EFFECTS OF CLONIDINE AS PREMEDICATION ON PLASMA RENIN ACTIVITY, SERUM AND URINE ELECTROLYTES AND BODY FLUIDS IN GENERAL ANESTHESIA

A Randomized Double Blind Placebo Controlled Clinical Trial

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Abstract

Objectives: Clonidine is a relative alpha2 agonist that´s used as a premedicative drug in anesthesia in recent years. The aim was to asses the effect of oral clonidine as premedicative drug on 24 hours urine output, urine specific gravity, serum and urine electrolyte level and renin plasma activity

Method: A randomized double blind controlled clinical trial was performed in Asali hospital Khoramabad-Iran during 2004. Sixty patients in ASA class 1 and 2, were randomly selected and divided into two groups. One group received clonidine tablet and control group received placebo tablet, orally, ninety minutes before induction of general anesthesia for cystocel-rectocel perineorraphy surgery. In this study we took blood and urine samples for laboratory measurements before as well as 6 hours after taking the tablets. Differences between two groups were analyzed by students T-test.

Results: Significant increase in 24 hours urine output ($P = 0.001$) was seen in clonidine group, compared to control group. Clonidine group had higher urine electrolyte levels ($P < 0.05$) however, no differences were seen in blood electrolyte level ($P > 0.05$). Urine specific gravity was lower in clonidine group ($P < 0.05$). Significant decrease in plasma renin activity was seen in clonidine group ($P = 0.001$).

Conclusion: This study suggested that clonidine is a safe premedication drug in anesthesia and does not change the serum electrolytes level.

Key words: Clonidine, Peremedication, Urine specific gravity, electrolytes, plasma rennin activity.

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Introduction

Clonidine, an imidazoline compound[1], is relative alpha2 adrenoreceptor agonist[2] that's used as a premedicant and valuable adjuncts in anesthesia in recent years.

Desirable effects of clonidine in anesthesia includes sedation, analgesia, perioperative hemodynamic stabilization, and diminishing the needed dosage of other anesthetic drugs[3].

Other reported clinical uses include: treatment of hypertension, opiate and ethanol and benzodiazepines withdrawal syndrome, panic disorder, cigarette craving after heavy smoking cessation, emesis in cancer chemotherpeutic regiment and diabetic diarrhea[3].

Clonidine affects different organs of which it's effect in renal system is diuresis, but it's exact mechanism is not clear. The probable mechanism includes: ADH reduction[4], stimulation of alpha2 adrenoreceptors in renal tubules and block of ADH effects in this site and thus induction of diuresis[5], increase in GFR that induces diuresis by increase plasma atrial natriuretic peptid (ANP), a vasodilator, diuretic and natriuretic hormone[1,6] and decrease cAMP levels[2] that may not be only centrally mediated. ST-91, a structural clonidine analogue that does not cross the blood-brain barrier, evokes renal responses similar to those observed with clonidine, which may suggest a peripheral action[1].

The mechanisms involved in ANP release may include imidazoline binding sites and/or alpha2 adrenoceptors present in the heart. Imidazoline receptors are distinct from adrenergic receptors because they show low affinity for catecholamines, epinephrine and norepinephrine[7]. Imidazoline receptors have been found in brain, kidney, urethra, liver and platelets[8].

Alpha2 agonists inhibit Renin-Angiotensin-Aldostrone axis and produce diuresis[9]. By alpha2 adrenoreceptor stimulation in periventricular nucleus they increase urine flow rate[10]. Clonidine increase free water and osmolar clearance, by this hypothesis that the alpha2 a-adrenoceptor subtype mediates osmolar clearance whereas the alpha2 b-sub type mediates free water clearance[6].

This study was designed to evaluate the effect of clonidine as premedication drug on plasma renin activity, 24 hours urine output, urine specific gravity and serum and urine electrolytes level.

Materials and Methods

Study design

After obtaining IRB approval at the Lorestan Medical Science University at Khoramabad –Iran, written informed consents was obtained from 60 women in ASA class I, II, aged 20-40 years undergoing repair of cystorectocele perineorraphy under general anesthesia in Asali hospital during 2004. These patients were studied according to a randomized, double blind, placebo controlled protocol. Patients were excluded if they had hypertension, cardiovascular, renal and psychotic disease.

