Comparative study between dexmedetomidine, magnesium sulphate and fentanyl as sedatives throughout awake fiberoptic intubation for patients undergoing cervical spine surgeries

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1. Introduction

Patients with cervical spine injuries pose a challenge to the anesthesiologist when attempting intubation since maneuvers like head tilt and chin lift are risky to perform [1]. Awake fiberoptic intubation is considered a successful and safe technique in such patients [2].

Anxiety leading to poor patient cooperation poses another challenge to the anesthesiologist while attempting awake fiberoptic intubation, therefore providing adequate sedation while preserving ventilation, patent airway, providing patient comfort, hemodynamic stability and cooperation is of utmost importance [3,4].

Several drugs have been used to provide adequate sedation to optimize awake fiberoptic intubation, those drugs include opioids as fentanyl and remifentanil, benzodiazepines as midazolam, ketamine and propofol, however their use isn’t devoid of side effects as emergency delirium, respiratory depression, hypoxemia and apnea [3,4].

Another addition has been dexmedetomidine, being a selective α2 adrenergic, its sympatholytic, analgesic and sedative effects have been considered in anesthetic practice [5]. It is a highly protein bound drug with a rapid distribution phase of around 5–10 min and an elimination half life of 2–3 h, it is metabolized mostly in the liver and its metabolites are excreted mainly in urine. For conscious sedation, usually a loading dose of 1 µg/kg is infused over 10 min followed by a maintenance of 0.2–1 µg/kg/h. It initially results in hypertension due to activation of α2 receptors in vascular smooth muscles leading to vasoconstriction accompanied by reflex bradycardia, that effect is followed by hypotension and bradycardia [6]. It has the advantage of providing adequate sedation without the previously mentioned side effects, thus it can be of great benefit during awake fiberoptic intubation for patients with cervical spine fractures [7].

On the other hand, Magnesium sulphate a N-methyl-D-aspartate receptor antagonist with potential analgesic, anticonvulsant and sedative properties has been increasingly used in anesthesia. It decreases catecholamine release following sympathetic stimulation, it acts as a calcium antagonist and it decreases acetylcholine and histamine release. Furthermore, it has been postulated to have both cardiac and neurological protective effects and is considered as a central nervous system depressant [8,9]. It has been used as analgesic during surgery in a loading dose of 30–50 mg/kg, followed by a maintenance dose ranging from 6 to 20 mg/kg [10]. When administered intravenously the onset of action is immediate and lasts for 30 min, it is excreted unchanged in urine [11].

Subsequently, the present study hypothesized that the sedative and analgesic properties of dexmedetomidine and magnesium sulphate might be beneficial in optimizing sedation and attenuation of stress response to intubation during awake fiberoptic intubation. The current study aimed at comparing the effects of dexmedetomidine, magnesium sulphate and fentanyl as regards sedative effects, hemodynamic stability, intubation time and intubation attempts during awake fiberoptic intubation.

2. Patients and methods

After approval of the Ethical Committee of the anesthesia department and obtaining written informed consents from all patients participating in the study, sixty patients presenting for elective anterior corpectomy and cervical fixation were randomly assigned to one of three groups, DEX group received dexmedetomidine, MG group received magnesium sulphate and FENT group received fentanyl as sedative agents prior to awake fiberoptic intubation.

Randomization program (research randomizer.org) was utilized to create random list and to allocate patients into the three study groups. Random generated numbers were secured in opaque closed envelopes.

2.1. Inclusion criteria

– Age between 18 and 50 years.
– ASA physical status class I–II.
2.2. Exclusion criteria

- Emergency surgery.
- Unstable cervical spine fracture surgery.
- Patients with coagulation defects.
- Unstable cervical spine fracture surgery diagnosed by the neurosurgeon by means of clinical examination and radiological investigations upon admission to the trauma department.

2.3. Preparation

One day prior to surgery, the technique of awake fiberoptic intubation under sedation was explained to the patients, as well as their needed cooperation.

On the day of surgery, a neurological examination was performed by the neurosurgeon to establish any neurological deficits prior to intubation. Afterwards, patients were monitored with electrocardiogram (ECG), pulse oximetry, noninvasive BP and bispectral index (BIS). After tracheal intubation, capnogram was attached.

Fifteen minutes before proceeding to awake fiberoptic intubation, patients were premedicated with intravenous atropine 0.4 mg, oxygen (3 L/min) was administered through a nasal cannula. Xylometazoline hydrochloride 0.1% nasal drops was used as decongestant and both nostrils were stuffed with cotton swabs soaked in 2% lidocaine with adrenaline in order to anesthesia nasal mucosa. Nasal intubation was achieved through the nostril displaying the least resistance during packing whereas oxygen was delivered through the other nostril throughout awake fiberoptic intubation.

