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Research Article

Dexmedetomidine Infusion as an Anesthetic Adjunct Reduce the Utilization of Sevoflurane during General Anesthesia

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Abstract

Purpose: The intravenous anesthetic adjunct Dexmedetomidine has been shown to be neuroprotective [1,2]. Dexmedetomidine HCl is an α2-agonist, and has been suggested to decrease the amount of inhalation agent required to prevent or reduce possible neurotoxic effects of volatile agents, to smooth emergence, to alleviate post-operative pain and to decrease post-operative nausea and vomiting. In this retrospective study, we compared if the use of dexmedetomidine as associated with decreased utilization of inhaled anesthetics [1,2,10].

Methods: The total 130 participants in this study were selected from the operating room cases at Virginia Commonwealth University. The patients underwent GA (General Anesthesia) were divided into two groups: A) control group (n = 80) and B) intravenous infusion dexmedetomidine during surgery (n = 50). The age, gender, body weight and the end of expiratory sevoflurane, were recorded for each patient during the anesthetic, data collected from Innovian electronic charting. Age was measured in years, gender was defined as being male or female, body weight was measured in kilogram. Amount of inhaled sevoflurane was defined as percentage of end expiratory inhaled anesthetics mathematically averaged by the Innovian program.

Results: The end of expiratory sevoflurane (%) in dexmedetomidine (Dex) group was significantly less than that in the control group (0.941 ± 0.046 vs. 1.444 ± 0.028, $p < 0.001$). There was no statistic significant difference in ages among groups (47.74 ± 2.2 in dexmedetomidine group vs. 42.95 ± 1.7 in control group, $p = 0.09$). Further, the reduction of sevoflurane in dexmedetomidine infusion group was not significantly related with sex gender and body weight when compared with control group.

Conclusion: An intraoperative infusion of dexmedetomidine combined with inhalation sevoflurane can reduce the use of sevoflurane (inhalation anesthetics) during general anesthesia. We aim to further study if this can possibly decrease sevoflurane usage during anesthesia and possible toxicity, as has been shown in rodent experimental study.

Keywords: *Sevoflurane; Dexmedetomidine (Dex); Intravenous Infusion (IV); General Anesthesia (GA); Minimum Alveolar Concentration (MAC)*

Introduction

Inhalation agents, Ketamine, Propofol, Midazolam, Opioids communally used for General anesthesia have recently been associated with widespread apoptotic neurodegeneration in brain animals, most studies have been conducted in neonatal rats [1,3-5]. In general inhalation agents are capable of inhibiting synaptic neurotransmission by potentiating y-aminobutyric-acid type A (GABAa) receptors,

inhibiting glutamate N-methyl-D-aspartate (NMDA) or activating potassium channels, with the final result of cellular hyperpolarization and reduction in neuronal activity [2,5,6,10]. Although volatile anesthetic agents have been used for hundred fifty years, concerns have recently arisen about neurotoxic effects of modern volatile anesthetic agents. This neurotoxic effect is probably related to the concentrations of volatile agents that are required, with deeper concentrations more neurotoxic. The neuronal cell apoptosis is a cascade process and the anesthetic toxic effect has been noted after as little as 60 min of below 1 MAC (minimum alveolar concentration) of isoflurane in baby rats [3,4,6], which the three α2-adrenoceptor subtypes of α2A, α2B, or α2C mediates the neuroprotective effect of Dexmedetomidine was examined in cell culture as well as in an *in vivo* model of neonatal asphyxia.

Dexmedetomidine dose-dependently attenuated neuronal injury [1] (IC_{50} = 83 ± 1 nM) in neuronal-glial co-cultures derived from wild-type mice; contrastingly, Dexmedetomidine did not exert neuroprotection in injured cells from transgenic mice (D79N) expressing dysfunctional α2A-adrenoceptors. Dexmedetomidine also protected against exogenous glutamate induced cell death in pure cortical neuron cultures assessed by flow cytometry and reduced both apoptotic and necrotic types of cell death Dexmedetomidine exhibited dose-dependent protection against brain matter loss *in vivo* (IC_{50} = 40.3 ± 6.1 μg/kg) and improved the neurologic functional deficit induced by the hypoxic-ischemic insult [11].

