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Original Article

Analgesic and antisympathetic effects of clonidine in burn patients, a randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Objectives: Unlike most other Analgesic drugs, α2 adrenoceptor agonists are capable of producing analgesia. The aim of this study was to evaluate the Analgesic and antisympathetic effects of clonidine, an α2 adrenoceptor agonist in burn patients.
Materials and Methods: This randomized, double-blind, placebo-controlled clinical trial performed on one hundred burn patients in Zarea Hospital, Mazandaran, Iran from august 2004 to July 2005. All patients divided in two groups. Case group (n=50) received oral clonidine, 3.3μg/kg TDS and controls (n=50) received placebo. Heart rate and systolic blood pressure and pain severity Visual analogue score (VAS), were recorded after clonidine administration. Statistical analysis was done by means of Mann Witney U test.
Results: 50 patients (mean age 28.96±10 years) in case group, and 50 patients (mean age 27.60±11.4 years) in control group were studied. VAS pain scores and heart rate in the clonidine group were significantly lower than the control group (P<0.0001, P<0.02).there were no significant difference in systolic blood pressure between the two groups on the first and second day but on third day the systolic blood pressure in clonidine group, was lower than controls significantly (P=0.002).
Conclusion: This study demonstrates that the use of oral clonidine affects the hemodynamic response to pain in burn patients. Our study demonstrated that clonidine can produce good analgesia and decreased in sympathetic over activity in burn patients, and also reduce opioid dose requirements.

KEY WORDS

Clonidine, analgesia, sedation, burns

The perception of pain from a given stimulus is influenced by numerous factors, including patient variability, ethnic background, socioeconomic class, previous life experiences and support systems. About 52% of patients report pain during burn wound debridement, whereas 84% describe extreme pain after therapeutic procedures.[1-3] Adequate analgesia and sedation are supposed to prevent stress-induced reactions such as hyper metabolism, sodium and water retention, hypertension, tachycardia and altered wound healing and to optimize patient comfort.[4,5] If sedation is too deep it can have negative side-effects such as increased risk of pneumonia, venous thrombosis, bowel motility problems, hypotension and a prolonged stay in the ICU, resulting in increased costs.[6,7] The requirements for ideal analgesia and sedation are the ability to sedate the patient deeply for necessary procedures, but with medication of short duration so that the patient can be quickly responsive and cooperative.[8]

Clonidine hydrochloride, an α_2 adrenoceptor agonist, is currently used for pre anaesthetic medication owing to its sedative and analgesic properties.[9] Unlike most other sedative drugs, α_2 adrenoceptor agonists are capable of producing sedation and analgesia and result in little, if any, respiratory change.[10] It has been reported to decrease opioid dosage without affecting the quality of analgesia,[2] although clonidine has side-effects of hypotension and bradycardia.[11] This combination makes them potentially useful in the postoperative, non ambulatory setting, especially in high dependency and intensive care situations. With the development of the new α_2-agonists, there has been a resurgence of interest in the use of this class of drugs for sedation purposes.[12-15] Unfortunately, only a few studies have been done about the effectiveness of clonidine in managing burn patients. In this study we conducted a clinical trial to evaluate the analgesic and antisympathetic effects of clonidine in burn patients.

MATERIALS AND METHODS

Study design

This study was a randomized, double-blind, placebo-controlled clinical trial of the analgesic and antisympathetic effects of clonidine in burn patients compared with placebo. The study was carried out from August 2004 to July 2005 at the Zarea Hospital, affiliated to the Mazandaran University of Medical Sciences, Iran. The study protocol was approved by the Institutional Ethics Committee and informed written consent was obtained from all the patients under study. The study was conducted in accordance with the guidelines for good clinical practice and the Declaration of Helsinki (1964), revised at Tokyo (1975), Venice (1983) and Hong Kong (1989).

Patients

One hundred patients with the American Society of Anesthesiologists physical status 1 and 2 who had suffered skin burns to approximately 30% of their body were admitted into the study. The patients ranged in age from 14 to 64 years. Patients were excluded from the study if they had severe systemic disease (e.g. renal failure, congestive heart failure) or sepsis, addiction, if they were pregnant or if they could not give informed consent.

Study procedures

Patients were divided equally and randomly assigned by lottery to two groups as following: Case group, the patients who received oral clonidine and the patients considered the control group, received placebo (prepared in the Pharmacology Institute of Mazandaran University of Medical Science) with the same procedure. The placebo was prepared in the same size and color packages as clonidine tablets. The two groups were matched for age, sex and total body burn surface area.

