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Original Research Article

Benefits of IV Clonidine in Premedication on Sympathetic Hyperactivity Related to Surgical Incision

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Abstract: ***Background:*** Clonidine stimulates the α2 receptors of the sympathetic nervous system which have a negative presynaptic feedback effect inducing a reduction in the secretion of adrenaline and noradrenaline. The main objective of our study was to evaluate the beneficial effects of clonidine on the hemodynamic response to surgical incision. ***Patients and Methods:*** This was a prospective, single-center, randomized, single-blind clinical trial that took place over a period of 4 months in the anesthesia department of the Essos hospital center in Yaoundé. All patients over the age of 18, ASA I or II, admitted for scheduled surgery were included in the study. The patients were randomly divided into two groups by drawing lots: group A (clonidine) and group B (non-clonidine). All patients in group A received clonidine IV (3µg/kg). Heart rate, systolic blood pressure, and diastolic blood pressure were observed at different times during the surgical procedure. ***Results:*** During the study period, 35 met the inclusion criteria: 20 patients for group A and 15 patients for group B. The average age was 34 years. The sex ratio was in favor of the male gender in both groups: 2.3 in group A and 2.7 in group B. ASA class 1 was the most represented (74.3%); visceral surgery most performed of all specialties in the two groups 55% (n=11) for group A and 53% (n=8) for group B. The systolic and diastolic arterial pressure curves are parallel in the two groups. There is a slight variation in PAS and PAD in group A "clonidine" compared to the baseline values. A tendency towards systolic arterial hypertension is observed in the "non-clonidine" control group. The heart rate remains stable in group A, while tachycardia is observed at the same time for the participants in group B. ***Conclusion:*** Clonidine is an alpha 2 adrenergic receptor agonist which makes it possible to limit the hypersecretion of catecholamines, potentially deleterious for the fragile patient, at the surgical incision.

Keywords: Benefits of clonidine, premedication, surgical incision.

INTRODUCTION

The surgical incision, a very painful operating time, induces significant physiological changes affecting particularly the circulatory, respiratory, endocrine, metabolic and immune functions [1-3]. This physiological response is characterized by activation of the sympathetic system and the hypothalamic-pituitary axis associated with changes in secretions and tissue effects of many peripheral hormones [1, 2]. The reaction can be poorly tolerated in some cases and lead to disturbances in the regulation of metabolism, arterial hypertension, heart rhythm disorders or visceral failure [4]. Adrenaline, noradrenaline and dopamine play an essential role in the immediate response to the tissue aggression caused by the surgical incision, because their secretions are the earliest and their actions are multiple. The peak plasma concentration of catecholamines lasts a maximum of 24 to 48 hours after the onset of the surgical aggression [5, 6]. After maximum stimulation comparable to a surgical incision, plasma concentrations of adrenaline reach 550 to 8,000 times the physiological values and those of noradrenaline 10 to 50 times [7]. These hormonal changes contribute to increased heart rate and myocardial contractility, cardiac and respiratory output, and blood pressure. Metabolically, catecholamines increase gluconeogenesis, glycogenolysis, lipolysis and muscle

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protein breakdown. The main objective of our study was to evaluate the beneficial effects of IV clonidine on the hemodynamic response to surgical incision.