At the end of the 20th century, Dexmedetomidine was approved as the most recent agent in the Alfa 2 adrenoceptor agonist group and was introduced into clinical practice as a short-term sedative (< 24 hours). Alfa2-Adrenoceptor agonists have several beneficial actions during the perioperative period. They decrease sympathetic tone, with attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery; reduce anesthetic and opioid requirements; and cause sedation and analgesia. They allow psychomotor function to be preserved while letting the patient rest comfortably [15]. The Alfa 2 agonists have a calming effect decreasing sympathetic release. Dexmedetomidine HCl is an Alfa 2-agonist, and it has been for long time used in veterinary facilities. Recently Dexmedetomidine (Dex.) has become available in the US, and approximately 5 years ago it became available for use in the Virginia Commonwealth University - Health System (VCU-HS) operating room. In January 2008, we began to use Dex as an anesthetic adjunct to volatile anesthetic agents. Dexmedetomidine infusion result in reversible sedation, mild analgesia, and mild memory impairment without cardiorespiratory compromise [12]. Dexmedetomidine has been suggested to decrease the amount of inhalation agent required, to prevent possible neurotoxic effects of volatile agents, to smooth emergence, to alleviate post-operative pain and to decrease post-operative nausea and vomiting.

This research is important because it will document whether the use of Dexmedetomidine does, indeed, decrease the required concentration of volatile anesthetic agents, and provide the valuable effects suggested for the recovery period. The goals of this project were to conduct a retrospective comparison of the use of Dex in adult patients in the last two years versus non-use of Dex. in matched historical controls. Dex-identified patient data will be obtained from the "Innovian" computerized anesthesia recordkeeping system, which has been in use at VCU for the past 8 years. The Innovian system includes a search function that allows patients to be selected if they fulfill specified criteria.

Materials and Methods

Patient selection

Ethics approval was obtained from Virginia Commonwealth Hospitals, VCU-HS, IRB. This retrospective chart study was based on the gathered intraoperative drug and volatile anesthetic administration data between 2005 and 2010. The participants were divided into two groups according to time period and dexmedetomidine use. The first group of participants was from before 2008 and none of these patients received dexmedetomidine. This group was identified as control group. The second group of participants was from after 2008 (when the drug was introduced to the formulary) and was identified as the Dex group. The age, gender, body weight and amount of inhaled anesthetic were recorded for each patient. The primary goal was to compare the end respiratory Sevofluorane % in patients

who received Dexmedetomidine with the normal accepted MAC (Minimum Alveolar Concentration) value of Sevofluorane without using Dexmedetomidine. Patients that were excluded were children (< 18 years of age), prisoners, pregnant women, and patients older than 70 years old, as well as all general anesthetic cases where regional block were placed and utilized during the surgery time (epidural infusion, regional single block, spinal, caudal), all cases where infusion of opioids, propofol, or other anesthetic adjunctive were utilized. All the neuro-cases with remifentanil drip were also excluded.

The control group is the one where after the exclusion criteria the patients who did not receive Dex loading dose and infusion during surgeries. Types of surgery were: general abdominal included: Laparoscopic gallbladder removal, appendectomy, and ovary and uterus resection. Facial surgery: Maxilla facial reconstruction, mandible fraction, ENT: Cochlear implant, mastoidectomy. Urology surgery: Prostate resection, cystoscopies, urinary stent implant. The type of surgeries and length were similar between two selected groups. Surgery lengths were from 45 min to 4 hours. Length and type of surgery are factors less relevant and significant to the study aim. The goal has been to demonstrate that the usage of Dex infusion decreases (in any general anesthetic) the percent of Sevofluorane utilization for the entire case. The requirement for written informed consent was waived by the IRB.

In a pilot study (n = 50), the average of the end respiratory sevoflurane (%) in patients without received dexmedetomidine was 1.45 ± 0.3 (Standard Deviation, SD). Power analysis (nQuery Advisor, two group t-test of equal means, unequal n's) showed that a sample size of 50 cases in each group (with dexmedetomidine and without use of dexmedetomidine) would allow the detection of a 0.15 (50% of SD) absolute difference in the % sevoflurane between groups, with $p < 0.05$ and power of 80%.

