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SCIENTIFIC ARTICLE

Subarachnoid clonidine and trauma response in cardiac surgery with cardiopulmonary bypass[☆]

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KEYWORDS

Clonidine;
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Abstract

Background and objectives: The intense trauma response triggered by cardiopulmonary bypass can lead to increased morbidity and mortality. The present study evaluated whether clonidine, a drug of the class of α -2 agonists, administered by spinal route, without association with local anesthetics or opioids, reduces this response in cardiac surgery with cardiopulmonary bypass.

Method: A total of 27 patients between 18 and 75 years old, divided by non-blinded fashion into a control group (15) and a clonidine group (12), were studied. All patients underwent identical technique of general anesthesia. Then, only the clonidine group received $1 \mu\text{g kg}^{-1}$ clonidine by spinal route. Levels of blood glucose, lactate and cortisol were measured at three consecutive times: T1, at the time of installation of invasive arterial pressure; T2, 10 min after the first dose for cardioplegia; and T3, at the time of skin suture; and troponin I values at T1 and T3. The variation of results between T2–T1, T3–T2, and T3–T1 was also evaluated.

Results: There was a statistically significant difference only with respect to the variation in blood glucose in the clonidine group: T3–T2, $p=0.027$ and T3–T1, $p=0.047$.

Conclusions: Spinal clonidine at a dose of $1 \mu\text{g kg}^{-1}$ did not decrease blood measurements of troponin, cortisol, or lactate. Blood glucose suffered a more moderate variation during the procedure in the clonidine group. This fact, already reported in the literature, requires further investigation to be clarified.

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PALAVRAS-CHAVE

Clonidina;
Estresse traumático;
Cirurgia cardíaca

Clonidina subaracnóidea e resposta ao trauma em cirurgias cardíacas com circulação extracorpórea

Resumo

Justificativa e objetivos: A intensa resposta ao trauma desencadeada pela circulação extracorpórea pode conduzir ao aumento da morbimortalidade. O presente estudo avaliou se a clonidina,

[☆] Study conducted at the Graduate Program in Clinical Surgery, Hospital de Clínicas, Universidade Federal do Paraná (UFPR).

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fármaco da classe dos α -2 agonistas, por via raquidiana, sem associação com anestésicos locais ou opioides, reduz essa resposta em cirurgias cardíacas com uso de circulação extracorpórea. *Método:* Estudaram-se 27 pacientes entre 18 e 75 anos, separados de modo não encoberto em grupo controle (15) e grupo clonidina (12). Todos foram submetidos a técnica idêntica de anestesia geral. A seguir, apenas o grupo clonidina recebeu $1 \text{ mg} \cdot \text{kg}^{-1}$ de clonidina por via raquidiana. Foram dosados os valores de glicemia, lactato e cortisol em três tempos consecutivos: T1, no momento da instalação da pressão arterial invasiva (PAM); T2, dez minutos após a primeira dose de cardioplegia; e T3 na sutura da pele, bem como os valores de troponina I em T1 e T3. Avaliou-se também a variação dos resultados entre: T2-T1; T3-T2 e T3-T1.

Resultados: Houve diferença estatisticamente significativa apenas quanto à variação da glicemia no grupo clonidina: T3-T2 valor de $p=0,027$ e T3-T1 valor de $p = 0,047$.

Conclusões: A clonidina espinal em dose de $1 \mu\text{g} \cdot \text{kg}^{-1}$ não diminuiu as dosagens sanguíneas de troponina, cortisol ou lactato. A glicemia sofreu uma menor variação durante o procedimento no grupo clonidina. Esse fato, já registrado na literatura, necessita de maiores investigações para ser esclarecido.

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Introduction

Surgical procedures induce an endocrine, metabolic and inflammatory response in the body that causes early and late changes in homeostasis with protein catabolism. These changes are directly related to the intensity of the surgical trauma induced.¹

Although this set of physiological changes have a biological function to facilitate the healing of injured tissue when the aggression is intense and prolonged, as occurs in major surgeries, the response to trauma becomes, in itself, a cause of increased morbidity and mortality.²

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) are subject to various forms of aggression, such as the exposure of blood to the non-physiological environment of CPB circuits, acute hemodilution and activation of the coagulation cascade and⁷ the complement system. As expected, many of these patients undergo intense physiological changes that may persist for several days.^{2,3} The systemic use of high doses of opioids and the neuraxial blockade with a local anesthetic seem to be able to modulate this neuroendocrine response to surgical stress. Both techniques, however, have their drawbacks, such as the respiratory depression prolonged by opioids and the hypotension triggered by neuraxial blockade.^{4,5}

Clonidine, a drug belonging to the class of α -2 agonists, has been associated with anesthetic-surgical procedures because of its ability to promote hemodynamic stability,⁶ to prolong the analgesia time of local anesthetics and to act in the treatment of postoperative pain.^{8,9} In addition, clonidine revealed the ability to modulate the response to surgical stress and a significant application in the treatment of chronic pain.¹⁰⁻¹³ Some studies also suggest that clonidine acts to reduce perioperative morbidity and mortality in patients at risk for coronary disease.^{14,15}

Numerous studies have shown that clonidine, when combined with local anesthetics and opioids by spinal route, plays a role potentiating their actions. However, spinal clonidine, as single drug, has been scarcely studied. This research aims to assess the role of clonidine in the endocrine-metabolic stress response in adult patients undergoing

cardiac surgery with CPB, with the use of troponin I, blood glucose, lactate and cortisol as markers.