PATIENTS AND METHODS

This was a prospective, single-center, randomized, single-blind clinical trial that took place over a period of 4 months (from February to May 2016) in the anesthesiology department of the Essos hospital center. This is a high reference hospital, located in the capital of Cameroon. After approval by the ethics committee, the data was collected anonymously and used for exclusively scientific purposes. All patients over the age of 18, ASA I or II, according to the American Society of Anesthesiologists, scheduled for surgery under general anesthesia with orotracheal intubation were included in the study. Pregnant women and surgical emergencies were excluded. Premedication was non-medication for all study participants. The patients were randomly divided into two groups by drawing lots: group A (clonidine) and group B (non-clonidine). All patients in group A received clonidine (3µg/kg) intravenously diluted in 250mL of isotonic saline 10 minutes before anesthetic induction. Intravenous (IV) induction of general anesthesia was standard, after 5 minutes of preoxygenation (FiO2 100%): fentanyl (3µg/kg), propofol (3mg/kg) and vecuronium (0.1mg/kg). Tracheal intubation was performed with an appropriately sized cuffed tracheal tube. Maintenance of anesthesia was provided with isoflurane, re-injections of fentanyl and vecuronium as needed for surgery. Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were observed at the following times: At the pre-anaesthetic consultation (t1), at installation on the operating table (t2), 5 minutes after the clonidine/placebo infusion (t3), at the 1st, 3rd and 5th minute after the surgical incision (which corresponded to the times: t7, t8 and t9 respectively). Noninvasive blood pressure and heart rate were monitored using an electronic device. Emergency drugs were atropine 0.5 mg IV if heart rate was less than 50/minute, or ephedrine titrated 5 mg IV if systolic blood pressure fell more than 25% of its value at baseline installation on an operating table. The primary endpoints were the effectiveness of micro-infusion administration of clonidine for 10 minutes in attenuating sympathetic hyperactivity (heart rate, diatolic blood pressure, and systolic blood pressure) induced by the surgical incision. The secondary endpoint was to look for the adverse effects of this procedure. The patients involved in the data collection were not aware of the distribution of the groups, only the anesthetist in charge of the procedure was informed. Data entry and analysis were done using Microsoft Word 2007, Microsoft Excel 2007, EPI Info 7 and SPSS16.0 software. A p-value less than 0.05 was considered as statistical significance.

RESULTS

During the study period, 562 patients were operated on in the operating area of the Essos hospital center; 35 met the inclusion criteria: i.e. 20 patients for group A and 15 patients for group B. The average age was 34 years with extremes ranging from 18 to 75 years. The sex ratio was in favor of the male gender in both groups: 2.3 in group A and 2.7 in group B. Table 1 presents the socio-demographic and clinical characteristics of the study population.

Table 1: Socio-demographic characteristics of the study population

Variables	Group A (n=20)	Group B (n=15)	Total
Age group (year)			
[19-35]	7	5	12
[35-50]	8	6	14
[50-65]	4	4	8
[65-80]	-	-	-
>80	1	-	1
Total	**20**	**15**	**35**
Weight			
Nomal	13	9	22
overweight	5	3	8
Obese	2	3	5
Total	**20**	**15**	**35**
Gender			
Male	6	4	10
Female	14	11	25
Total	**20**	**15**	**35**
ASA classification			
I	16	10	26
II	4	5	9
Total	**20**	**15**	**35**

ASA class 1 was the most represented (74.3%), the most common visceral surgery of all specialties in the two groups (table 2) i.e. 55% (n=11) for group A and 53% (n=8) for group B.

Surgical specialty	Group A		Group B	
	n	%	n	%
visceral	11	55	8	53
Traumatology	8	40	4	26.7
ENT surgery	1	5	2	13.3
Gynecology	-	-	1	6.7

In the non-clonidine group or group B, the slope of the systolic blood pressure curve is positive between times t7 and t9 (figure 1), with maximum SBP values reaching 150 mmHg. In group A, also called "clonidine group", the systolic blood pressure evolution curve is also increasing. But this increase in systolic blood pressure is minimal and remains lower than the baseline values obtained at the anesthesia consultation (the reference value for systolic blood pressure at the pre-anaesthetic consultation was 130 mmHg).

Diastolic blood pressure increased in the same direction as systolic blood pressure in both groups. Diastolic blood pressure is maintained stable in both groups between the first and the 5th minute after the surgical incision.

The surgical incision is responsible for an extreme tachycardia of up to 145/minute in the non-clonidine group, while it remains stable in the "clonidine" group after the surgical incision (figure 3).

