Original Article

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Prospective Study of Dexmedetomidine-Propofol versus Dexmedetomidine-Ketamine for Sedation and Anesthesia in Hysteroscopic Examination and Procedures

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Abstract

Context: Dexmedetomidine a wonderful drug with vital organ protective properties. When combined with other intravenous anaesthetic agents useful in surgical procedure without intubation. Less research work was done on this subject. *Objectives:* The aim of this study was to compare the effects of dexmedetomidine + propofol with dexmedetomidine + Ketamine combinations for sedation and anesthesia in patients undergoing hysteroscopy and procedures regarding hemodynamic changes, drug requirements and the recovery criteria and post-operative complications. *Patient and Methods:* Sixty patients aged between 20–50 years, ASA I& II scheduled for hysteroscopy were enrolled in this study. Patients were randomly allocated into two equal groups: dexmedetomidine+propofol (DP) group and dexmedetomidine+ Ketamine (DK) group. Every patient received a loading dose of intravenous (IV) dexmedetomidine 1 μg/kg over 10 min and Propofol 1mg/kg (DP) or ketamine1mg/kg (DK) group and then maintained by a 0.5 μg/kg/h of dexmedetomidine. Mean arterial pressures (MAP) and heart rates (HR), drug consumption, recovery time, visual analog scale (VAS) and postoperative complications were recorded. *Results:* The intra and post procedural HR and MAP showed statistically significant differences between the both groups throughout the procedure with lower values in DP group ($p < 0.01$). After procedure recovery time was significantly shorter in DK group (12.2 ± 8.2 min) compared with (15.7±9.6 min) DP group ($p = 0.012$). VAS was comparable in the two groups. Drug consumption similar in both the groups. *Conclusion:* Dexmedetomidine +propofol combination as total intravenous anaesthesia showed better intra-and post-procedural hemodynamic stability with fewer complications.

Keywords: Hysteroscopy; Dexmedetomidine; Propofol; Ketamine.

Introduction

Hysteroscopy is a procedure that allows gynecologist to look inside the uterus in order to diagnose and treat intrauterine causes [1,2]. Hysteroscopy performed to correct the uterine conditions like adhesions, Septum, Polyps, fibroids, abnormal bleeding and dilatation of ostium and 1st portion of fallopian tube (infertility) [3].

Pain and surgery causes sympathetic stimulation and raise in blood pressure and heart rate. To suppress this effect many drugs are being used. Present anaesthesia practice is to prevent sympathetic stimulation and provide haemodynamic stability perioperatively.

Dexmedetomidine offers a unique ability by providing both sedation and analgesia without sympathetic stimulation, less respiratory depression with neuro, cardio and renoprotection [4].

Subjects and Methods

The study was conducted in the department of anesthesiology and critical care after approval from the Institutional ethical committee. A written informed consent was obtained from each the participant in this study. Sixty patients of female sex aged 20–

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50 years scheduled for diagnostic and therapeutic hysteroscopy were enrolled in this study which was conducted from March 2015 to November 2016. All patients were of American Society of Anesthesiologist (ASA) class I, II. Exclusion criteria included patients with allergy to study drugs, cardiovascular disease (hypertension, congestive heart failure, and coronary artery disease), cerebrovascular insufficiency, increased intracranial tension, personality disorders or suspected pregnancy in addition to those receiving antipsychotic or sedative medication.

Patients were randomly allocated into one of two parallel treatment groups with allocation ratio of 1:1 and thirty in each group.

Dexmedetomidine/propofol (DP) group received IV dexmedetomidine (1 μg/kg loading), followed by (0.5 μg/kg/h infusion) and IV propofol loading dose 1mg /kg followed by infusion (0.5 mg/kg/h).

Dexmedetomidine /Ketamine group (DK) group received IV dexmedetomidine (1μg/kg loading), followed by (0.5 μg/kg/h infusion) and IV ketamine (1 mg/kg loading, followed by 0.5 mg/kg/h infusion).

Pre-procedural evaluation included history taking, physical examination and laboratory investigations (complete blood picture, liver and kidney function tests, and coagulation profile) and ECG. All patients were explained about the 10 cm visual analogue scale score (VAS) identifying 0 as no pain and 10 as the worst imaginable pain.

Before giving anesthesia the study drugs (dexmedetomidine, propofol or ketamine) were prepared in identical 50 ml infusion syringes as follows: Dexmedetomidine infusion syringe contained 100 μg dexmedetomidine diluted by normal saline to have 50 ml filled syringe (2μg/ml).The propofol infusion syringe: A 50 ml syringe contained 2 mg/ml propofol or 2mg/ml Ketamine infusion diluted with normal saline to have 50 ml filled syringe (2 mg/ml).