Method

All patients underwent a similar technique for general anesthesia, with puncture of two peripheral veins, peripheral arterial catheter and induction of general anesthesia with etomidate $0.2-0.5 \text{ mg} \cdot \text{kg}^{-1}$ or propofol $1.0-2.5 \text{ mg} \cdot \text{kg}^{-1}$, fentanyl up to $5 \mu\text{g} \cdot \text{kg}^{-1}$ and pancuronium or vecuronium $0.1 \text{ mg} \cdot \text{kg}^{-1}$. Maintenance of anesthesia was performed with fentanyl at a maximum total dose of $25 \mu\text{g} \cdot \text{kg}^{-1}$, distributed during the procedure, isoflurane at a maximum concentration of 2.5% and repetition of neuromuscular blocker as needed. Vasoactive drugs could be used at any time at the discretion of the anesthesiologist.

The study excluded patients with contraindications to spinal block, history of acute myocardial infarction within the past six months, emergency surgery and use of corticosteroids or clonidine.

The patients allocated to the clonidine group were placed in lateral decubitus position and underwent lumbar puncture with disposable needle 25 G type Quincke, immediately after tracheal intubation. As soon as the liquor flowed through the needle, $1 \mu\text{g} \cdot \text{kg}^{-1}$ clonidine was administered, using a 1-mL syringe. An interval of at least one hour between lumbar puncture and heparin administration was observed. Subsequently, urinary catheterization and installation of a central venous catheter were performed.

All patients were monitored with continuous ECG with ST segment analysis, nasopharyngeal temperature, invasive blood pressure (MAP), capnography, pulse oximetry, urine output, blood gas, ventilatory monitoring with spirometry and gas analysis.

Blood for glucose, lactate and cortisol determination was collected on three consecutive occasions: at the time of arterial puncture for invasive blood pressure monitoring (T1), 10 min after the first dose for cardioplegia (T2), and during skin suture (T3). Troponin I values at Times 1 and

3 were measured. We also assessed the variation in results between T2–T1, T3–T2 and T3–T1.

CPB was performed with Braile Biomedica® or Nipro® equipment, with oxygenators of the respective brands. For the infusion of blood from the CPB machine to the patient, Medtronic® or Terumo® centrifugal pumps were used. Throughout the period of CPB, the temperature was maintained above 31 °C.

Parametric data were described as mean, median, standard deviation, and minimum and maximum values. The groups were compared using non-parametric Mann–Whitney test. *p*-Values lower than 0.05 were considered as statistically significant.

Results

The study included 27 patients: 15 in the control and 12 in the clonidine group. The mean ages of the control group and of the clonidine group were 52.53 ± 13.10 and 51.75 ± 14.75 years ($p=0.885$), respectively. The general characteristics of the groups are shown in Table 1.

Table 1 General characteristics of groups.

	Control group (%)	Clonidine group (%)
Hypertension	60	67
Diabetes	13.30	16.70
Beta-blocker	60	33.30
Valve surgery	40	75.00
Coronary surgery	60	25

The groups were homogenous in terms of ejection fraction, fractional shortening percentage, plasma creatinine and duration of CPB (Table 2).

Plasma cortisol values in control and clonidine groups are shown in Table 3.

Blood glucose values are shown in Table 4.

Table 5 displays serum lactate values in both groups.

Troponin values for the two groups are shown in Table 6.

There was no statistical difference at the significance level of 5% for blood levels of troponin I, lactate, glucose and cortisol in all times analyzed in isolation. There was a

Table 2 Serum creatinine, PS (%), EF (%) and CPB time in both groups.

	Control group	Clonidine group	<i>p</i> -Value
Creatinine (mg/dL)	1.15 ± 0.38	1.09 ± 0.28	0.684
PS (%)	34.52 ± 8.39	33.43 ± 9.75	0.762
EF (%)	58.81 ± 14.45	60.67 ± 13.68	0.737
CPB (min)	92.27 ± 23.53	78.75 ± 37.13	0.260

PS, percentual shortening; EF, ejection fraction; CPB, cardiopulmonary bypass.

Table 3 Serum cortisol ($\mu\text{g/dL}$) at Times 1, 2 and 3 (mean \pm standard deviation).

	Control group	Clonidine group	<i>p</i> -Value
Time 1	11.09 ± 4.93	11.9 ± 4.47	0.997 ^a
Time 2	7.09 ± 4.13	7.49 ± 3.77	0.727 ^a
Time 3	9.06 ± 5.91	8.16 ± 2.93	0.667 ^a
Difference 2, 1	-3.993 ± 5.386	-4.009 ± 6.102	0.893 ^a
Difference 3, 2	1.971 ± 2.539	0.818 ± 1.746	0.244 ^a
Difference 3, 1	2.02 ± 7.21	2.93 ± 7.08	0.980 ^a

Time 1, puncture for PAM monitoring; Time 2, 10 min after first cardioplegia; Time 3, skin suture.

