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Antipyretic Effect of Clonidine in Intensive Care Unit Patients: A Nested Observational Study

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Abstract

Fever in the intensive care unit (ICU) is usually an adaptive response to infection or inflammation. Pharmacological intervention is often required in addition to addressing the underlying causes of fever. Animal studies have examined the antipyretic effect of clonidine; however, to our knowledge there are no clinical data available in humans. The observation of an antipyretic effect of clonidine was made during a single-center randomized control trial that was designed to study the effect of clonidine addition to the commonly used sedative agents in mechanically ventilated ICU patients. Forty patients 18 years or older on mechanical ventilation for 3 days or longer were randomized into 2 groups receiving clonidine and placebo. In addition to the usual sedation/analgesia, patients in the clonidine arm received enteral clonidine in doses of 0.1 mg 3 times a day (TID), which was increased to 0.2 mg TID if the hemodynamics remained stable. Vital signs, laboratory data, all cultures, and daily ICU events were recorded. The odds ratio of temperature higher than 38.3°C was 3.96 times higher in the placebo group, after adjustment for the illness severity and the time of follow-up ($P = .049$). A lower temperature (0.52°C) was observed in the clonidine group after adjustment for the time of follow-up ($P = .006$). Our report is the first of its kind in humans that demonstrates possible antipyretic properties of enteral clonidine in the critically ill intensive care unit patient.

Keywords

ICU, clonidine, fever

When fever occurs in intensive care unit (ICU) patients, it is usually an adaptive response to infection or other inflammatory stimuli.[1–3] It is generally caused by a complex interplay of neuroendocrine, autonomic, and behavioral responses, coordinated by the hypothalamus.[4]

The Society of Critical Care Medicine (SCCM) and the Infectious Disease Society of America (IDSA) define a fever in the ICU as a body temperature of 38.3°C or greater. It should prompt a clinical assessment.[3] After the cause(s) of the fever have been addressed, patients are usually treated with drug and/or mechanical antipyretics. The choices of antipyretic drugs are limited.

It is known that noradrenergic receptors have a role in the body's thermoregulatory processes.[4,5] Several animal studies have shown that hypothermia is produced by norepinephrine (NE) microinjected into the anterior hypothalamic, preoptic area (AH/POA)[6,7]or by the noradrenergic agonist phenylephrine.[8]

Clonidine, an α_2-receptor agonist, is used to treat various conditions including hypertension, menopausal flushing, and opioid or alcohol withdrawal symptoms. In addition, clonidine has analgesic and sedative properties.[9–11] Animal studies have shown α_2-receptor agonists, clonidine and dexmedetomidine, to have an inhibitory effect on fever through either the effect on thermoregulatory circuits in the preoptic area or the blockage of thermogenic premotor neuron activation in the medullary rostral raphe pallidus area (rRPa).[12–18] These mechanisms could contribute to antipyretic effects of these agents. To our knowledge, however, there are no human studies examining the antipyretic effect of clonidine in critically ill ICU patients.

The following observation of clonidine's effect on body temperature is derived from a single-center, randomized, controlled trial. The study was originally

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designed to assess the impact of adding clonidine to the sedating agent(s) already in use in mechanically ventilated ICU patients in a teaching hospital.[11]

Material and Methods

The original trial was registered and approved by the Iranian Registry of Clinical Trials with reference number IRCT2012102910178N3.[11] All patients or their next-of-kin consented to the investigation and report. This study was conducted in the general ICU of a 550-bed university hospital in Tehran, Iran. Forty patients, aged 18 years and older, with stable hemodynamics who required mechanical ventilation for 3 days or longer were included in the study.

Patients were excluded if they had sepsis (based on surviving sepsis campaign guidelines),[19] volume depletion, second- or third-degree atrioventricular node block, systolic blood pressure less than 90 mm Hg, clonidine administration for less than 3 days after randomization, acute or chronic renal insufficiency (GFR <15 mL/min), severe liver failure based on the Child-Pugh scoring system, Glasgow Coma Scale (GCS) <8, history of clonidine use during the past 90 days, and inability to tolerate enteral feeding.