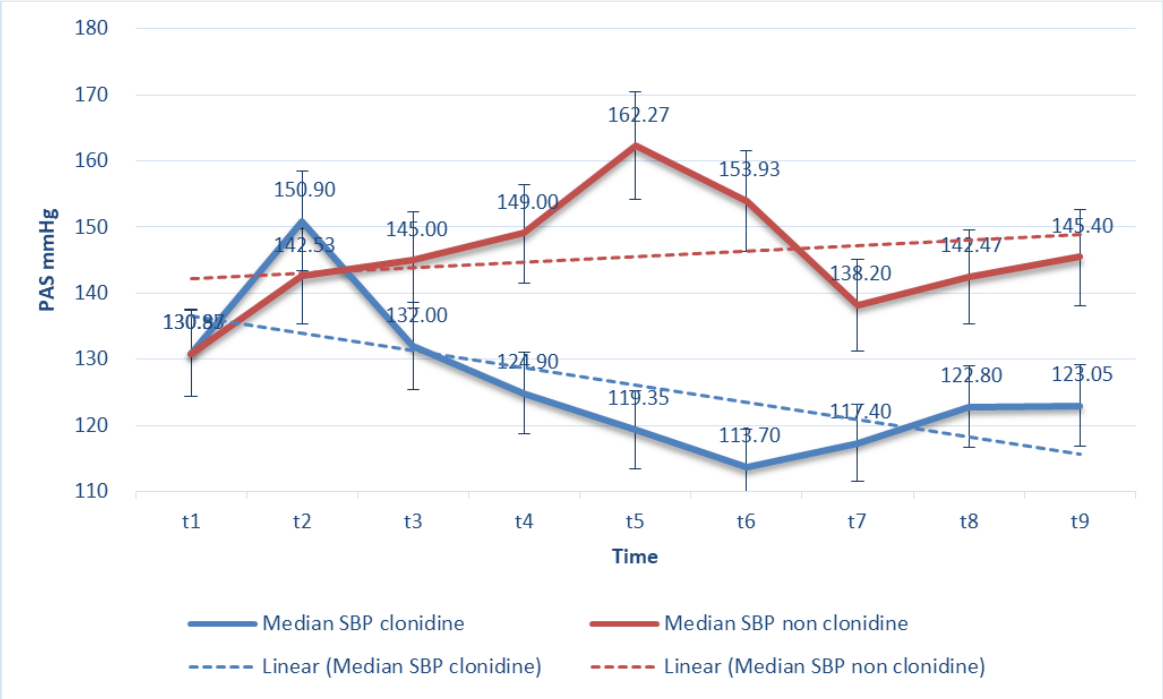

Figure1: Evolution of SBP in groups A (clonidine) and B (non-clonidine)

