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Evaluation of the Effect of Dexmedetomidine on the Suppression of the Adrenergic Response to Laryngoscopy and Intubation

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Abstract

Objectives: Dexmedetomidine is a potent agonist of α-2 receptors with sympatholytic, sedative and analgesic properties. Direct laryngoscopy and endotracheal intubation are associated with hemodynamic changes due to reflex sympathetic discharge; causing hypertension, tachycardia and arrhythmias. Several drugs have been used to control this haemodynamic response however, none harmless.

Materials and methods: Sample of 60 patients, divided into two groups, the DM1 group received a dexmedetomidine dose of 0.5 µg/kg, and the DM2 group received a dose of 1 µg/kg of the same drug diluted in 100 cc of solution, which it was administered in 10 min. The hemodynamic variables (HR, SBP, DBP and MAP) and sedation during two periods were verified.

Results: In the first stage there was a decrease in the SBP in the DM1 group of 9 and 11% with respect to the baseline at 5 and 10 min (p=0.8443 and p=0.1650). Similar trends were found with the DBP and the PAM. In the second stage, SBP, DBP and MAP showed statistically significant differences.

Conclusion: Dexmedetomidine at an intravenous loading dose of 0.5 µg/kg presents hemodynamic stability before and after intubation, with no evidence of adverse effects.

Keywords: Dexmedetomidine; Laryngoscopy; Intubation; Response; Suppression

Introduction

The effective use of sedative, hypnotic and analgesic agents is part of the comfort and safety of the patient. The choice of agent or its appropriate combination is essential to alleviate harmful stimuli, stress and anxiety, while reducing the risk of adverse events [1].

Dexmedetomidine is a potent and selective α-2 adrenergic agonist with sympatholytic, sedative, amnesic and analgesic properties [2,3]. Initially it was used for sedation in intensive care units. However, its sedative, analgesic and anxiolytic effects without impaired ventilatory function allow its use in surgery as an intravenous anesthetic [4].

It provides neurovegetative protection, and has predictable cardiovascular and respiratory effects in a dose-dependent manner. Likewise, it allows reducing the use of analgesics for the control of postoperative surgical pain, providing sedation with preservation of memory, suppression of tremor and improvement of postoperative recovery [5,6].

Dexmedetomidine blocks the deleterious adrenergic response in the perioperative period, provides low potency analgesia and has a stable cardiovascular profile applied at doses that are still to be adequately defined [4].

It should be taken into account that direct laryngoscopy and endotracheal intubation after the induction of anesthesia is associated with hemodynamic changes due to reflex sympathetic discharge caused by epipharyngeal and laryngopharyngeal stimulation. This increase in sympathetic-adrenal activity can cause hypertension, tachycardia and arrhythmias, which are often unpredictable [7,8].

Hypertension and transient tachycardia are probably not deleterious in healthy individuals, but they are deleterious in hypertensive patients with myocardial insufficiency and/or cerebrovascular diseases [9-11].

The magnitude of the response is proportional to the strength and duration of laryngoscopy. The elevation of blood pressure typically begins within five seconds of laryngoscopy, with peaks in 1-2 min and returns to control levels at 5 min [12]. Reid and Brace in 1940 were the first to report the circulatory responses to tracheal and laryngeal stimulation in an anesthetized man [13].

A variety of drugs have been used to control the hemodynamic response caused by laryngoscopy and orotracheal intubation, tales such as beta blockers, calcium channel blockers, alpha2 agonists and opioids. However, no modality lacks drawbacks and limitations. It has been shown that dexmedetomidine reduces the induction dose of intravenous anesthetics and intraoperative opioids and the volatile anesthetic requirements for maintenance of anesthesia. In addition, it has been shown that it decreases the perioperative levels of catecholamines and favors hemodynamic stability [12].

Multiple studies have been published in relation to the many applications of dexmedetomidine in the field of anesthesia: Studies like those of Sukhminder et al. [14], like Tanskanen et al. [15] and Keniya et al. [16], showed the capacity of intravenous dexmedetomidine in reducing the dose of opioids and anesthetics for the attenuation of the hemodynamic response during laryngoscopy and orotracheal intubation.

On the other hand, Gulabani et al. [17] described the superiority of dexmedetomidine at 1 µg/kg over 0.5 µg/kg and lidocaine at 1.5 mg/kg in terms of the decrease in sympathetic response after orotracheal intubation.