The baseline data recorded were age, sex, reason for ICU admission, and APACHE II scores.[20] Daily observations such as vital signs, laboratory data, all cultures, antibiotics use, and all ICU events were documented.

Patients who met the inclusion criteria were randomized into 2 groups. The intervention arm received the usual sedative/analgesic agents plus enteral clonidine, 0.1 mg 3 times a day (TID) via nasogastric tube. The dose was increased to 0.2 mg TID on the second day if hemodynamics remained stable, and those who could not tolerate this dose were excluded from the study. The control group received placebo in addition to the prescribed sedative regimen. All patients who developed body temperature over 38.3°C received antipyretics. Observations were made for at least 3 days and continued for 7 days when longer duration of mechanical ventilation was required.

Statistical Analysis

Statistical analysis was performed using SPSS® 19 software. Continuous variables in each group of subjects were expressed as mean ± standard deviation (SD). Differences between means of the 2 groups were determined using the Mann-Whitney U test. The chi-square test to compare dichotomous variables was used. A generalized linear mixed model was applied for the assessment of clonidine's effect on body temperature. In all cases, a P value of less than .05 was considered statistically significant.

Table 1. Demographic Data of Patients in Intervention and Placebo Arms

	Total	Clonidine	Placebo	P
Age	57 ± 21	57 ± 25	58 ± 18	.9[a]
Sex	F 14 (35.0%)	5 (25.0%)	9 (45.0%)	.1[b]
	M 26 (65.0%)	15 (75.0%)	11 (55.0%)	
APACHE II score	19 ± 5	19 ± 5	19 ± 4	.8
Baseline temperature >38.3°C	>18	>7(35%)	11(55%)	.2
ICU diagnosis				
Multiple trauma	15	7	8	
CVA and neurologic problems	9	5	4	
Abdominal complication	7	2	5	
COPD	5	3	2	
DVT	1	1	0	
Insulin poisoning	1	1	0	
CHF	1	1	0	
Hysterectomy	1	0	1	
Days on antibiotics[c]	215	99	116	.87[b]
Positive cultures[d]	30	17	13	.144[b]
Duration of study	5.9 ± 1.3	5.8 ± 1.4	6.1 ± 1.3	.4[a]

[a]Based on Mann-Whitney test.

[b]Based on chi-square test.

[c]Total antibiotic-days (single or multiple antibiotics) in all patients for the duration of the study.

[d]Number of positive cultures (single or multiple sites) in all patients for the duration of the study.

Results

Patients

Fifty-five patients, 30 in the intervention group and 25 in the control group, were enrolled in the study. Ten patients were excluded in the treatment group: 5 due to extubation after less than 3 days, 2 for administration errors, 2 due to hypotension, and 1 who died on the second day of enrollment (unrelated to the study interventions). Five patients were excluded in the control arm: 3 due to extubation after less than 3 days, 1 with a decreased level of consciousness, and 1 for hypotension (SBP <90 mm Hg.)

Patient characteristics, severity of illness based on APACHE II scores, number of days remaining in the study, and baseline body temperature greater than 38.3°C were not statistically different in the 2 arms of the study (Table 1).

In both study groups and during all study days, the number of positive cultures from different sites were, 17 and 13 ($P = .144$), and the total antibiotics-days (single or multiple antibiotics) used were 99 and 116 ($P = .87$) in the clonidine and placebo arms, respectively (Table 1). The use of medications with potential to increase the body temperature, such as anticonvulsants and antipsychotics, was similar in both study groups ($P = .92$).