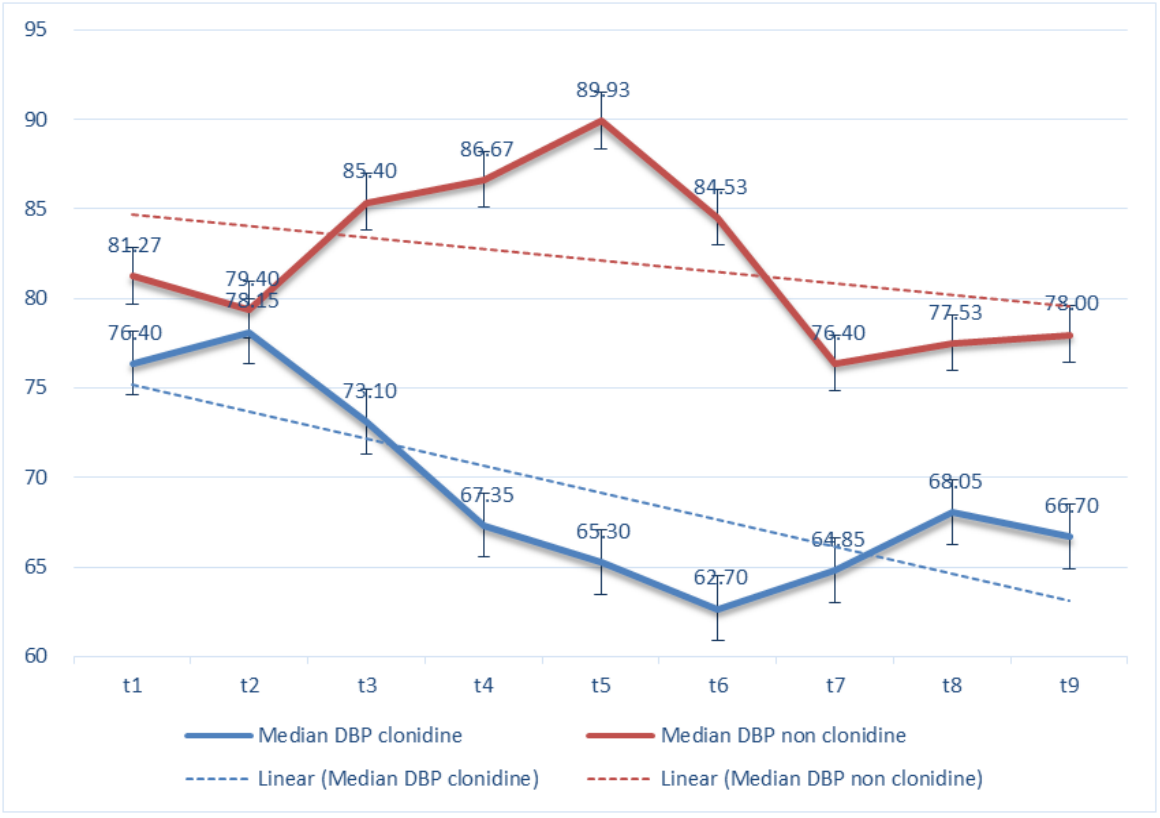

Figure 2: Evolution of DBP in groups A (clonidine) and B (non-clonidine)

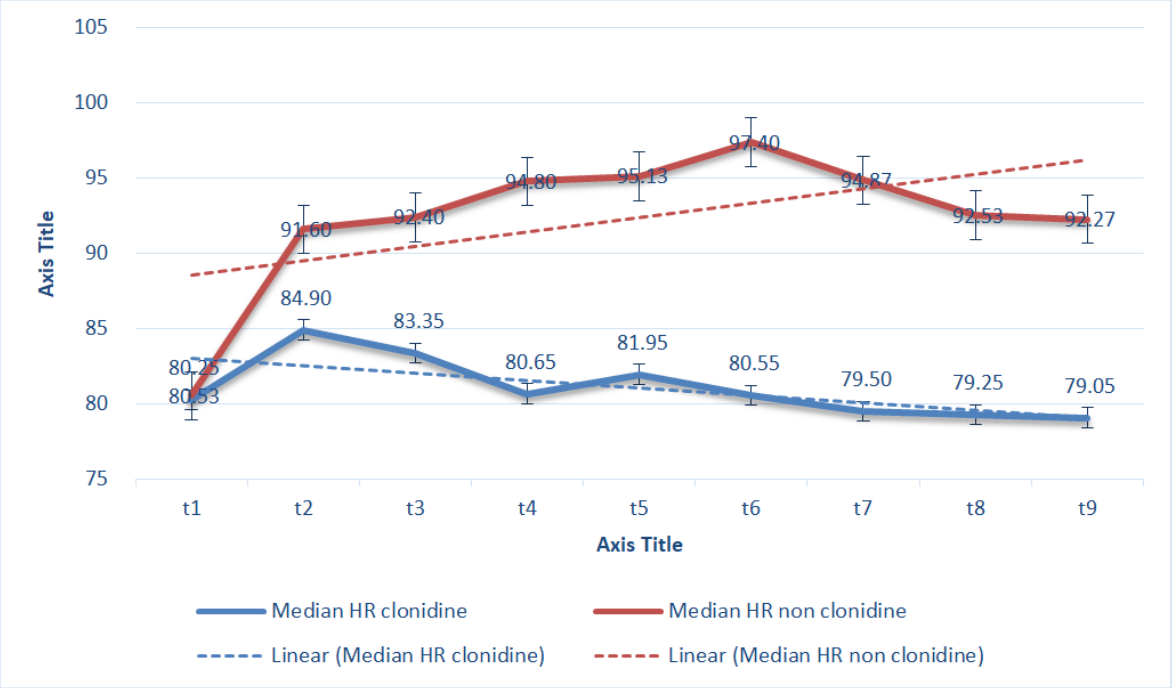

Figure 3: Evolution of HR in groups A (clonidine) and B (non-clonidine)