Premedication

The patients were randomly divided into two groups; first group (n = 30) received clonidine tablets at the dose of 5 μg/kg, and the second group (n = 30) received placebo tablets, with 30cc water 90 minutes before induction of anesthesia. Then foley catheter was introduced for patients.

Anesthesia

General anesthesia was induced with sufentanil (2 μg/kg) and thiopental (5 mg/kg) and tracheal intubation was facilitated with atracurium (0.3 mg/kg), followed by oxygen and nitrous oxide (30%, 70%) in combination with halothane 0.5% to 1.5%.

Patients were monitored for blood pressure, pulse rate, ECG and pulse oximetry. At the end of operation, residual neuromuscular block was reversed by neostigmine and atropine.

Injected fluids in anesthesia course were crystalloid solution (Nacl 0.3% plus dextrose 3.33%) based on this formula:

Replacement of insensible loss (2 ml/kg/h) plus moderate surgical trauma loss (5 ml/kg/h) plus blood loss (every 1 ml of blood loss with 3 ml of serum) plus urine loss (every 1 ml urine loss with 1 ml of serum). In the ward, patients received 2 ml/kg/hour of (dextrose 5%-Nacl 0.9%) serum, in first day of their surgery.

Table 1
Summary and comparison of mean blood and urine Na and K and urine specific gravity in placebo group before and after receiving placebo

Parameter	Before tablet usage (placebo) (Mean ± SD)	After tablet usage (placebo) (Mean ± SD)	T	Degree of Freedom	P value
Serum Na (meq/lit)	137.87 ± 5.10	140.83 ± 4.65	-5.52	29	0.06
Serum K (meq/lit)	4.14 ± 0.564	4.24 ± 0.438	-1.55	29	0.13
Urine Na (meq/lit)	188.37 ± 40.21	192.77 ± 34.24	-0.92	29	0.36
Urine K (meq/lit)	33.99 ± 1.986	34.18 ± 2.047	-0.93	29	0.36
Urine specific gravity	1021.43 ± 5.33	1021.43 ± 5.11	-1.01	29	0.32

Na: Natrium, K: potassium

Evaluation

Blood and urine samples were assessed prior as well as 6 hours after taking the tablets for Na, K, urine specific gravity and plasma renin activity. Twenty four hours urine output was charted. Blood sample was transferred to the laboratory with cold chain.

Data was analyzed by Mann- Whitney U-test, x^2 test and t-student. P value of <0.05 was considered statistically significant.

Results

Base line demographic and background characteristics were similar between the two groups.

Differences between the two groups were analyzed by student´s T-test.

There was no significant difference in blood pressure (BP), pulse rate (PR), ECG and pulse oximetry in both groups.

In placebo group, there was no significant difference in urine and blood Na and K and urine specific gravity before and after receiving tablets (P >0.05) (Table 1).

Although clonidine group had higher urine Na and K level after taking clonidine (P = 0.05) but no significant difference was seen in blood Na and K level (P >0.05) (Tables 2 and 3).

Urine Specific gravity was lower in clonidine group after receiving tablet (P <0.05) (Table 2). This change was significant compared to placebo group (Table 3).

Significant increase in 24 hours urine output (P = 0.001) was seen in clonidine group compared to placebo group (Table 4).

Significant decrease in plasma renin activity was seen in clonidine group (P = 0.001) (Table 4).

Significant decrease in plasma renin activity

Table 2
Summary and comparison of mean blood and urine Na and K and urine specific gravity in clonidine group before and after receiving clonidine

Parameter	Before tablet usage (Clonidine) (Mean ± SD)	After tablet usage (Clonidine) (Mean ± SD)	T	Degree of Freedom	P value
Serum Na (meq/lit)	138.4 ± 6	137.67 ± 4.88	1.05	29	0.30
Serum K (meq/lit)	4.11 ± 0.46	3.76 ± 1.11	1.53	29	0.13
Urine Na (meq/lit)	175.53 ± 28.69	199.60 ± 19.21	-6.41	29	0.001
Urine K (meq/lit)	34.38 ± 2.25	36.24 ± 2.10	-6.97	29	0.001
Urine specific gravity	1023.03 ± 0.08	1021.13 ± 3.96	2.79	29	0.009

