Original Research Article

Evaluation of the merits of two drugs-dexmedetomidine and ketamine for day care hysteroscopic procedures

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ABSTRACT

Background: The aim was to compare the hemodynamic changes intra-operatively and to ascertain the superior efficacy of the study drugs Dexmedetomidine, a highly selective alpha-2-adrenocceptor agonist having sympatholytic, dose dependent sedation, analgesic properties, amnestic effect without respiratory depression and Ketamine, a n-methyl-d-aspartate receptor antagonist, a dissociative sedative hypnotic with potent analgesic properties and marked sympathomimetic effects, have been taken for day care (ambulatory) hysteroscopic procedures. The objectives are to evaluate the requirement of rescue sedative and/or analgesic during the procedure and any complication of the drugs per-operatively.

Methods: About 25 patients in each group in the range of age 20 to 55 years, weight 40-60 kg, height 145-155 cm, ASA I and II were injected with dexmedetomidine (D) 100 µg IV or Ketamine (K) 75 mg IV both over 10 mins at the onset of the procedure. Maintenance of anaesthesia had been done on mask ventilation with 30% oxygen and 70% nitrous oxide.

Results: The demographic data was statistically insignificant. The haemodynamics were stable in the group D, not in group K, ‘p’ value <0.0001. The request for rescue sedation propofol and rescue analgesic fentanyl and the number of top up doses were higher in the group K, ‘p’ value <0.01, statistically highly significant. Group K had suffered more per-operative complications.

Conclusions: Dexmedetomidine for day care hysteroscopic procedures can be the anaesthetic drug of choice.

Keywords: Dexmedetomidine, Ketamine, Hysteroscopic procedures

INTRODUCTION

Escalating health care costs and recent advances in the techniques of anesthesia in terms of quality as well as safety ,improved monitoring devices to minimize the adverse effects of anaesthesia on the recovery process, availability of short acting anaesthetic, analgesic and sympatholytic drugs have resulted in a number of surgical procedures being done in a daily case basis. This has led to the concept of fast tracking where the post-operative care unit is being by-passed. The terms ambulatory surgery, day care surgery, out-patient surgical procedures are synonymus to indicate that the patient is discharged the same day of surgery without overnight hospital stay. The global economic constrains and increasing financial awareness of 1970,1 has led to the increase in the incidence of ambulatory surgery. Main advantages are reduced risk of nosocomial infection, cost reduction and...
short duration of hospital stay. Federated ambulatory surgery association (FASA) has observed that in an ambulatory setting there is no significant relationship between pre-existing diseases and incidence of post-operative complications. The federal drug administration has approved the use of dexmedetomidine, as a sedative analgesic and/or total anaesthetic in adults and paediatric patients undergoing minimally invasive procedures causing no respiratory depression or the need for intubation of trachea.\(^4\) Dexmedetomidine possesses selective alpha adrenoceptor agonism especially for the 2α receptor subtype and reduces upload requirements without causing significant respiratory depression, affects the locus caeruleus area, which controls respiration and causes modulation of sleep.\(^3\) Activation of the α2-adrenergic receptor of central nervous system results in analgesia causing lowering of the biological stress response and catecholamine secretion resulting reduction of blood pressure and heart rate to a moderate level. Ketamine, a n-methyl-d-aspartate (NMDA) receptor and glutamate receptor antagonist is a dissociative sedative hypnotic drug with potent analgesic properties and marked sympathomimetic effects on the cardiovascular system.\(^4\) In this study of hysteroscopic procedures, the patients were anaesthetically maintained on mask ventilation with oxygen and nitrous oxide using the drugs dexmedetomidine or ketamine both of which are sedative and hypnotic anesthetic agents. Hysteroscopy is the procedure for inspection of the insufflated uterine cavity through an endoscope (hystroscope) with access through the cervix for the diagnosis and/or surgical intervention of intrauterine pathology. Other common and popular drugs used for sedation in the day care hysteroscopies are propofol, remifentanyl, remimazolam.

The aim of this study is to compare the superiority - one above the other of the drugs dexmedetomidine and ketamine for day care hysteroscopic procedures.

The objectives for this study are comparison of the hemodynamic changes between the study drugs intra-operatively, requirement of rescue sedative and/or analgesic during the procedure, comparison of complications of the drugs per-operatively and duration of surgery.