Srivastava et al. [18] compared dexmedetomidine versus esmolol in neurosurgical patients and found that dexmedetomidine was more effective than esmolol in attenuation to the hemodynamic response to laryngoscopy and intubation in this group of patients.

Sarkar et al. [19] on the other hand, did not find differences when comparing the infusion of dexmedetomidine with clonidine for this purpose

Menda et al. [20] concluded that it can be used safely in patients undergoing myocardial revascularization who receive beta-blockers.

Yildiz et al. [21] evaluated the effect of a single dose (preinduction) of dexmedetomidine 1 µg/kg on the cardiovascular response during laryngoscopy and endotracheal intubation, the need for anesthetic agents and perioperative hemodynamic stability, demonstrating that with the use of dexmedetomidine there was a progressive increase in sedation, suppression of hemodynamic response during laryngoscopy, and reduction of opioid and anesthetic requirements; In addition, there was a decrease in blood pressure and heart rate, as well as the recovery time after surgery.

Even its efficacy has been evaluated by other routes such as intranasal and in pediatric patients with satisfactory results as in the study by Wang et al. [11].

Likewise, Fan et al., Demonstrated its effectiveness even for an adequate and smooth extubation after otologic surgery [12].

However, studies such as that of Laha et al. [2] in which the effect of a single intravenous dose of dexmedetomidine preinduction of 1 µg/kg was evaluated, did not abolish the cardiovascular response to tracheal intubation.

Consequently, the importance of this research lies in the possibility of comparing different doses of dexmedetomidine in the adequate protection to the hemodynamic response to laryngoscopy and orotracheal intubation.

Materials and Methods

Prior approval of the ethics committee of the "Méndez Gimón" polyclinic and the "Dr. Miguel Pérez Carreño" central hospital in Caracas; the consent of the patients participating in the investigation was obtained; A multicentre, prospective, comparative, double-blind, randomized clinical study was conducted, which included a total of 60 patients who met the inclusion criteria.(American Society of Anesthesiologists (ASA) Physical Status 1 in the age group of 18–65 years of either sex, posted for elective surgeries under general anaesthesia). Patients who were physically dependent on narcotics, those with a history of bronchial asthma, drug or alcohol abuse, known drug allergy to either clonidine or dexmedetomidine, cerebrovascular,

neurologic, respiratory or ischemic heart disease (history of angina, previous myocardial infarction) and renal and hepatic dysfunction were excluded from the study. The study protocol was carried out between July and December 2016.

All the included patients were randomized into two groups: Group dexmedetomidine 1 (DM1) and Group dexmedetomidine 2 (DM2) by assigning a sealed envelope where the dose of the drug to be administered was specified with the letters "A" and " B ", according to the coding specified in a sealed envelope prepared by an Anesthesiologist Physician who collaborated in the research that was delivered and maintained at the Headquarters of the Anesthesiology Department of the research headquarters until the completion of the collection phase data. In the area of pre-anesthesia, patients belonging to the DM1 group received a dose of dexmedetomidine of 0.5 µg/kg, and the patients belonging to the DM2 group received a dose of 1 µg/kg of the same drug diluted in 100 cc of 0.9% NaCl solution, which was administered in a period of 10 min. Both the patient and the person responsible for administering the medication were completely unaware of its dosage.

In this first phase of the protocol, systolic (SBP), diastolic (DBP) and mean (MAP) blood pressure were recorded; heart rate (HR) and level of sedation through the application of the Ramsay sedation scale [22] at the beginning, at 5 and 10 min after infusion. Once this first phase is completed, the patient is transferred to the operating room where is monitored according to the protocol of the American Society of Anesthesiology (ASA). A standardized induction with Lidocaine 20 mg was performed to attenuate the irritant effect of propofol, propofol at a dose of 2 mg/kg and rocuronium bromide at a dose of 0.6 mg/kg.

In this second phase of the protocol, systolic, diastolic and mean blood pressure were recorded, as well as the heart rate prior to laryngoscopy, immediately after intubation and at minute 1 and 3 of said procedure by the anesthesiologist in charge of the case who was blind to the dose of the drug administered. The maintenance of the anesthetic was performed by the criteria of each anesthesiologist.