Anesthetic procedure: On arrival to the operating room standard monitoring were applied (ECG, automated non-invasive blood pressure monitoring and pulse oximetry) with recording of base line HR, MAP, and oxygen saturation, then a 18 gauge iv cannula was inserted on the dorsum of the hand and lactated ringer solution was infused (6–8 ml/kg/h). Every patients received a loading dose of intravenous (IV) dexmedetomidine 1 μg/kg over 10 min and Propofol 1mg/kg(DP) or ketamine1mg/kg (DK) group over 2 min. Group DP patients maintained throughout the procedure by a rate of 0.5 μg/kg/h of dexmedetomidine and 0.5mg/kg/h of propofol. Group DK patients maintained throughout the procedure by a rate of 0.5 mg/kg/h of dexmedetomidine and 0.5mg/kg/h of ketamine.

Whenever patient moved extra dose of propofol or ketamine was given. Drug infusion rate increased or decreased on occurrence of hypotension or respiratory depression (a decrease <20% of baseline value). Whenever there was airway obstruction head tilt and chin lift procedure was done to prevent obstructive apnea might be a problem in predisposed deeply sedated patients. Patients oxygenated by face mask at a rate of 6 liters/min and whenever insufficient respiratory effort observed ventilated with open circuit.

All operations were performed in the lithotomy position. At the end of the procedure all infusion drugs discontinued and patients were transferred to recovery room.

The primary outcome was: assessment of heart rate and mean arterial blood pressure changes during the procedure at 5 minutes interval during the procedure and for 15 and 30 minutes at post-procedure. Secondary outcomes were as follows: total drug consumption by both groups was recorded at the end of the procedure along with recovery time, level of postoperative pain assessed by visual analogue scale, and incidence of side effects (nausea and vomiting, psychomotor and respiratory complications).

The recorded data: Mean arterial pressure (MAP) and heart rate (HR) were recorded before administration of dexmedetomidine and propofol or ketamine loading (baseline), and continued every 5 min after beginning of loading doses and throughout the course of the procedure. Any hemodynamic complications were recorded which included hypotension (a decrease >20% of baseline value) or bradycardia (HR < 50 beat/min) and they were treated according to the cause. In hypotension infusion rate of drugs decreased, IV fluids rapidly infused and IV ephedrine 3–6 mg incremental doses repeated after 5 min if no improvement. If bradycardia occurred the gynecologist was asked to stop stimulation, and atropine 0.01 mg/kg was given. Hypertension or tachycardia (an increase >20% of baseline values) also managed by giving 0.5 mg/kg IV dexmedetomidine to increase depth of anesthesia.

MAP and HR were also recorded at 15 min and 30 min postoperatively. Drug consumption was calculated and recorded at the end of the procedure. Recovery time (time of spontaneous eye opening) was recorded.

After the procedure, patients were assessed every 15 min for 30 min regarding pain which was assessed by VAS, if VAS > 3 pain was treated by 10–15 mg/kg paracetamol IV infusion. Postoperative nausea and vomiting (PONV) managed by giving IV 4 mg ondansetron. Any respiratory complications as labored breathing, respiratory depression (RR < 10 bpm), or oxygen desaturation ($SpaO_2$ < 92%) were recorded. Oxygen mask was applied to improve oxygen saturation in all patients.

Statistical Analysis

Data were analyzed using Microsoft excel, Social science statistics calculator(SSSC) and Comparison of repeated measures was done using ANOVA test for repeated measures. A *p*-value <0.05 was considered significant.

Results

This comparative randomized study was between two groups; group-DP and group-DK with 30 patients in each group. Both groups had no statistical significant differences in demographic data (age and weight), ASA grading and duration of the procedure, also, there were no statistical significant differences between both groups as regard baseline of hemodynamic parameters (HR and MAP) (Table 1).

The intra-procedural heart rates lower significantly in DP group. From 5 min HR slightly decreased in DP group and there after increased during procedure till end of the procedure, while it increased significantly in DK group and ($p < 0.01$) from 5 min to till the end of the procedure. This value is statistically significant between both groups throughout the procedure (at 5 min, 10 min, 15 min, 20 min, 25 min); *p*-value was <0.01 at all measured time, while at post-op 15 at min and 30 min also *P* value was <0.05, denoting statistical significant difference between both groups;. HR values were lower in dexmedetomidine+propofol (DP) group as shown in (Table 2).

The intra-procedural MAP decreased significantly in DP group at 5 min and slightly increased during procedure till end of the procedure, while it was increased significantly in DK group from 5 min to till the end of the procedure. The MAP had a high statistical significant difference between both groups; *p*-value was <0.05 at (5-min, 10-min, 15-min, 25-min), while at post-op 15 min and 30 min also *P* value was <0.05, denoting statistical significant difference between both groups; MAP values were lower in dexmedetomidine–propofol group (Table 3).