The amount of Dex used as intravenous was 0.5 to 1 mcg/kg/hr. It was started at 2 - 3 minutes after induction and D/C 20-25 minutes before the end of surgery.

There were N (total) = 130 patients included in the study. There were N (control) = 80 patients in the control group and N (Dex) = 50 in the Dex group.

Statistics

The age was measured in years. Sex was defined as being male or female. Body weight was measured in kilogram (kg) and amount of inhaled anesthetic was defined as percentage of end expiratory sevoflurane, entirely calculated by the Innovian program. Normality was assessed with a normal quantile plot. Representativeness was presumed. A significance level $\alpha = 0.05$ was used for all analyses. SPSS statistical software was used for statistical computations.

Results

All patients' data was analyzed according to the available demographic variables of age, sex and body weight. Overall, the data appear to be normally distributed. This was determined by observing the data in a normal quantile plot. Because the data are normally distributed, the best measure to describe the continuous data is mean and standard deviation. The average age, body weight, sex and % inhaled sevoflurane of patients in the study are shown in table 1.

The end expiratory sevoflurane in percentage (%) was observed significantly less in Dex group (0.942 ± 0.046; mean ± standard error; SE; confidential interval, 95% CI: 0.849 - 1.035) when compared with the control group (1.444 ± 0.028, CI: 1.388 - 1.499). There was no significant difference in age between two groups. The average age in year of control group was 43 ± 1.708 (CI: 39 - 46) compared with 48 ± 2.270 (CI: 43 - 52) in Dex group ($p > 0.05$). Also, there was no significant difference in patient's body weight in kilogram between two groups. The average body weight in control group was 82.2 ± 2.555 (CI: 77.1- 87.3) compared with 86.6 ± 3.458 (CI: 79.7 - 93.6) in Dex group ($p > 0.05$) (Table 1 and figure 1).

N = 130	Control (n = 80)	With Dexmedetomidine (n = 50)
End Exp Sevoflurane (%)	1.444 ± 0.028 (CI 1.388 - 1.499)	0.942 ± 0.046 ** (CI 0.849 - 1.035)
Age (year)	43 ± 1.708 (CI 39 - 46)	48 ± 2.270 (CI 43 - 52)
Body weight (kg)	82.209 ± 2.555 (CI 77.123 - 87.295)	86.640 ± 3.458 (CI 79.691 - 93.589)

Table 1: *Comparison of end of expiratory sevoflurane in GA.*

*GA: General Anesthesia. Value = Mean ± SE; Comparing the value of end expiratory Sevoflurane between control and treated group, the value of Dexmedetomidine group is significantly lower than that in control group (F = 97.5, **p < 0.001). There is no significant difference compared with age or body weight between two groups p > 0.05).*

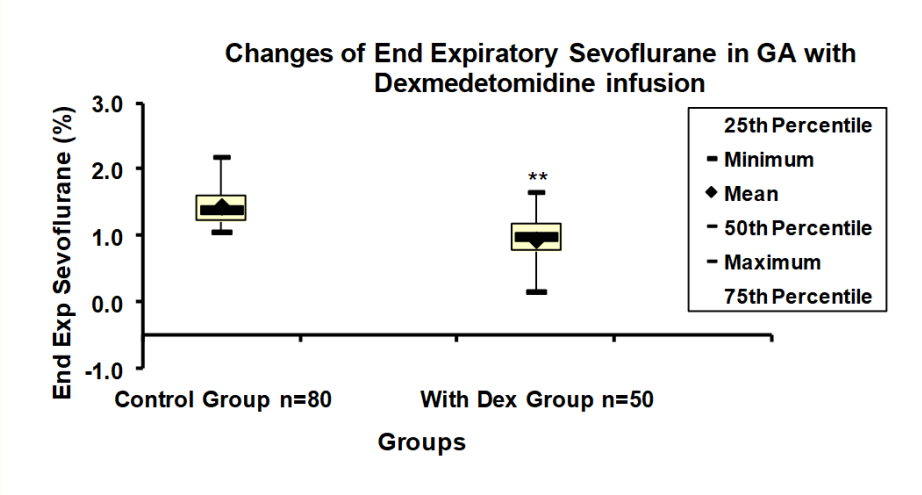

Figure 1: *Box plot of End expiratory sevoflurane. Group mean of end expiratory Sevoflurane with dexmedetomidine was significantly lower than the control group (0.942 ± 0.046 vs. 1.444 ± 0.027; t = 1.979, ** p < 0.001).*