Na: Natrium, K: potassium

Table 3
Comparison of serum and urine laboratory tests before and after receiving tablet in clonidine and placebo groups

Parameter	T-test	Degree of freedom	P value
Serum Na	-4.12	28	0.05
Serum K	-1.89	28	0.06
Urine Na	3.24	28	0.002
Urine K	4.37	28	0.001
Urine specific gravity	-2.92	28	0.005

Na: Natrium, K: potassium

was seen in clonidine group (P = 0.001) which may describe one of the diuretic mechanisms of clonidine.

Although clonidine group had higher urine electrolytes level (P = 0.001), but no significant differences was seen in blood electrolytes levels (P >0.05).

Discussion

In a study by Laisalmi et al in 2001 the effect of clonidine 4.5 µg/kg and placebo on hemodynamics and neuroendocrine response and parameters was compared in 30 patients undergoing laporascopic cholecystectomy. Results showed that there were no differences in urine output, urine oxygen tension and antidiuretic hormone between the groups[11]. In another study, transdermal clonidine in patients with proximal jejunostomy increased weekly urine volume, but p-value was not significant[12].

Lenaert in 2006 added clonidine to diuretics in order to mobilize ascites and it was seen that clonidine induced an earlier diuretic response associated fewer diuteric requirements[13]. The results of these investigations are parallel with our results which showed induced dieresis with clonidine.

Poliak et al concluded that clonidine causes decrease in noradrenaline and dopamine level and plasma renin activity but no change in epinephrine level[14].

Mase et al in 1996 showed that in awake dogs IV clonidine increased renal prostaglandins and decreased plasma renin activity that induced hypo-osmotic diuresis[15]. In the present study, plasma rennin activity diminished too.

El-mas demonstrated that clonidine (150 microgram/kg per day) for 12 weeks in rats increased urine output during 8 hours treatment period but not during 24 hours period. Plasma and urine osmolality and electrolytes were not altered by clonidine[16], but in our study clonidine group had higher urine electrolytes level and lower urine osmolality.

Intengen by intrarenal infusion of clonidine showed an osmolar and free water response that mediated with alpha2 a/d adrenoreceptor subtypes[17] that could be dissociated pharmacologically into naltrexone-sensitive and prazosin-sensitive responses, respectively. Clonidine (1.0 nmol kg-1 min-1) infused into the renal artery increased osmolar and free water clearance. By pretreatment with prazosin, an alpha2 b-adrenoceptor subtype selective antagonist, the increase in free water but not osmolar clearance

Table 4
Comparison of plasma renin activity and 24 hour urine volume in placebo and clonidine groups after taking drug

Variable	Clonidine group (Mean ± SD)	Placebo group (Mean ± SD)	T	Degree of freedom	P value
Plasma renin activity (ng/mL/hr)	0.247 ± 0.243	0.779 ± 0.482	9.91	58	0.001
24 hour urine volume (mL)	2884.66 ± 384.05	2161.33 ± 422.29	7.24	58	0.001

Na: Natrium, K: potassium

decreased. Pretreatment with the opioid receptor antagonist, naltrexone increases osmolar but not free water clearance. This disparate antagonism of clonidine by prazosin and naltrexone was consistent with two distinct sites.

Selective in vivo activation of imidazoline receptors by moxonidine is associated with dose-dependent diuresis, natriuresis, and kaliuresis[18]. The urinary actions of moxonidine mediated through natriuretic peptide receptors[6]. Moxonidine is another alpha2 agonist that like clondine in our study can induce diueresis and increase Na and K in urine.

Conclusion

In conclusion clonidine as premedicative drug does not decrease serum electrolytes but increases 24 hours urine output and urine Na and K level and decreases plasma renin activity and urine specific gravity.

However, as clonidine increases diuresis, replacement therapy with appropriate fluid in perioperative period should be considered.

Clonidine is a safe premedication in general anesthesia and does not change the serum electrolytes levels.

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