**METHODS**

After the Ethical committee approval and written informed consent from the patients, the prospective study was conducted in a rural hospital Medical College during the period of November 2016 to October 2017. Study design was an interventional one with computer generated randomly allocated patients. Number of patients 50, divided in groups D (n=25) and K (n=25).

**Inclusion criteria**

- ASA grade I or II
- Age 20-55 years

**Exclusion criteria**

- Emergency surgeries
- Pregnant or breast-feeding patients
- Significant arrhythmia or high degree atrioventricular nodal block
- Significant hepatic, endocrinial or renal dysfunction
- Chronic use or addiction to opiates or sedatives
- History of alcohol usage (>4 drinks/day)
- Psychiatric or emotional disorder
- Chronic user of α2-agonists
- Patients with OSA or BMI greater than 30
- Allergy to study drugs with a history of egg or soya bean allergy or anesthetic medications utilized in the protocol
- Patients who had difficulty in communication (due to language problem or deafness).

All patients were subjected to thorough pre-anesthetic evaluation and relevant laboratory investigations

**Anaesthetic protocols followed were:**

On arrival to the operation theatre base line heart rate, systolic and diastolic blood pressure recorded, SpO2 attached, ECG leads connected.

The 18-gauge IV cannula inserted and Lactated Ringers solution through a drip set 15ml/kg infused.

**Premedication**

Inj. Glycopyrrolate 0.2mg and Inj Ondensetron 4mg IV at the onset of the procedure before administering the study drugs.

- Group D (n=25) received dexmedetomidine 100 µg IV,
- Group K (n=25) received ketamine 75mg IV Both the drugs were diluted with 10 mL of normal saline and injected over 10 mins at the onset of the surgical procedure,
- Both the groups received Inj Midazolam 1.5mg IV after the study drug was administered.

Scoring for sedation was done using Ramsay sedation score (RSS) prior to commencement of the surgical procedure.

- Score 1: Anxious, agitated, and restless
- Score 2: Awake, co-operative, oriented, tranquil
- Score 3: Semi asleep responds only to verbal commands
• Score 4: Asleep with brisk response to glabellar tap or loud auditory stimulus
• Score 5: Asleep with sluggish response to glabellar tap or loud auditory stimulus
• Score 6: Nonresponsive.

As a rescue sedative drug (0.5 mg kg$^{-1}$) aliquots of Propofol IV bolus and Fentanyl in the dose of 1 μg kg$^{-1}$ IV bolus as rescue analgesics had been given in either of the groups until patient reached (RSS) 3-4. Maintenance of anaesthetic procedure has been done on mask ventilation with 30% oxygen and 70% nitrous oxide.

**Intra-operative monitoring**

The blood pressure and heart rate monitored at 2 mins interval for first 10 mins and then every 10 mins till the surgery was over. During the procedure bradycardia (HR under 50 beats/min or a 20% decrease from the baseline) or tachycardia (HR over 110 beats/min or an increase of more than 20% from the baseline level) and any hypotension (MAP value lower than 60 mmHg or 20% less than the baseline) or HTN (MAP levels of over 150 mmHg or 20% more from the baseline) and hypoxia (fall of RR to 8 breaths or less per minute or a fall of arterial SpO2 value to <90%) was observed, recorded and treated accordingly. Bradycardia was treated with intravenous atropine sulphate 0.01 mg kg$^{-1}$, hypotension with fluid replacement and IV ephedrine hydrochloride 5 mg in incremental doses if needed, in case of bradypnoea, patient had been woken up and was asked to take deep breaths, fall of saturation was treated by increasing O2 flow up to 10 liters in bag mask ventilation.

Time taken for surgery and requirement of rescue drug in each group, complications such as respiratory depression, allergies, dizziness, restlessness, loss of analgesia, cough, nausea and vomiting during the procedure were also recorded and compared.