All patients were fluid-resuscitated according to Parkland formula guidelines. Patients in the case group were tested with oral clonidine (0.1 mg) and blood pressure measured after one hour. If no hypotensive events occurred (decreases in blood pressure to <20% of baseline values), 0.1 mg clonidine TDS was administered on the first day followed by 3.3 μg/kg TDS on the second and third days. In both groups, if any patient suffered from pain, a *Cocktail* drug (containing pethidine 100 mg, promethazine 100 mg and chlorpromazine 100 mg in 14cc sterile water, 3cc per dose) was administered, according to patient requirement. Pain severity, heart rate and systolic blood pressure were recorded before and one hour after clonidine administration and during debridement. The severity of overall pain was assessed using a 10 point visual analog scale (VAS), 0 = minimal or no pain, 10 = maximal or the most severe pain the patient has ever had, to determine the baseline level of pain before the surgical procedure. The dose of clonidine was gradually decreased and discontinued.

Statistical analysis

Values were expressed as the mean±SD. The significance of a difference between two groups was calculated using Mann Whitney U test. A *P* value less than 0.05 was considered to be significant statistically.

RESULT

One hundred burn patients (50 in case group, mean age 28.96±10 years; and 50 in control group mean age 27.60±11.4 years) were enrolled. The two groups of patients were similar with respect to demographic data and total body burn surface area [Table 1].

The VAS pain scores in the clonidine group were significantly lower when compared with the placebo on the first, second

Table 1: Demographic data of the burn patients

	Placebo (n = 50)	*Clonidine (n = 50)*	*P-value*
Age (year)	27.60±11.4	28.96±10	NS
Gender, male/female	33/17	28/22	NS
Body burn surface area (%)	22.70±10.7	20.76±4.6	NS

NS: Not Significant, *P*>0.05

Table 2: Patients' characteristics after clonidine administration

	First day	*Second day*	*Third day*
Analgesia score after clonidine (VAS)			
Placebo	1.68±1.9	6.46±0.81	6.24±0.8
Clonidine	6.70±0.8*	1.78±2.1*	1.34±2.01*
Analgesia score during debridement (VAS)			
Placebo	9.22±0.6	9.14±0.7	8.36±0.7
Clonidine	7.02±2.7*	6.20±3.1*	4.36±2.8*
Systolic blood pressure (mmHg)			
Placebo	107.08±24.4	110.40±13.9	113.20±12.6
Clonidine	113.10±9.1	108.70±7.0	106.80±8.9*
Systolic blood pressure changes (%)			
Placebo	13.10±9.1	10.4±13.9	13.2±12.6
Clonidine	9.6±15.5*	8.7±7.0*	6.8±8.9*
Heart rate (beat/min)			
Placebo	96.32±11.2	94.14±5.3	93.24±5.2
Clonidine	82.40±5.3*	80.12±6.3*	78.38±5.3*

Values are expressed as the mean±SD. Significant difference was observed between the groups; *P<0.05

and third day (1.68±1.9 *vs.* 6.70±0.8, P=0.0001; 1.78±2.1 *vs.* 6.46±0.81. P=0.0001; 1.34±2.01 *vs.* 6.24±0.8, P=0.0001 respectively). Pain severity in the case group was significantly lower than controls during debridement procedure (P=0.0001) on all days. Hemodynamic data obtained after drug administration revealed appreciably higher heart rates in the placebo group than in the group receiving clonidine, on the first, second and third days (P=0.001, P=0.001, P=0.0001 respectively). Systolic blood pressures were not appreciably different among the groups on the first and second days but on the third day a statistically significant difference between the two groups were observed (P=0.01) [Table 2]. All the patients in both groups requested cocktail for analgesia. The number of cocktail requirements in the clonidine group were significantly lower than the controls on the first day (mean 1.96±0.6 *vs.* 2.60±0.6, P=0.0001), second day (mean 1.57±0.6 *vs.* 2.14±0.6, P=0.0001), third day (mean 1.45±0.5 *vs.* 2.00±0.7, P=0.0001).

On the other hand, following the treatment with clonidine in the case group, the mean of VAS pain score, systolic blood pressure and heart rate decreased significantly compared with the prior treatment (P=0.0001) [Figures 1-2].