Further, there was no sex gender difference between male and female in end expiratory sevoflurane (%) within the control group (1.437 ± 0.039, CI: 1.358 - 1.5161 vs. 1.451 ± 0.040 CI: 1.369 - 1.532) or Dex group (0.965 ± 0.055, CI: 0.854 - 1.077 vs. 0.912 ± 0.080 CI: 0.745 - 1.079). However, when comparing the end expiratory sevoflurane in male between control and Dex groups, a significant less end expiratory sevoflurane in Dex group was observed (0.965 ± 0.055 vs. 1.437 ± 0.039; p < 0.001) and the same result was also seen in female patients as comparison between groups (0.912 ± 0.080 vs. 1.451 ± 0.040; p < 0.001; Table 2 and figure 2). There was no sex gender difference between male and female in age and body weight (Table 2, figure 3 and 4).

Total n = 130	Control (n = 80)		With Dexmedetomidine (n = 50)	
Sex	**Male (n = 39)**	**Female (n = 41)**	**Male (n = 28)**	**Female (n = 22)**
Age (year)	40.64 ± 2.589	45.15 ± 2.221	46.82 ± 2.953	48.91 ± 3.597
Weight (kg)	85.11 ± 3.897	79.45 ± 3.325	93.18 ± 4.442	78.32 ± 5.023
End Exp Sevo (%)	1.437 ± 0.039	1.451 ± 0.040	0.965 ± 0.055**	0.912 ± 0.080**

Table 2: *Summary of end expiratory sevoflurane among sex, age and body weight in GA.*

*Value = Mean ± SE; **p < 0.001 (as compared with controls in the same sex subgroups).*

There is no statistic significant difference in ages and body weights among the groups.

When compared the value of end expiratory sevoflurane between male and female groups either within control group or Dex group, there is no significant difference (p > 0.05).

There is a significant difference between control and Dex group as compared the value of end expiratory sevoflurane in male or female sub-groups (1.437 ± 0.039 vs. 0.965 ± 0.055, p < 0.001 between male groups; 1.451 ± 0.040 vs. 0.912 ± 0.080, p<0.001 between female groups).

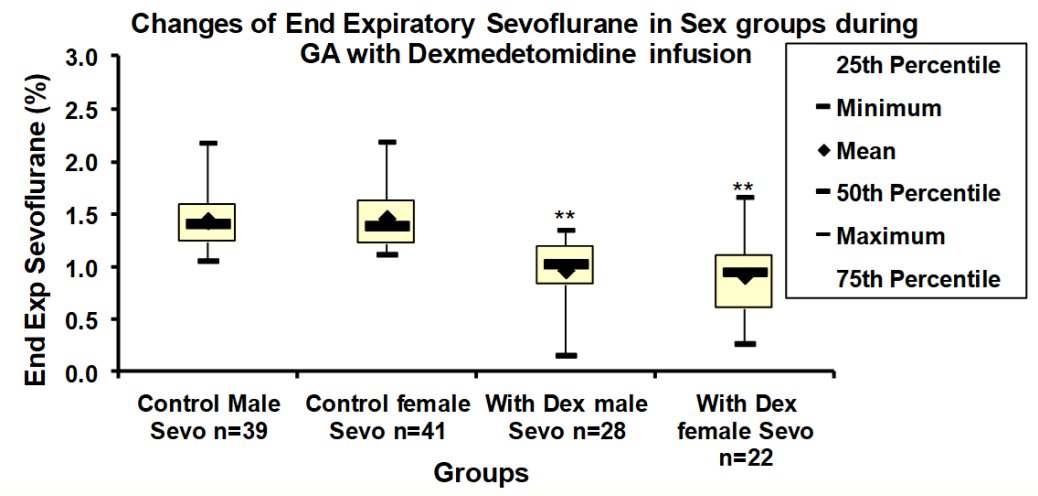

Figure 2: *Box plot shows the mean of the end expiratory sevoflurane with dexmedetomidine in different sex groups. There are no significant changes of the end expiratory sevoflurane when comparing male and female values within the same group (control group or Dex group). But there are significant changes of the end expiratory Sevoflurane between control and dexmedetomidine treated group (**p < 0.001, $F_{(3,129)}$ = 32.276, table 2).*