Table 1: Demographic and clinical characteristics and duration of the procedure in the two studied groups.

S. No	Particulars	DP(n=30)	DK(n=30)	p-value
1	Age (years)	31.2±8.06	30.1±7.2	0.75
2	Weight (kg)	55.8±4.26	54.6±4.86	0.56
3	Duration of Operation (Minutes)	25.4±5.38	24.6±5.68	0.75
4	Heart rate(Base line)	83.7±5.73	81.9±5.69	0.49
5	Mean blood pressure (Base line)	91.4±2.63	90.9±2.33	0.66

*Data are mean ± SD, or numbers. *P* value >0.05 was considered statistically not significant. *P* value <0.05 was considered statistically significant. Group DP: dexmedetomidine / propofol group, Group DK: ketamine / propofol group.

Table 2: HR values were lower in dexmedetomidine–propofol / ketamine groups

S. No	Particulars	DP(n=30)	DK(n=30)	p-value
1	Heart rate(Base line)	83.7±5.73	81.9±5.69	0.49
2	After study drugs 5 min	80.4±2.79	85.6±4.38	0.005
3	10 min	85±3.29	90.1±5.32	0.004
4	15 min	87.2±3.71	91±3.39	0.028
5	20 min	88.1±4.04	93.3±4.06	0.012
6	25 min	87.7±3.59	95±4.57	0.001
7	Post –op after15 min	88.2±4.47	93.5±4.19	0.014
8	30min	86.2±3.82	92.2±3.46	0.002

*Mean intra-procedural HR changes in the two studied groups statistically significant with *P* - value< 0.01

Atropine required in two cases and ephedrine in one case of DP group for management of bradycardia or hypotension and no requirement in DK group.

The total 30 minutes dose of Dexmedetomidine, propofol or / and ketamine were comparable in the two groups (100.4±18.3µg) in DP group versus (101.2±14.93 µg) in DK group ($p = 0.796$) and propofol / ketamine doses (97.3±13.02and 95.7±14.74) with p=0.379. (Table 4) Post procedural recovery time (time from end of the procedure to spontaneous eye opening) was significantly shorter in DK group (12.2 ± 8.2 min) compared with (15.7 ± 9.6 min) in DP group ($p = 0.012$) which is statistically significant. Respiratory depression (Spo_2 <92%) occurred in 2cases in DP group and one case DK group (Table 4).

Table 3: MAP in both the groups

S. No	Particulars	DP(n=30)	DK(n=30)	P-value
1	Mean blood pressure (Base line)	91.4±2.63	90.9±2.33	0.66
2	After study drugs 5 min	88.7±2.06	93.1±2.08	0.0002
3	10 min	89.9±2.11	97.2±2.97	0.001
4	15 min	87.1±4.53	92.7±4.27	0.0107
5	20 min	85.3±3.09	93.2±5.39	0.0008
6	25 min	87.8±4.64	93.1±4.58	0.019
7	Post –op period after 15 min	83.9±2.77	92.3±5.69	0.0005
8	30 min	89±2.54	88.8±2.25	0.854

*Figure 3. Mean intra-procedural MAP changes in the two studied groups - $^{*}P < 0.01$, Significant.

Table 4: Total dose of dexmedetomidine, propofol and ketamine, recovery time in the two studied groups.

S. No	Drug	DP(n=30)	DK(n=30)	p-value
1	Dexmedetomidine- µg	100.4±18.3	101.2±14.93	0.796
2	Propofol or Ketamine-mg	97.3±13.02	95.7±14.74	0.379
3	recovery time	15.7±9.6 min	12.2 ± 8.2 min	0.012
4	Respiratory depression	2(6.67%)	1(3.33%)	

*P value >0.05 considered statistically not significant. P value <0.05 was considered statistically significant

Table 5: Post-procedural VAS score, PNOV and complications in DP and DK groups

S. No	Particulars	DP(n=30)	DK(n=30)
1	VAS 1-2	27(90%)	28 (93.33%)
2	VAS 3-5	3(10%)	2(6.67%)
3	PNOV	1(3.33%)	3(10%)
4	Hallucinations	0-Nil	4(13.33%)
5	Shivering	2(6.67%)	0 -Nil

*Post-op VAS, shivering scores more in DP group, PNOV & hallucinations more in DK group.

Post-procedural no pain as assessed by VAS was comparable in the two groups as 27 patients in DP group and (28 patients) patients in DK group had VAS 1–2 and only 3 patients in DP group two in DK group had VAS of (3–5) (Table 5).

PONV occurred in about 3.33% of patients in DP group, while it was more 10% in DK group. This was managed by giving 4 mg IV ondansetron. Post-operative cognitive disorders (in the form of hallucination, agitation and excitation) nil in DP group and 13.33% in DK group showed a high statistical significant difference between both groups. Shivering occurred 6.67% in DP group and nil DK group (Table 5).