Recurrent laryngeal nerve block was achieved with transtracheal injection of 4 ml of 2% lidocaine without adrenaline, through 22 gauge needle on 5 ml syringe to induce sensory block of the vocal cords and trachea [12].

2.3.1. Study groups

Patients were randomized among three equal groups:

- Dexmedetomidine group (DEX group): 20 patients received dexmedetomidine in dose of 1 μg/kg followed by 0.5 μg/kg/h.
- Magnesium sulphate group (MG group): 20 patients received magnesium sulphate in dose of 30 mg/kg followed by 10 mg/kg/h.
- Fentanyl group (FENT group): 20 patients received fentanyl in dose of 1 μg/kg followed by 0.5 μg/kg/h.

The loading volume adjusted to be 50 ml infused intravenously over 10 min followed by maintenance infusion rate of 20 ml/h to ensure operator blindness of the study medication. The infusion drugs have been prepared by a clinical pharmacist not involved in data collection.

Following infusion of the loading dose of the study drugs, the patient’s conscious level was evaluated using Ramsay sedation scale (RSS) interpreted as following; 1 = Anxious, agitated or restless, 2 = cooperative, oriented and tranquil, 3 = sedated but responds to command, 4 = asleep with brisk response to stimulus, 5 = asleep with sluggish response to stimulus and 6 = asleep with no response) [13].

In addition to RSS, conscious level was also evaluated using bispectral index (BIS COVIDIEN_VISTA Monitoring System using unilateral disposable sensors) [14] as follows, values from 90 to 100 are associated with an awake state, values in the 70–80 s associated with conscious sedation, values in the 60–70 s associated with deep sedation, and values from the 40 s to 60 s associated with general anesthesia. [15]

If the RSS was <2 and/or BIS > 90, rescue doses in the form of 50 mg of propofol were administered.

2.4. Procedure of fiberoptic intubation

Fiberoptic nasal intubation started once the Ramsay scale ≥2 and BIS < 90 by means of topical anesthesia of the airway by spray as you go technique, using 2% lidocaine solution through the side channel of the fiberoptic bronchoscope until the epiglottis was visualized. The fiberoptic bronchoscope was then maneuvered beneath the epiglottis to visualize the vocal cords, the area was anesthetized with 2 ml of 2% lidocaine solution applied onto the glottic area. Upon entering the trachea, the anesthetist advanced the endotracheal tube over the bronchoscope. Capnogram was then applied and general anesthesia was administered.

Before administration of general anesthesia a second neurological examination was carried on by the neurosurgeon to ascertain any new neurological deficits.

2.5. Data collection

1. Level of sedation was evaluated by BIS and RSS just after completion of infusion of study drug.
2. Number of patients needing supplementary propofol infusions in each group.
3. Intubation time: from placing the fiberoptic bronchoscope into the nasal cavity till verification of tracheal intubation with capnogram.
4. Number of intubation attempts.
5. Heart rate (HR) and mean arterial blood (MAP) pressures at the following times: baseline, 5 and 10 min after starting the infusions and at intubation time.
6. Oxygen saturation (SpO2) at the following times: baseline, 5 and 10 min after starting the infusions and at intubation time.
7. Hypoxic episode defined as SpO2 < 90% and were managed with supplemental oxygen.

2.6. Primary outcome

BIS index after completing the loading dose of the study medications.

2.7. Secondary outcomes

RSS after completing the loading dose of the study drugs, number of patients needing supplementary propofol in each group, intubation time and number of intubation attempts, hemodynamics till time of intubation, O2 saturation and number of hypoxic episodes till time of intubation.

2.8. Sample size (number of participants included)

A minimum sample size of 17 patients per group had 80% power to detect an assumed clinically important difference of 20% or more in the mean bispectral index values relative to baseline readings (effect size f = 0.46, β error = 0.2, α error = 0.05; two-tailed). Statistical power calculations was performed using computer program G’Power 3 for Windows. The sample size in
each group was increased to 20 patients to compensate for possible dropout. 60 patients were assigned to this study.

2.9. Statistical analysis

Obtained data were presented as mean ± SD, median (IQR) and numbers and percentages as appropriate. Nominal variables were analyzed using Chi-squared ($\chi^2$) test or Fisher exact test as appropriate. RSS was analyzed using Kruskal Wallis test or Mann Whitney test as appropriate. Continuous variables were analyzed using one way and repeated measures analysis of variance (ANOVA) with post hoc Dunnett’s test as appropriate. A statistically significant difference was considered when $P$ value <0.05.