Patients who presented cardiac frequencies equal to or less than 40 beats per minute or equal to or less than 50 beats per min with hemodynamic compromise received atropine 0.5 mg as required and those who presented a decrease in blood pressure greater than 30% received a dose of rescue with ephedrine of 100 µg/kg.

Statistical treatment

The data was systematized in a master table in Microsoft ®Excel and then presented through descriptive statistical techniques in contingency tables. The quantitative variables such as age and Body Mass Index were presented in means and standard derivation, and the qualitative variables such as sex and physical status ASA and Ramsay Scale were presented in frequency and percentages. The statistical analysis of the averages of the percentage variations of the hemodynamic variables such as systolic, diastolic and mean blood pressure as well as heart rate was made from the hypothesis test for difference between means (student t). For these purposes, P values lower than 0.05 (P<0.05) were adopted as statistical significance level.

Results

A total of 60 patients were studied, 30 for each group, all statistically comparable with respect to age, sex, body mass index and ASA physical status (Table 1).

Variables	0,5 µg/kg		1,0 µg/kg	
n	30		30	
Age (*)	42 ± 14		36 ± 11	
BMI (*)	24,7 ± 3,7		23,4 ± 2,4	
Gender				
Male	13	43,3%	17	56,7%
Female	17	56,7%	13	43,3%
ASA				
I	11	36,7%	16	53,3%
II	19	63,3%	14	46,7%
Age: p=0,050; BMI: p=0,123; Gender: p=0,302; ASA: p=0,194; (*) mean ± standard deviation				

Table 1: Characteristics of the sample according to groups.

	0,5 µg/kg		1,0 µg/kg		
First time					
Measurements	**Mean**	**DE**	**Mean**	**DE**	**p**
Basal	132	17	125	15	-
5 min	125	17	115	16	-
Variation (%)	-9	-	-8	-	0,8443
10 min	122	19	115	15	-
Variation (%)	-11	-	-8	-	0,1650
Second time					
Preintubation	114	18	115	14	-
Postintubation	139	20	123	13	-
Variation (%)	24	-	8	-	0,0002
Postintubation 1 min	132	20	119	14	-
Variation (%)	21	-	6	-	0,0011
Postintubation 3 min	124	19	117	13	-
Variation (%)	18	-	7	-	0,0025

Table 2: Variation of the SBP according to groups.

In the first stage of the study, the DM1 group presented a decrease in SBP of 9 and 11% compared to baseline at 5 and 10 min respectively of the start of the dexmedetomidine infusion; while in the DM2 group such variation was 8% both at 5 and 10 min, which was not statistically significant when compared to the DM1 group with a P=0.8443 at 5 min and P=0.1650 at 10 min (Table 2). The same happened with the DBP with a decrease at 5 and 10 min of 3 and 5% for the DM1 group and of 6 and 8% for the DM2 group with a P=0.4073 at 5 min and P=0.4426 at 10 min (Table 3). The MAP presented a similar behavior with a variation of its basal levels of 4 and 7% for the DM1 group and 6

and 7% for the DM2 group at 5 and 10 min with a P=0.4538 at 5 min and P=0.8664 at 10 min (Table 4).

This trend was maintained when measuring the variations of HR, showing a decrease of 11 and 13% for the DM1 group and of 9 and 15% for the DM2 group with a P=0.3638 at 5 min and P=0.4707 at 10 min respectively (Table 5).

In the second stage of the study, the SBP, DBP and MAP of both groups presented statistically significant differences. In the case of SBP, the percentage of variation with respect to the parameters measured prior to intubation was 24% compared to the parameters recorded immediately after endotracheal tube placement, 21% at min and 18% at 3 min postintubation in the DM1 group. In the case of the DM2 group, the variation upwards was 8, 6 and 7% respectively, which when compared to the DM1 group presents P=0.0002 immediately after intubation, P=0.0011 per min, P=0.0025 after 3 min (Table 2).

	0,5 µg/kg		1,0 µg/kg		
First time					
Measurements	**Mean**	**DE**	**Mean**	**DE**	**p**
Basal	77	12	77	13	-
5 min	74	11	71	13	-
Variation (%)	3	-	6	-	0,4073
10 min	72	10	70	11	-
Variation (%)	5	-	8	-	0,4426
Second time					
Preintubation	67	11	70	12	-
Postintubation	85	13	75	11	-
Variation (%)	29	-	9	-	0,0001
Postintubation 1 min	78	13	73	11	-
Variation (%)	21	-	6	-	0,0019
Postintubation 3 min	73	12	70	10	-
Variation (%)	12	-	3	-	0,1089

Table 3: Variation of the DBP according to groups.