**Post-operative monitoring**

In the recovery room, patients were recorded every 5 min by an anesthesiologist for any adverse effect such as nausea, vomiting, hypotension, bradycardia, oxygen desaturation, restlessness, shivering, abdominal discomfort and in the case of any adverse event the patients were observed in the hospital for at least 12 hour. Complete recovery was defined as achievement of modified Aldrete score (MAS) of 9-10.$^5$

**Table 1 : Aldrete's scoring system (modified).**

| Variables                        | Additional criteria by Marshall and Chang in 1999 for ambulatory surgery |
|----------------------------------|------------------------------------------------------------------------|
| Activity                         | Steady gait without dizziness or meets pre-anaesthetic level (2 Points) |
|                                  | Requires Assistance (1 Point)                                          |
|                                  | Unable to ambulate (0 Points)                                          |
| Respiration                      | Not included                                                           |
| Circulation                      | BP± ±20% of pre-anaesthetic level (2 Points)                           |
|                                  | BP± ±20-40% of pre-anaesthetic level (1 Point)                          |
|                                  | BP± ±40% of pre-anaesthetic level (0 Points)                           |
| Consciousness                    | Not included                                                           |
| Colour or O₂ saturation          | Not Included                                                           |
| Pain                             | Minimal to no pain, controllable with oral analgesics (2 Points)        |
|                                  | This target not met (1 Point)                                          |
| Surgical bleeding (as expected for procedure) | Minimal/Does not require dressing change (2 Points) |
|                                  | Moderate/Up to two dressing changes required (1 Point)                 |
|                                  | Severe/More than three dressing changes required (0 Points)            |
| Nausea and vomiting              | None to minimal (2 Points)                                             |
|                                  | Moderate (1 Point)                                                    |
|                                  | Severe (0 Points)                                                     |
| Interpretation of score          | "Patients who score 9 or greater and have an appropriate escort can go home." |

**Statistical analysis**

The parameters were expressed as M (mean), ±SD (standard deviation) and analysed using chi square test or student ‘t’ test as appropriate, with the p value reported at the 95% confidence interval. The result obtained in the study were analysed using Microsoft Excel and SPSS for analysing the collected data. ‘p’ value >0.05 statistically not significant (NS), ‘p’ value of <0.05 as statistically significant (S), ‘p’ value of <0.01 as statistically highly significant (HS) ‘p’ value of <0.0001 as statistically very highly significant (VHS).
RESULT

The demographic data in terms of age, weight, height and the duration of surgery were comparable in both the groups and not significant (Table 2). Number of patient in each group 25 'p' value of <0.0001 statistically very highly significant. The base line value of systolic and diastolic blood pressure and heart rate immediately before applying the study drugs (at 0 min) were not significant statistically and were comparable between the groups. The changes in systolic and diastolic blood pressure and heart rate in the groups starting from 2mins after the study drugs injected were statistically very highly significant. The haemodynamics were stable in the group D (Table 3).

No major adverse event was observed in this study and no patient had to be converted to an alternative sedative or anesthetic technique in either of the groups. In the group D, 4% cases had bradycardia which was treated with intravenous 0.6 mg atropine sulfate.

In the group K 4% had nausea, vomiting, treated with inj. Ondensetron 4mgIV, 16% had 02 desaturation to 90-94%, 24% were restless, 28% suffered post-operative shivering, 8% had abdominal discomfort post the procedure. All were given symptomatic treatment (Table 5).

Table 2: Patients' demographic data.

| Demographics       | Group                | N   | M±SD      | p value       |
|--------------------|----------------------|-----|-----------|---------------|
| Age (year)         | Dexmedetomidine (D)  | 25  | 32.56±9.05| p 0.57 (NS)   |
|                    | Ketamine (K)         | 25  | 31.16±8.38|               |
| Weight(kg)         | Dexmedetomidine (D)  | 25  | 51.1±7.07 | p 0.33 (NS)   |
|                    | Ketamine (K)         | 25  | 49.24±6.49|               |
| Height(cm)         | Dexmedetomidine (D)  | 25  | 148.46±4.74| p 0.93 (NS)  |
|                    | Ketamine (K)         | 25  | 148.36±4.41|               |
| Duration of procedure (min) | Dexmedetomidine (D) | 25  | 44.04±7.50| p 0.60(NS)    |
|                    | Ketamine (K)         | 25  | 45.2±8.22 |               |

N= number of patient, 'p' value >0.05 statistically not significant, (NS).