3. Results

3.1. Demographic characteristics

Demographic characteristics age, gender, ASA I and II, weight and height showed no statistically significant differences between the study groups (Table 1).

3.2. Operative data

3.2.1. Patients sedation scores

At the end of study drugs infusion, there was statistically significant lower BIS values in DEX group when compared to FENT and MG groups, moreover, statistically significant lower BIS values were observed in FENT group when compared to MG group (Table 2).

Besides, RSS was higher in DEX group when compared to FENT and MG groups, as well as for FENT group when compared to MG group (Table 2).

Twelve patients in MG group (60% of patients) failed to achieve RSS of two and/or BIS < 90 and were given rescue dose of propofol (50 mg), while none of the patients in FENT and DEX groups needed propofol.

3.2.2. Intubation time and intubation attempts

There were no statistically significant differences in intubation time (Table 2) nor in intubation attempts ($P = 0.676$) (Fig. 1) between the three study groups.

3.2.3. Hemodynamic changes (heart rate and blood pressure changes)

There were no statistically significant differences in MAP readings between the three groups at baseline, 5 min and 10 min after drug infusions, however there was statistically significant lower MAP readings in DEX group when compared to FENT and MG groups at time of intubation with no statistically significant differences between FENT group and MG group at same time (DEX group 81.10 ± 5.02, MG group 85.40 ± 5.22, FENT group 86.35 ± 6.08, $P = 0.008$) (Fig. 2).

In addition, no statistically significant differences were evident in HR readings between the three groups at baseline, 5 min and 10 min after drug infusions, however there was statistically significant lower HR readings in DEX group when compared to MG group at time of intubation with no statistically significant differences between FENT group and MG group at same time (DEX group 64.55 ± 3.58, MG group 68.15 ± 3.23, FENT group 66.95 ± 3.50, $P = 0.006$) (Fig. 3). Moreover, two patients in DEX group (10% of dex group) had bradycardia (HR < 60 beat/min) and were treated with atropine 0.4 mg.

3.2.4. Oxygen saturation (SpO2) and hypoxic episode

There were no statistically significant differences in SpO2 readings between the three groups at baseline, 5 min and 10 min after "RETRACTED"
drug infusions and at intubation time, in addition there were no hypoxic episodes in the three groups (Table 3).

3.2.5. Neurological deficits

None of the patients in any of the groups demonstrated worsening in neurological function upon examination after awake fiberoptic intubation.

4. Discussion

When anticipating difficult laryngoscope positioning in cases like cervical spine injuries, awake fiberoptic intubation is recommended. Preparing patients for such a procedure includes adequate anxiolysis and sedation while maintaining proper ventilation [4].

The present study was designed in patients undergoing cervical spine surgery to compare the effects of dexmedetomidine next to magnesium sulphate and fentanyl as regards sedative effects, hemodynamics, hypoxic episodes as well as intubation time and intubation attempts during awake fiberoptic intubation.

The study showed that all patients in dexmedetomidine and fentanyl groups achieved RSS ≥ 2 and BIS < 90 with significantly higher scores of RSS and lower values of BIS in dexmedetomidine group, while 60% of patients in magnesium sulphate group failed to reach RSS ≥ 2 and/or BIS < 90 and required additional sedative in the form of propofol 50 mg.

In addition, dexmedetomidine provided favorable hemodynamics in comparison to both magnesium sulphate and fentanyl groups.

The three groups were comparable as regards intubation time and intubation attempts, moreover no hypoxic episodes were recorded in the 3 groups and the least SpO₂ reached was 96%.

The sedative effects of the study drugs can be interpreted by their different mechanisms of action.

Fentanyl produces its action through binding to μ-opioid receptors, it provides mild sedation while preserving hemodynamics, making it a suitable drug in awake fiberoptic intubation, though it is not devoid of risks such as nausea, vomiting and chest wall rigidity [16].

Dexmedetomidine comprises several effects that are beneficial during awake fiberoptic intubation which include sympathetic, sedation, anxiolysis and analgesia, it also reduces salivation. The sedative effect of dexmedetomidine has been attributed to the high density α-2 receptors found in the locus coeruleus, an essential modulator of vigilance in the brain. It results in an exclusive form of sedation in which the patients become sleepy, but arousable, cooperative and with minimal respiratory depression [17,18].

Magnesium sulphate is a N-methyl-D-aspartate receptor antagonist, binding to these receptors results in antinociceptive, anti-convulsant and sedative properties [19].