Discussion

Dexmedetomidine is a highly specific α_2-adrenoreceptor agonist with sedative, analgesic, and anesthetic-sparing effects [13,14]. The dose suggested is 0.5 - 1.mcg/Kg/hr IV infusion and as the data available on dexmedetomidine mainly relates to its use as an anesthetic and opioid- sparing agent at these doses and when used in combination with other anesthetic, sedative, and analgesic agents. We anticipated that the patient treated with dexmedetomidine would require a sensible decrease of Sevoflurane usage. The normal MAC of sevoflurane in adult humans is reported in the literature to be 2.0%. This amount of inhalational agent will prevent 50% of patients from moving in response to surgical incision.

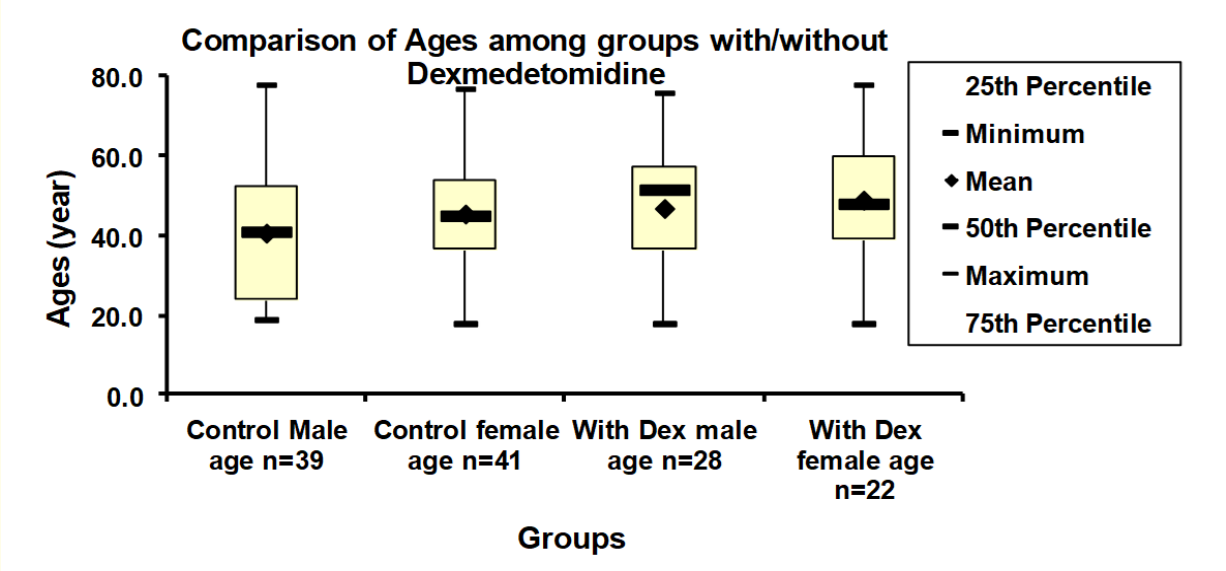

Figure 3: *Box plot shows the mean of the age in groups.*
There is no statistic significant difference in ages among groups (p = 0.193; $F_{(3,129)}$ = 1.60).