Effects of Clonidine in Patients With a Body Temperature >38.3°C

Generalized linear mixed-model analysis showed that the odds ratio of having a body temperature >38.3°C

Table 2. The Effect of Clonidine on Body Temperature in Two Study Arms During All Study Days in Patients Who Remained in the Study for 3 Days or More

	Clonidine		Placebo	
Day	N	Mean ± SD	N	Mean ± SD
1	20	38 ± 0.6	20	38.2 ± 0.7
2	20	37.9 ± 0.8	20	38.2 ± 0.8
3	20	37.7 ± 0.7	20	38.2 ± 0.8
4	19	37.7 ± 0.6	19	38.05 ± 0.5
5	13	38.05 ± 0.7	17	38.05 ± 0.7
6	12	38.07 ± 0.6	15	37.9 ± 0.6
7	10	37.9 ± 0.8	13	38.08 ± 0.8

was 3.96 times greater in patients belonging to the placebo arm than in the patients who received clonidine during all study days ($P = .049$) after adjustment for the time of follow-up. With the same model of analysis, patients belonging to the clonidine group had a lower body temperature by 0.52°C during all study days after adjustment for the time of follow-up ($P = .006$) (Table 2).

Discussion

We observed a significantly higher number of patients in the placebo arm with fever that required intervention, such as acetaminophen use, during all study days compared to the treatment arm of our study.

The statistically significant reduction in body temperature observed in the treatment arm could be related to the administration of clonidine after data adjustment for the status of cultures from different body sites, antibiotic-days, and the use of medications with the potential to increase body temperature.

Fever can occur in critically ill patients in an ICU due to infectious or noninfectious etiologies.[1–3] This may cause irreversible protein denaturation and, if untreated, will lead to significant cell-function dysregulation and tissue damage, contributing to morbidity and mortality.[18]

Many animal studies have supported the central inhibitory role of catecholamines in the regulation of body temperature, which is mediated via α-adrenergic receptors.[5,18,21,22] The α_2-adrenergic receptor agonists have been noted to cause mild hypothermia in rodents,[12,13] decrease febrile responses in rabbits,[14] and decrease body temperature in horses.[15]

A variety of underlying mechanisms have been proposed for the hypothermic effects of α_2-agonists.[13,17,18,23] Thermogenesis and decreased heat loss to the environment contribute significantly to elevated core body temperature.[24,25] Thermogenesis is an indispensable component of the homeostatic system, which keeps body temperature relatively constant when the human body is exposed to low environmental temperatures.

Thermogenesis in brown adipose tissue (BAT), stimulated by pyrogens, raises body temperature. BAT thermogenesis is regulated through pathways that transmit signals of ambient temperature from skin thermal receptors to the hypothalamus. The signals, along with the brain's temperature information, lead to activation of efferent pathways to the thermal receptors.[25]

Earlier studies have proposed that the hypothermic properties of the α_2-agonists are due to their effect on the thermoregulatory circuits in the preoptic area.[13,17,23] On the other hand, the thermogenic effector activation is controlled by the premotor neurons mainly located in the region of the medullary rRPa. These project to the BAT sympathetic preganglionic neurons (SPN) in the spinal intermediolateral nucleus and are inhibited by neurons in the ventrolateral medulla (VLM).[25,26] Catecholaminergic neurons within the VLM reach to the rRPa and through the spinal pathways reach neurons in the rRPa, with subsequent expression of α_2-adrenergic receptors.[27,28] A recent animal study has proposed that the α_2-adrenergic receptor agonists clonidine and dexmedetomidine have an inhibitory effect on fever generation through the blockage of thermogenic premotor neurons activation in the rRPa.[13]

The limitations of our study are its observational nested nature and small sample size. We also could not draw a meaningful antipyretic dose-effect relationship due to the clonidine dose limitations (0.2 mg TID for all study patients after the first day) dictated by the original study design.

Conclusion

Significant progress has been made in the development of mechanical devices, both extracorporeal and intravascular, for cooling critically ill febrile patients, but the number of antipyretic drugs for this patient population remains limited. This human observational study is the first of its kind to report a possible antipyretic effect of clonidine in critically ill ICU patients. Larger studies specifically designed to examine clonidine's effect on body temperature are needed.

Declaration of Conflicting Interests

All authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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