To our knowledge, no available studies compared the effects of magnesium sulphate against dexmedetomidine and fentanyl as a sole agent for conscious sedation during awake fiberoptic intubation. However, in a recent study by Ghosh et al. while comparing the analgesic effects of intravenous dexmedetomidine versus magnesium sulphate given as adjuvants prior to spinal anesthesia, they found that dexmedetomidine provided better sedation than magnesium sulphate, a finding supports the results of the current study [20]. In another study by Adly et al., they evaluated the postoperative sedative effect of dexmedetomidine in comparison to magnesium sulphate, both drugs were started prior to induction of general anesthesia and continued as infusions till the end of surgery, although both provided sedation, the sedative effect of dexmedetomidine was superior to that of magnesium sulphate in the first 8 hours following surgery which comes in accordance with our study, the disparity in the sedative effect of magnesium in comparison to our study could be attributed to the larger dose used.

Table 3

Comparison between the three groups as regards oxygen saturation.

| Drug       | DEX group (n = 20) | MG group (n = 20) | FENT group (n = 20) | P value |
|------------|-------------------|------------------|--------------------|---------|
| SpO₂ (%) baseline | 99.80 ± 0.41      | 99.80 ± 0.41     | 99.80 ± 0.41       | 1       |
| SpO₂ (%) 5 min   | 99.75 ± 0.55      | 99.75 ± 0.55     | 99.65 ± 0.75       | 0.842   |
| SpO₂ (%) 10 min  | 99.65 ± 0.59      | 99.65 ± 0.59     | 99.65 ± 0.67       | 1       |
| SpO₂ (%) at intubation | 99.60 ± 0.75 | 99.30 ± 1.17     | 99.65 ± 0.67       | 0.414   |

Values are expressed as mean ± standard deviation.

SpO₂ (%) = oxygen saturation
prior to induction 40 mg/kg, the cumulative effect and the combined effect of general anesthesia [21].

In several studies including the current one, dexmedetomidine granted adequate sedation during awake fiberoptic intubation. In a series of patients with abnormal airways Abdelmalak et al. used dexmedetomidine successfully as a sedative agent for awake fiberoptic intubation [22], Chopra et al. and Niogyi et al. as well found that dexmedetomidine infusion provided optimum level of sedation with favorable hemodynamics and no hypoxic episodes when compared to saline infusion. A decreased need of midazolam in dexmedetomidine group to achieve RSS ≥ 2 prior to intubation was observed in the Chopra et al. study, while none of the patients receiving dexmedetomidine in the Niogyi et al. study required supplementary fentanyl as opposed to 60% of the patients in the placebo group [23,24].

When comparing dexmedetomidine with fentanyl for conscious sedation during awake fiberoptic intubation, Mondal et al. and Chu et al. found better intubating conditions and favorable hemodynamics in dexmedetomidine group which is consistent with the results of our study. In the Mondal et al. study all patients achieved RSS ≥ 2 with a higher score in dexmedetomidine group, however it was associated with hypoxic episodes in both groups with a significantly higher incidence in the fentanyl group which is in variance with our study, this may be due to the higher dose of fentanyl used 2 μg/kg and the use of oxygen supplementation only when SpO2 < 95% while we used oxygen supplementation from the start. On the other hand, no hypoxic episodes were observed in the Chu et al. study and intubation time was comparable between the two groups which is congruent with the present study [4,25].

Conversely Cattano et al. found a lower RSS in dexmedetomidine group in comparison to remifentanil group during nasal and oral awake fiberoptic intubation, this was attributed to the smaller loading dose of dexmedetomidine at 0.4 μg/kg followed by 0.7 μg/kg/h. Nevertheless, no respiratory depression occurred in either groups which is in accordance with our study [26,27].

Studies evaluating the role of magnesium sulphate as sole agent for sedation are scarce. Maulik et al., studied the sedative and analgesic effects of magnesium sulphate versus saline on 86 severe preeclamptic patients undergoing caesarean sections under spinal anesthesia. The study showed that patients in the magnesium group achieved good sedation scores when compared to the control group. This comes in contrast with our study, which may be attributed to the higher dose used during loading and the longer duration of infusion of magnesium sulphate as well as the difference in the study population in the Maulik et al. study. On the other hand, there was no respiratory depression or hypoxic episodes in the magnesium group which is in agreement with the present study [27].

4.1. Conclusions and limitations

Dexmedetomidine provides optimum sedative effects and favorable hemodynamics for awake fiberoptic intubation. Magnesium sulphate failed to produce adequate sedation in the current study. In further studies, larger doses and longer duration of magnesium sulphate infusion may be tried. Furthermore, side effects as gag reflex and cough should be reported.

Conflict of interest

The authors declared that there is no conflict of interest.

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