Table 3: Haemodynamic parameter.

| Time (min) | Systolic BP | Diastolic BP | Heart rate |
|------------|-------------|--------------|------------|
|            | D M±SD      | K M±SD       | D M±SD     | K M±SD       | D M±SD     | K M±SD     | p         |
| 0          | 115.1±7.7   | 116.8±7.1   | 68.8±5.6   | 6.5±7.2      | 0.63±5.6   | 76.4±5.6   | 5.6±7.6   | 75±0.6   |
| 2          | 108.8±4.6   | 122.4±4.5   | 65.8±6.4   | 4.2±7.11    | 0.0005±6.7 | 67.8±5.3   | 6.7±7.6   | 78.6±0.001|
| 4          | 110.6±6.4   | 127.9±5.3   | 65.2±5.8   | 4.5±7.25    | 0.0001±6.8 | 68.2±6.3   | 8.0±7.9   | 79.8±0.001|
| 6          | 107.5±5.8   | 127.5±6.1   | 67.0±6.8   | 4.2±7.65    | 0.0001±6.6 | 67.6±6.4   | 6.4±7.8   | 82.8±0.001|
| 8          | 109±4.3     | 127.8±5.0   | 68.9±5.1   | 5.1±7.66    | 0.0001±6.3 | 63.8±5.4   | 6.1±7.9   | 79.8±0.001|
| 10         | 106.6±5.3   | 128.2±4.8   | 68.8±6.7   | 4.7±7.71    | 0.0001±6.2 | 62.9±5.0   | 7.5±8.1   | 81.0±0.001|
| 20         | 106.9±5.4   | 127.5±5.8   | 70.8±3.2   | 4.1±80      | 0.0001±6.5 | 65.3±6.2   | 5.4±8.1   | 81.8±0.001|
| 40         | 109.9±6.5   | 128.6±4.4   | 74.7±3.1   | 7.1±8.1     | 0.0001±6.2 | 62.3±3.1   | 8.6±8.6   | 86.6±0.001|
| 60         | 114.9±5.6   | 127.2±6.1   | 6.0±0.001  | 7.0±3.4     | 3.8±8.3    | 0.0001±7.5 | 6.9±4.4   | 81.9±0.001|

Table 4: Rescue sedative and analgesic.

| Rescue propofol | Dexmedetomidine M±SD | Ketamine M±SD | p value |
|-----------------|-----------------------|---------------|---------|
| Yes/Number      | 1/24                  | 0.04±0.20     | 7/18    |
|                 | No. of top-ups (1/2/3)| 1/0/0         | 2/3/2   |
| Rescue Fentanyl | Yes/Number 2/23       | 0.08±0.27     | 9/16    |
|                 | No. of top-ups (1/2/3)| 1/1/0         | 3/7/5   |

*p value of <0.01 as statistically highly significant (HS).
Table 5: Per-operative complication.

|        | D (Dex) | K (Ket) |
|--------|---------|---------|
| Nausea, Vomiting | 0/25 | 1/25 (4%) |
| Hypotension | 0/25 | 0/25 |
| Bradycardia | 1/25 (4%) | 0/25 |
| O₂ desaturation | 0/25 | 4/25 (16%) |
| Restlessness | 0/25 | 6/25 (24%) |
| Shivering | 0/25 | 7/25 (28%) |
| Abd. discomfort | 0/25 | 2/25 |

DISCUSSION

The prospective study was conducted to evaluate the merits, efficacy and safety of IV dexmedetomidine versus IV ketamine for day care hysteroscopic procedures. Dexmedetomidine, a highly selective alpha-2-adrenoceptor agonist and Ketamine, a NMDA receptor antagonist are both sedative and hypnotic anesthetic agents.

At low doses, dexmedetomidine produces sedative effect that mimics natural stage 2 non-rapid eye movement sleep. Patients remain drowsy but are co-operative and arousable.³ Dexmedetomidine has dose dependent sedation effect.³ The distribution half life of dexmedetomidine is about 5 to 10 mins. Our study dose of dexmedetomidine 100 µg IV over 10 min is within an arousable limit.