^a Without statistical significance.

Table 4 Blood glucose (mg/dL) at Times 1, 2 and 3 (mean \pm standard deviation).

	Control group	Clonidine group	<i>p</i> -Value
Time 1	101.4 ± 12.84	109.75 ± 24.42	0.615 ^a
Time 2	154.4 ± 48.69	150.64 ± 22.1	0.919 ^a
Time 3	176.13 ± 57.38	146.67 ± 36.7	0.126 ^a
Difference 2, 1	53 ± 39.86	39.821 ± 23.63	0.433 ^a
Difference 3, 2	21.73 ± 25.14	-2.83 ± 29.13	0.027 ^b
Difference 3, 1	74.73 ± 48.41	36.92 ± 17.49	0.047 ^b

Time 1, puncture for PAM monitoring; Time 2, 10 min after first cardioplegia; Time 3, skin suture.

^a Without statistical significance.

^b With statistical significance.

Table 5 Determination of serum lactate (mg/dL) at Times 1, 2 and 3 (mean \pm standard deviation).

	Control group	Clonidine group	p-Value
Time 1	1.35 \pm 0.55	1.68 \pm 0.56	0.152 ^a
Time 2	2.8 \pm 0.98	2.64 \pm 1.19	0.702 ^a
Time 3	3.29 \pm 1.39	3.16 \pm 1.78	0.719 ^a
Difference 2, 1	1.446 \pm 0.947	0.895 \pm 1	0.077 ^a
Difference 3, 2	0.485 \pm 0.901	0.605 \pm 1	0.0761 ^a
Difference 3, 1	1.931 \pm 1.312	1.487 \pm 1.715	0.126 ^a

Time 1, puncture for PAM monitoring; Time 2, 10 min after first cardioplegia; Time 3, skin suture.

^a Without statistical significance.

Table 6 Determination of troponin I (μ /dL) at Times 1 and 3 (mean \pm standard deviation).

	Control group	Clonidine group	p-Value
Time 1	0.021 \pm 0.04	0.039 \pm 0.072	0.399 ^a
Time 3	1.571 \pm 2.289	1.575 \pm 1.636	0.236 ^a
Time 3, 1	1.550 \pm 2.298	1.536 \pm 1.657	0.299 ^a

Time 1, puncture for PAM monitoring; Time 3, skin suture.

^a Without statistical significance.

statistically significant difference in blood glucose variation at times T3–T2 ($p=0.027$) and T3–T1 ($p=0.047$).

Discussion

The present study evaluated the effects of spinal clonidine on surgical stress response in patients undergoing cardiac surgery with CPB. The surgical trauma response is formed by complex hormonal and metabolic changes that profoundly alter homeostasis and participate in the morbidity and mortality observed in medium and major surgeries.

The use of neuraxial clonidine in humans began in 1984.¹⁶ Since then, numerous studies suggest that spinal clonidine potentiates the effects of opioids and local anesthetics.^{7,13} Therefore, when this association occurs, it may be difficult to separate the effects produced only by clonidine. Spinal clonidine not associated with other drugs or other forms of anesthesia was the object of analysis in a group of obstetric patients. The patients were randomly assigned to receive either 50, 100 or 200 μ g of subarachnoid clonidine in the first stage of labor. The results indicate that clonidine has an analgesic action in the spinal cord. The authors point out that the dose of 100 μ g offers the best dose-side effects relation.¹⁷

It is known that the action of spinal clonidine is mediated by the activation of α -2 receptors in the *substantia gelatinosa*, with blockage of potassium conductance of fibers C and A.^{18,19} The drug also acts in the *locus coeruleus* by reducing the central release of norepinephrine, with attenuation of the central sympathetic action.^{16,20} Both actions could occur with intrathecal clonidine, which would act both in the dorsal horn of the spinal cord and in the *locus coeruleus* after migrating, through the liquor to the higher centers. There is, therefore, a theoretical basis to justify a protective action of clonidine on stress responses.

Troponin I, cortisol, glucose and lactic acid were the markers used in this study to identify stress responses and

their modifications by the intervention of clonidine. These markers have already been extensively validated in previous studies.^{21–26}

In the present study only blood glucose exhibited more moderate elevation in the group receiving spinal clonidine. This suggests that somehow there was a lower activation of stress in this group. One cannot say that this glycaemic change has clinical significance, although with statistical significance. Thus, there is no sufficient evidence to contend that clonidine has a protective role in stress, when used by spinal route.

Conclusion

There were no statistically significant differences in troponin I, cortisol or lactic acid determinations between the groups. Blood glucose showed a more moderate increase in the group receiving spinal clonidine. We conclude that the use of clonidine at the spinal dose of 1 μ g kg⁻¹ was not able to reduce the intensity of response to surgical trauma and showed only modest activity on glucose levels.

Conflicts of interest

The authors declare no conflicts of interest.

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