DISCUSSION

Clonidine is an alpha 2 adrenergic receptor agonist of the imidazoline class, long used as an antihypertensive, but replaced in this indication by new classes of antihypertensive drugs [8]. In addition to its ability to lower blood pressure and heart rate, clonidine has many other properties that make it often used in the context of anesthesia, resuscitation and pain management. Alpha-2 adrenergic receptors are distributed throughout the central and peripheral nervous system, particularly in the pontine locus coeruleus, medullospinal tracts, rostral ventrolateral medulla, and dorsal horn of the spinal cord [8, 9]. Alpha-2 agonist agents cause neuromodulation in these centers, and lead to sedation, analgesia, vasodilation and bradycardia without effect on respiratory function, which explains their good safety profile [9]. The 2 main drugs in this group are clonidine and dexmedetomidine. We proposed to study the beneficial effects of clonidine on the hemodynamic response to surgical incision. In our study, 35 participants were included, ie 20 for group A "clonidine" and 15 for control group B "non-clonidine). These were mostly young patients, and mainly male. In a work on clonidine as premedication in maxillofacial surgery, Farnoosh M *et al.*, [10] found a total of 10 men and 5 women with an average age of 22.9 ± 2.9 years in the study group and 13 men and 2 women with a mean age of 22.1 ± 2.1 years in the control group. The predominance of young subjects in these different works could be linked to the selection criteria set by the different authors. The study being experimental, the pediatric population was systematically excluded, as well as elderly subjects. The age group of young subjects is an active population generally without any particular past medical history; this explains the predominance of the ASA1 class in our study. Moreover, the exclusion of pregnant women in these two studies partially justifies the predominance of the male gender. For patients in group "A" or the clonidine group, a clinical translation of the attenuation of the effects of hypersecretion of endogenous catecholamines is observed. The systolic and diastolic blood pressures remain well below the baseline values observed at the anesthesia consultation between times t7 and t9. In "non-clonidine" group B, we notice a considerable rise in blood pressure figures, sometimes reaching critical thresholds. The heart rate remains stable in group A after the surgical incision, while tachycardia is observed at the same time in all participants in group B. our results lead us to conclude that clonidine makes it possible to maintain stable hemodynamic parameters at the surgical incision. The work of Farnoosh M *et al.*, [10] shows that blood pressure was significantly lower in the clonidine group ($P < 0.001$) compared to the control group (or non-clonidine group). Many authors also demonstrate the cardiovascular moderating effects of clonidine during painful procedures such as laryngoscopy, tracheal intubation, peritoneal insufflation of carbon dioxide during laparoscopy or upper digestive video-endoscopy [11-15]. The explanation for these beneficial effects on the cardiovascular system probably lies in the pharmacology of this drug. Clonidine acts at the locus coeruleus where stimulation of α2 receptors results in indifference to the environment and sedation [16]. α2 receptors have a negative pre- synaptic feedback effect inducing a decrease in adrenaline and noradrenaline secretion in the synaptic cleft. Noradrenaline has analgesic properties through α2 receptors, particularly in the dorsal horn of the spinal cord [16-19]. Through

its affinity for the α2 receptor, clonidine activates the same intracellular pathways as endogenous norepinephrine [16]. This involves opening a potassium channel facilitating the hyperpolarization of WDR (wide dynamic range) neurons, thus depressing their activity [16, 17, 19]. These neurons are usually stimulated by Aδ or C fibers coming from the periphery. Clonidine can therefore attenuate a nociceptive nerve impulse.

CONCLUSION

Alpha-2 adrenergic receptor agonists are substances that have gained renewed interest in anesthesia in recent years. Their clinical applications are based on sedative properties, muscle relaxation and good quality analgesia. In its indications, clonidine has been replaced by dexmedetomidine, but it still retains a large place in premedication in poor countries of sub-Saharan Africa where the economic environment remains uncomfortable for the patient. The beneficial effects on the cardiovascular system (haemodynamic stability at the surgical incision) make clonidine an adjuvant of choice for general anesthesia.

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