Dexmedetomidine also has sympatholytic, amnestic and the analgesic properties without respiratory depression.⁸ For scoring of RSS, the sedated patients are to be made alert for assessment and depending on the response of the patient the assessor makes a subjective assessment. In our study, the assessment was based on the response of the patient on painful stimuli amenable to the surgical procedure and then the rescue drugs had been used as per requirement (Table 4). So, no extra effort needed to be taken for assessing the RSS. Dexmedetomidine causes decrease in the HR which might be attributed to its sympatholytic effects and decrease in circulating catecholamine levels.⁹ Taniyama et al, found statistically significant lower HRs in the dexmedetomidine group.¹⁰ In our study, we observed decrease in HR, comparatively stable blood pressure (BP) values and better SpO₂ (Table 5) (O₂ desaturation ) in Group D than in Group K. In 2013, Devangi A Parikh et al, observed lower HR and MAP and their findings support other studies.¹¹,¹² Table 3 in our result, shows that dexmedetomidine has clinical advantages over ketamine in controlling hemodynamic variability and the ‘p’ value of <0.0001 is statistically very highly significant.

The effects of dexmedetomidine are not mediated by the Y aminobutyric system so it does not cause respiratory depression. This finding is similar to other studies.¹³,¹⁴ We observed that there was no evidence of bradypnea in either of the groups.

Major side effect of alpha-2-agonist agents is bradycardia, which is mediated by activation of alpha-2-adrenoceptors, especially in the solitarius nucleus tract.¹⁷ In the dexmedetomidine group (D), there was no intra or postoperative adverse effects as respiratory depression, restlessness, nausea and vomiting. So our results were similar to Abdellatif et al, Ghali et al, Arain and Ebert, Takimoto et al, which proved the sedation safety and reduced adverse effects of dexmedetomidine.¹⁸,²¹ In our study, the dose of dexmedetomidine to induce sedation in patients who underwent anaesthesia was used in the range of those used in other studies.²²,²⁴

Verma R et al, in 2014 have demonstrated that dexM provides adequate levels of sedation without clinically significant respiratory depression in the perioperative period and observed that rescue analgesia as injection fentanyl was required in less number of patients in dexM group that explains the analgesic property of the drug, which is consistent with the findings of Arain and Ebert.²⁰,²⁵ Our study results also support the same and had less number of requests for rescue sedation and analgesia in group D and the statistical ‘p’ value was <0.01.

Ketamine, at subanesthetic doses has sedative and amnestic properties and analgesic activity.²⁶ Nightmares and hallucinations may occur in 5-30% of patients, at high doses, but occurrence is significantly less frequent at doses < 1 mg kg⁻¹.²⁷ Low dose of Ketamine is not associated with respiratory depression.²⁸ In the present study the dose we used was 75 mg for all the patients which comes in the range of < 2 mg kg⁻¹.

But still 16% had 02 desaturation intra-operatively, 28% suffered shivering, 24% were restless .8% felt abdominal discomfort post procedure (Table 5). There was hemodynamic unstability regarding hypotension and bradycardia in the Ketamine group in comparison to the dexmedetomidine one (Table 5). Propofol (2, 6-di-isoproplyphenol) is a short-acting, hypnotic/amnestic agent administered IV. Since propofol has no analgesic property, fentanyl, a synthetic opioid, related to phennliperidine is used as adjuvant to alleviate pain.²⁹ It acts on µ receptors as agonist. For diagnostic, endoscopic, angiographic and other minor procedures in poor risk patients, fentanyl with benzodiazepine combination can be used as an ideal agent.³⁰ In our study, there was a significant difference between the two groups D and K regarding the requirement of propofol as rescue sedative and fentanyl as rescue analgesic (Table 4), with an increasing trend of using these in Group K (p < 0.01, statistically highly significant (HS)). Postoperatively, an Aldrete score of 10 was the end point of study.

CONCLUSION

So, the authors can claim that dexmedetomidine for day care hysteroscopic procedures can be the drug of choice. Unlike ketamine, dexmedetomidine is a safe drug with
improved analgesia, without any requirement of narcotic analgesic in the postoperative period, good hemodynamic and recovery profile having slower onset and offset of sedation. Very few studies are published regarding its use in day care hysteroscopies and no study has been found with ketamine in comparison.

The patients in this study are either ASA physical status I or II, who are free from significant co-morbidities. ASA physical status III or IV might cause exaggerated cardiovascular side-effects with dexmedetomidine or ketamine. So further multicenter Randomised Control Trial is needed. Dexmedetomidine as an infusion along with the bolus dose, can be tried to make the drug a sole anaesthetic agent.

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