DISCUSSION

Clonidine proved to be an effective drug to control blood presure and heart rate with a slight sedative effect that is desirable in the hemodynamic laboratory. Adequate analgesia and sedation for burn patients are important.[16] In addition to continuous burn pain, control of acute pain due to therapeutic procedures such as dressing changes and burn wound debridement is frequently necessary for such patients. Moreover, because skin incision for decompression and skin graft operation might be necessary for many burn patients, adequate analgesia is indispensable for postoperative patient care.[11] Clonidine produces sedation and analgesia.[17-19]

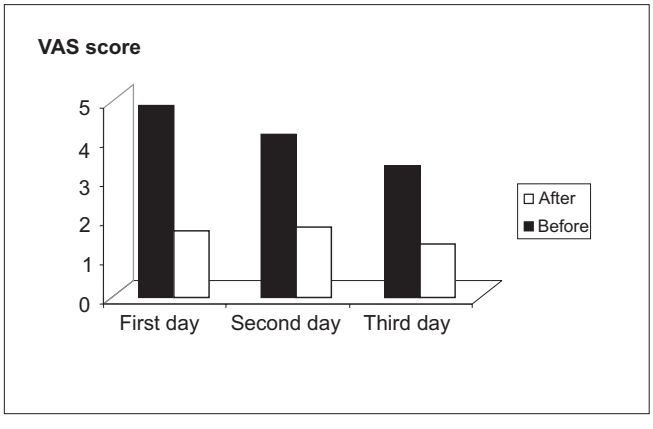

Figure 1: Pain score (VAS) before and after of clonidine administration in burn patients, P<0.05

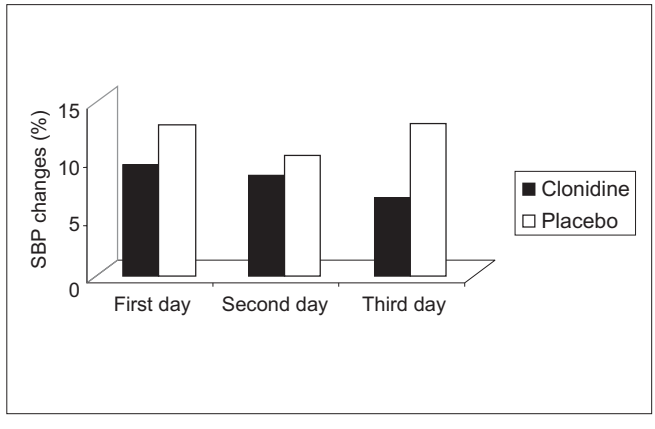

Figure 2: Systolic blood pressure changes (%) before and after of clonidine administration in burn patients, P<0.05

Our study demonstrated that clonidine can produce good, analgesia and decrease in sympathetic over-activity in burn patients and can also reduce opioid dose requirements. In this study a mild hypotension (about 9.7%) was observed, which is acceptable. A study by Lyons *et al* prospectively assessed the role of clonidine analgesic effects in a child with burns and they found that IV clonidine, dramatically reduced morphine consumption.[20]

Although intravenous opioids, administered after therapeutic burn procedures, are the primary method of pain management, non opioid-based approaches have recently become popular. This change relates to the realization that narcotics may be underused by clinical staff in an effort to reduce side-effects such as depression of ventilation and consciousness, decreased gastrointestinal motility and constipation, nausea and vomiting, urinary retention and physical dependence.[2] These side-effects increase the morbidity associated with thermal injury and prolong recovery time. In addition, opioid pharmacodynamics is altered in patients with burns, with requirements increasing over time so that even high doses of opioids may not totally relieve the pain in some patients.[21] Burn trauma elicits increased sympathetic activity and elevation of circulating catecholamines acting on adrenoceptors in the vascular tissue, thus playing an important role in the regulation of organ blood flow.[22] The inhibition of post burn edema induced by stimulation of α_2-receptors by clonidine, could be secondary to increased vascular resistance and reduced tissue perfusion pressure and/or suppressed inflammatory reaction in the burn injury.[23] In the treatment of burn patients, clonidine is particularly interesting because of its induced potent analgesia and anti inflammatory effects in the thermally injured.

Kariya *et al* studied the effect of clonidine in a burn patient and reported that the lower dose of clonidine administered orally was equally effective compared with the dose of IV clonidine that Tryba *et al* reported.[11,24] It might be necessary to reduce doses of oral clonidine in critically ill patients because the half-life of clonidine was prolonged in burn patients with renal failure.

Rebound hypertensive episodes have been reported after withdrawal of long-term clonidine treatment,[11] although short-term use of clonidine proved to be safe. The clonidine dose should be decreased slowly so as to avoid rebound hypertension. We did not observe any severe hypotension and our patients did not suffer a hypertensive episode following withdrawal of clonidine.

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