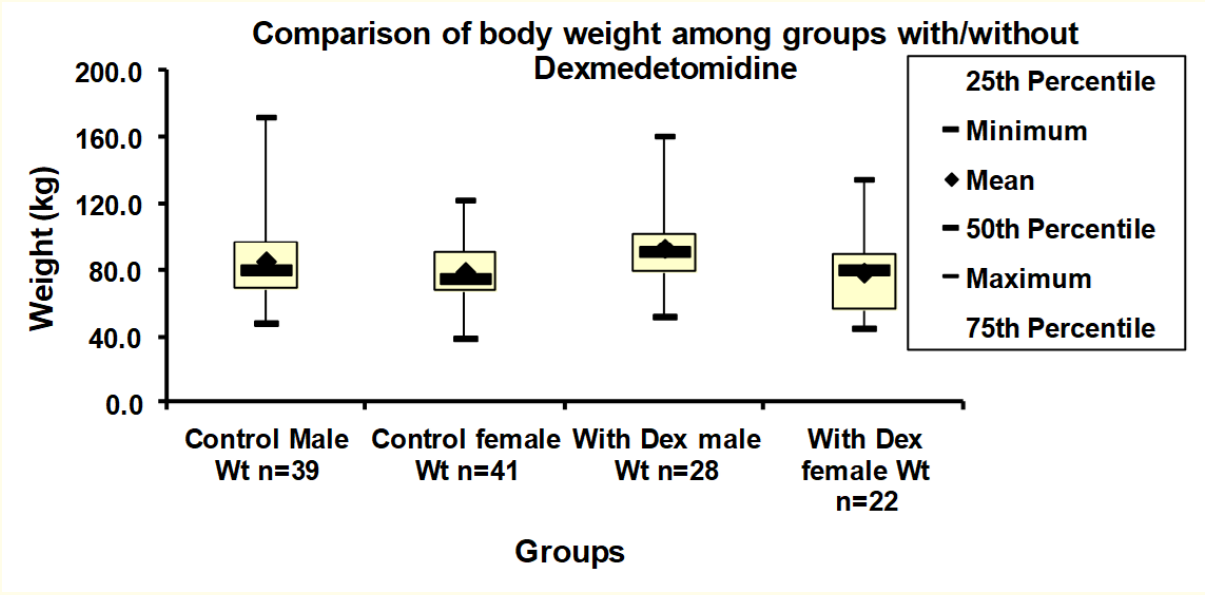

Figure 4: *Box plot shows the mean of the body weight (kg) in groups.*
There are no significant changes of weight (kg) in groups (p = 0.064; $F_{(3, 129)}$ = 2.447).

In those patients who were given Dexmedetomidine we studied the percent of end respiratory usage of sevoflurane and calculated a normal distribution were significantly less than those without given dexmedetomidine.

The study showed that dexmedetomidine may be used as an adjuvant together with intravenous and inhalation anesthetic agents. The present retrospective study demonstrated that and 0.5 - 1.0 -$\mu g \cdot kg^{-1} \cdot h^{-1}$ infusions of dexmedetomidine (small and moderate doses) produced significant reduction of Sevoflurane during General Anesthesia. Cardiovascular stability and respiratory function were both well maintained.

An initial computerized patient query was generated and identified that in those patients receiving a Dexmedetomidine load and infusion during the GA had a sensibly decreased requirement of volatile anesthetic agent between 47 - 53%. Dexmedetomidine, when infused during General Anesthesia may be considered an excellent adjuvant, helping to decrease the percent usage of Sevoflurane. Dexmedetomidine infusions resulted effective as anesthetic adjuvant without cardiorespiratory compromise.

We did not note any complications associate with its usage, as increase pain and, or vomiting.

Actually, clinically we observed our patients being in a very comfortable status in Recovery room. Because of these positive effects noted clinically post operatory, we would like to continue this study and further analyze the same patients charts looking on post op pain and antiemetic medications requirement in the recovery room, both in the Dex group vs. the non Dex Group.

In addition, we will review the future literature on CNS anesthetic toxicity to learn if any decrease of inhalation agents and narcotics use would have a less impact on the CNS anesthesia toxicity. If it will be the case the usage of Dexmedetomidine as General anesthetic adjuvant would make a great difference and lesser potential CNS toxicity consequences of a traditional General anesthetic.

Conclusion

In conclusion, among patients that receive dexmedetomidine, there is a significantly lower amount of inhaled sevoflurane that has been used. The relationship between dexmedetomidine use and the amount of inhaled sevoflurane is not affected by age, weight and gender.

We would like to continue this study looking at the recovery period required for these patients, total usage of narcotics, antiemetics, and level of calmness post- operatively compared to a group of patient anesthetized with conventional anesthetic techniques. We believe that the intra operatory dexmedetomidine infusion helps to decrease the sevoflurane utilization, this property could be easily assumed for the other inhalation agents, and maybe decrease the potential toxicity of conventional General Anesthesia (GA).

Authors Contribution

All author contributed equally.

Conflict of Interest

The author has no conflict of interest to declare.

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