The DBP presented a higher percentage of variation for the first two times of this second stage, being for the DM1 group of 29 and 21% against 9 and 6% of the DM2 group with a P=0.0001 and P=0.0019 respectively (Table 3). And with regard to MAP, there was an increase of 26 and 18% in the DM1 group and of 8 and 5% for the DM2 group with a P=0.0001 immediately after intubation and P=0.0041 per min (Table 4). At three minutes post-intubation there were no statistically significant differences between both groups in terms of DBP and MAP.

There were only statistically significant differences in the variations of the heart rate at the time of immediate intubation with an increase of 21% for the DM1 group and only 10% for the DM2 group, which represents a P=0.0043 (Table 5).

Regarding the level of sedation established through the application of the Ramsay Scale, 5 min after the start of the dexmedetomidine infusion, 83.3% and 13.3% of the patients were placed on the scale in

Ramsay 2 and 3 for the DM1 group respectively against 63.3% and 36.7% of the DM2 group with a P=0.079. However, for the 10 min after the infusion began, 76.7% of the patients in the DM2 group were already located in Ramsay 3 according to the scale with 3.3% of them classified as Ramsay 4; while for the DM1 group the greater percentage of its members 60% were still located in Ramsay 2, establishing a statistical significance with P=0.005 (Table 6).

	0,5 µg/kg		1,0 µg/kg		
First time					
Measurements	**Mean**	**DE**	**Mean**	**DE**	**p**
Basal	95	13	93	13	-
5 min	91	12	86	13	-
Variation (%)	4	-	6	-	0,4538
10 min	88	13	85	12	-
Variation (%)	7	-	7	-	0,8664
Second time					
Preintubation	82	13	85	12	-
Postintubation	102	15	92	11	-
Variation (%)	26	-	8	-	0,0001
Postintubation 1 min	96	14	89	12	-
Variation (%)	18	-	5	-	0,0041
Postintubation 3 min	90	13	86	10	-
Variation (%)	12	-	2	-	0,0652

Table 4: Variation of the MAP according to groups.

	0,5 µg/kg		1,0 µg/kg		
First time					
Measurements	**Mean**	**DE**	**Mean**	**DE**	**p**
Basal	77	15	78	12	-
5 min	67	12	71	15	-
Variation (%)	11	-	9	-	0,3638
10 min	67	14	66	19	-
Variación (%)	13	-	15	-	0,4707
Second time					
Preintubation	67	13	69	13	-
Postintubation	80	14	75	11	-
Variation (%)	21	-	10	-	0,0043
Postintubation 1 min	77	16	73	11	-
Variation (%)	15	-	7	-	0,0625
Postintubation 3 min	73	16	70	12	-

| Variation (%) | 9 | - | 3 | - | 0,1750 |

Table 5: Variation of the HR according to groups.

	0,5 µg/kg		1,0 µg/kg	
RAMSAY	**n**	**%**	**n**	**%**
Basal				
RAMSAY 1	3	10,0	4	13,3
RAMSAY 2	27	90,0	25	83,3
RAMSAY 3	0	0,0	1	3,3
RAMSAY 4	0	0,0	0	0,0
RAMSAY 5	0	0,0	0	0,0
RAMSAY 6	0	0,0	0	0,0
5 min				
RAMSAY 1	1	3,3	0	0,0
RAMSAY 2	25	83,3	19	63,3
RAMSAY 3	4	13,3	11	36,7
RAMSAY 4	0	0,0	0	0,0
RAMSAY 5	0	0,0	0	0,0
RAMSAY 6	0	0,0	0	0,0
10 min				
RAMSAY 1	0	0,0	0	0,0
RAMSAY 2	18	60,0	6	20,0
RAMSAY 3	12	40,0	23	76,7
RAMSAY 4	0	0,0	1	3,3
RAMSAY 5	0	0,0	0	0,0
RAMSAY 6	0	0,0	0	0,0
Basal: p=0,543; 5 min: p=0,079; 10 min: p=0,005				

Table 6: Changes of RAMSAY according to groups.