Discussion

This randomized comparative study was performed to compare the effects of dexmedetomidine / propofol or ketamine combinations in patients undergoing hysteroscopy operations regarding hemodynamic effects, intra-procedural drug requirements as well as the recovery criteria and side effects.

Dexmedetomidine is a selective α_2 agonist with 8 times more affinity for α_2 adrenergic receptors compared to clonidine and possesses all the properties of α_2 agonist without respiratory depression [5,6]. Intravenous use of dexmedetomidine

in the perioperative period had been found to decrease serum catecholamine levels by 90% [7], provide sedation without respiratory depression [4] and decrease post-operative analgesic requirements [8].

Perioperative innovative applications using dexmedetomidine include administration as a total intravenous anesthetic, no suppression of respiratory drive with stable vitals [4].

In co-administration of dexmedetomidine with other anesthetic agents, sedatives, hypnotics, or opioids is likely to cause additive effects and attenuates but not completely abolishes stress-induced sympatho-adrenal responses protecting the patients from noxious sympathetic stimulation and hemodynamic changes and that is one of the main anesthetic goals [10,11,12].

Propofol is a non barbiturate sedative hypnotic; it has a favorable pharmacokinetic profile as the lipid solubility confers a quick onset and short recovery time. It has also an anti-emetic, anticonvulsant, antipruritic and amnestic effects [13].

Ketamine is a phencyclidine derivative, provides excellent amnesia and analgesia, and preserves muscle tone with maintaining airway reflexes and spontaneous respiration. Despite its obvious advantages over other agents, cause frightening emergent reactions; sympathomimetic effects, vomiting and excessive salivation even when administered in sedating doses [14].

We hypothesized that the combination of dexmedetomidine with either propofol or ketamine will improve the analgesic and anesthetic effects of these drugs at lower doses and less side effects. This will help in providing adequate anesthesia and analgesia in hysteroscopy procedures without intubation.

HR and MAP values were lower in dexmedetomidine–propofol group throughout the procedure, while in dexmedetomidine- ketamine group mean arterial pressure was elevated above the base line. This was due to ketamine effect owing to increased systemic vascular resistance. In both the groups haemodynamic stability maintained throughout the operations including maintenance of respiration and saturations.

Kang and his colleagues [15] supported the hemodynamic stability of dexmedetomidine. Mester R, Easley B, et al [16], reported that dexmedetomidine with ketamine/propofol combination reduced need for airway intervention throughout the procedure. The recovery time was shorter and hemodynamic stability is good.

Canpolat DG, Esmaoglu A, et al [17]; reported that adding dexmedetomidine to the ketamine or propofol combination decreased movement during the procedures. No significant differences in blood pressure, or respiration rates were found between the two groups.

Koruk S, Mizrak A, et al. [18] reported that neither respiratory depression nor severe hypotension (i.e., >20% change over baseline or requiring intervention) was observed in any patient. Patients developed agitation in the ketamine group.

Bajwa SJ, Gupta et al [19]. reported that the α_2-receptor agonists are known to prevent shivering to a moderate extent without any associated respiratory depression as with other anti-shivering drugs like meperidine. Dexmedetomidine reduces shivering by lowering vasoconstriction and shivering thresholds.

The results of this study also indicate that Dexmedetomidine–propofol combination provided more hemodynamic stability than DK group (Table 2, 3). Total drugs consumption by the end of the procedure in the current study was almost similar in both the groups. Post-procedural recovery time of the current study was significantly longer in dexmedetomidine–propofol group than dexmedetomidine- ketamine group (Table 4). PNOV was in 1 person (3.33%) in DP and more in ketamine group 3 (10%) (Table 5). No postoperative cognitive dysfunction in DP group when compared with DK group 4 (13.33%) persons. Post-procedural HR and MAP changes in the current study showed high statistical significant difference between both groups throughout procedural period; with HR and MAP values were lower in dexmedetomidine–propofol group. Shivering was present in DP and not in DK group. VAS scores were at level 1-2 almost equal in two groups, but at 3-5 more in DP 3 (10%) group and 6.67% in DK group (Table 5).

The current study has some potential limitations as the small sample size, not monitored intraoperative depth of anesthesia as BIS monitor was unavailable.

Dexmedetomidine–propofol/ketamine combination as TIVA technique requires further studies to be adequately evaluated with recommendation to include larger number and different types of patients; as elderly and critically ill patients.

Conclusion

Dexmedetomidine–propofol combination as TIVA

during hysteroscopy showed better intra and post-procedural hemodynamic stability, less PONV, less postoperative cognitive dysfunctions when compared with dexmedetomidine- ketamine combination.

Conflict of Interest

No conflict of interest to declare.

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