et al. (11) administered an initial dexmedetomidine dose of 1 µg/ kg⁻¹/10 min in patients undergoing hand surgery under local anesthesia and subsequently administered an infusion dose of 0.6 µg/ kg⁻¹/h⁻¹ for anesthetic maintenance. In our study, dexmedetomidine 1 µg/kg/10 min bolus was administered in the DR group, followed by an infusion dose of 0.4-0.7 µg/kg/h. The doses administered in our study did not only produce good sedation but also led to no negative effects on the hemodynamic and respiratory parameters and the recovery status of the patients.

Kaygusuz et al. (12) compared the use of dexmedetomidine and propofol infusions in patients scheduled for extracorporeal shock wave (ESWL) and also evaluated the requirement for additional fentanyl and noted that the requirement for fentanyl was relatively lower in the dexmedetomidine group. In our study, we found that remifentanyl requirement was lower in our patients due to

the analgesic effect of dexmedetomidine.

Ramsay et al. (13) used dexmedetomidine to perform conscious sedation in a morbid obese patient with sleep apnea syndrome who was planned for tracheal resection. The authors reported that the patient breathed spontaneously on room air and no desaturation occurred. Scher and Gitlin administered sedation in a patient who had a history of difficult intubation and was scheduled for fiber optic intubation and preferred dexmedetomidine for sedation due to its antisialagogue effect and as it does not cause respiratory depression. The authors reported that good sedation was achieved and the patient tolerated the procedure comfortably, with no need for an extra modification in the oxygen saturation and ventilation and no need for airway manipulation (14). Similarly, in our study, no desaturation and respiratory depression occurred in the DR group, whereas respiratory depression was significantly higher in the PR group.

In our study, we used a test called Mini-Mental State Examination (MMSE), which was developed by Folstein et al. (15) in 1975. MMSE is a standard test used for evaluating the cognitive functions of the patients such as recalling, attention, and calculation. MMSE is widely used all over the world and is not a definitive diagnostic test but is used by clinicians for screening and monitoring the treatment process to measure the degree of cognitive destruction of the patients. The validity and reliability of MMSE in the Turkish population was performed by Istanbul University Cerrahpaşa Medical School Department of Psychiatry (16).

In our study, a significant difference was observed in the DR group compared to the PR group with regard to early recovery. When the MAS scores of 9 and 10 were achieved, the MMSE was administered in both groups and it was found that the dexmedetomidine group had significantly faster recovery of cognitive functions compared to the propofol group. However, although the recovery of cognitive functions has been mostly evaluated after general anesthesia in the literature, we evaluated it before and after sedation in daily anesthesia.

The neuroprotective effect of dexmedetomidine proven by experimental studies, its action on a single receptor type, and the absence of its anticholinergic adverse effects (17, 18) may have been the reasons for its minimal effect on postoperative cognitive functions.

CONCLUSION

The DR group had higher MAS scores but lower WBS scores compared to the PR group, which can be attributed to the fact that dexmedetomidine reduces pain sensation and increases its analgesic effect in increased plasma concentrations. There is strong evidence suggesting that the stimulation of α -2 receptors produces analgesia at the level of the spinal cord. Dexmedetomidine provides an analgesic effect by binding to the α -2 adrenoreceptors in the spinal cord. We found that the dexmedetomidine-remifentanil combination provided more favorable

outcomes in terms of the recovery of postoperative cognitive functions, recovery parameters, analgesia, and patient and surgeon satisfaction compared to the propofol-remifentanil combination, although the dexmedetomidine-remifentanil combination caused a decrease in blood pressure at various time periods.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports

Ethical approval: Van Yuzuncu Yil University Ethics Committee of Clinical Research (Date: November 21, 2017; No: 08)

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