Discussion

Laryngoscopy and endotracheal intubation are considered the most critical events during general anesthesia, since they provoke a marked but transient sympathetic response, which may not be tolerated by patients with comorbid, generating cardiovascular complications [8]. The hemodynamic response begins in a matter of seconds after direct laryngoscopy and increases with the passage of the endotracheal tube. The response begins within 5 s of the laryngoscopy, with peaks in 1-2 min and returns to normal levels in 5 min [16]. Alpha-adrenergic drugs attenuate the possible cardiovascular deleterious effects during anesthetic induction [12]. Analgesia, sedation, anxiolysis, sympatholysis and the control of exaggerated hemodynamic responses with the administration of dexmedetomidine have been extensively studied, and are mediated by the presynaptic activation of the α-2A

receptors in the locus caeruleus, inhibiting the release of noradrenaline and causing sedation and hypnosis as well as acting on alpha 2 adrenergic receptors located in postsynaptic terminals in the central nervous system, which causes a decrease in sympathetic activity (decrease in plasma concentrations of adrenaline and noradrenaline) with an increase in vagal activity [17,18]. In this study, different doses of dexmedetomidine (0.5 μg/kg and 1 μg/kg) were compared to evaluate the effectiveness in the suppression of the adrenergic response to laryngoscopy and intubation.

In the present study, the dose of 1 mcg/kg of dexmedetomidine attenuated the hemodynamic response to laryngoscopy and endotracheal intubation. The dose of 0.5 mcg/kg was not sufficient because of a greater than 20% increase in systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate after endotracheal intubation. Smitha et al. They compared the effect of 0.5 and 1 mcg/kg of dexmedetomidine on the attenuation of the stress response. They found that dexmedetomidine 1 mcg/kg was more effective than dexmedetomidine 0.5 mcg/kg in the control of hemodynamic responses to tracheal intubation [19]. These results were correlated with the findings in our study. Neil et al. studied dexmedetomidine at doses of 0.5 and 0.75 μg/kg and concluded that the dose of 0.75 μg/kg completely attenuated the response to haemodynamic stress at laryngoscopy and endotracheal intubation, compared to 0.5 μg/kg. Both doses of dexmedetomidine lacked significant adverse effects [20].

Another relevant observation is the patients' state of consciousness when presenting mostly a Ramsay 2 in all the different study times in the DM1 group, however, in the DM2 group, although Ramsay 2 patients were present at the baseline time and at 5 minutes, it was observed that 10 min after the administration of dexmedetomidine, a high percentage of these patients had a Ramsay 3 and even 4. Dexmedetomidine can lead to cardiovascular depression, causing bradycardia and hypotension [21,22]. However, in our study there were no adverse events related to the administration of the drug. It can be attributed to the slow bolus infusion in our patients. Like Sulaiman et al. [12] the dose of dexmedetomidine in the DM1 group was 0.5 mcg/kg in an infusion administered in 10 min, presenting an adequate hemodynamic response, without the evidence of bradycardia that warranted the use of atropine. .

The pharmacology of dexmedetomidine has proven advantages for use in the context of critical medicine and anesthesiology, but lately there have been benefits in contexts such as pain medicine, pediatrics and gynecology, where, both in infusion and in boluses, it achieves sedate adequately, that are a depression of consciousness combined with an adequate response to stimulation during procedures. The advantage of a rapid onset and a short duration of action make it an appropriate agent for the intensive care unit, in pediatric or adult patients and invasive or non-invasive procedures [15].

There were certain limitations in this study, in which we can mention the sample size, the non-inclusion of patients with ASA III-IV physical status. Therefore we urge to perform studies with a larger sample of patients as well as the use of an intermediate dose of dexmedetomidine, for example 0.75 μg/kg.

Conclusion

Dexmedetomidine at an intravenous loading dose of 0.5 μg/kg presents hemodynamic stability pre- and post-intubation, with no evidence of transoperative adverse effects. The administrations of a single intravenous dose of dexmedetomidine of 1 μg/kg resulted in a significant attenuation of the increase in heart rate, systolic blood pressure and diastolic blood pressure and mean arterial pressure, upto 3 min post-intubation.

Conflict of Interests

The manuscript was prepared and reviewed with the participation of all authors, who declared that there is no conflict of interest that jeopardizes the validity of the results presented.

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