Original article

Dose calcium channel blocker verapamil decrease urinary VMA levels in sympathoadrenal hyperactive patients with posttraumatic stress disorder?

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Abstract

Objective: The majority of the patients with posttraumatic stress disorders (PTSD) embrace augmented urinary flow of Vanillylmandelic Acid (VMA) than normal subjects owing to superior sympathetic doings, which steer to cardiovascular catastrophe. Urinary flow of VMA was evaluated as sympathoadrenal bustle marker in patients with posttraumatic stress disorder. Calcium ion shows a noteworthy dependability in nervousness owing to its special effects on brain synaptosomes. So this study was conducted to explore the effects of Verapamil on sympathoadrenal motion in patients with PTSD. **Methods**: Placebo controlled clinical tryout was conducted. At first hundred (100) PTSD patients were chosen and enrolled in the study, from department of Psychological Medicine Dow University of Health Sciences, Karachi. Verapamil 120 mg/day was specified in divided doses to group-I ($n=50$) patients and group-II ($n=50$) patients received placebo therapy on a daily basis for nine weeks. Each and every patient was monitored weekly, all the way through extent of study. **Results**: Underneath the posttraumatic stress disorder, urinary excretion of VMA was greater. Calcium channel blocker verapamil additionally abolished the embellished retort in urinary flow of VMA appreciably in patients with PTSD. **Conclusion**: Verapamil was experiential to be exceedingly effectual treatment. It reduces VMA levels in urine, and on the whole cardiovascular threat in PTSD patients.

Keywords: PTSD; Sympathetic activity; Urinary VMA and verapamil

INTRODUCTION

In wide-ranging inhabitants, potentially distressing proceedings are comparatively frequent and radical attacks have been happening extra recurrently in everyday life, and are interrelated to psychiatric injury. Posttraumatic stress disorder is one of the slightest studied clinical evils and tiny is acknowledged with reference to its psychiatric complications. Current study is an effort to emphasize the emotional and medical impacts of these disasters and their management in survivors.

Amplified noradrenergic bustle in posttraumatic stress disorders has been noticed in quite a lot of studies [1, 2]. Psychological anxiety has been coupled with amplified noradrenergic action in patients with PTSD. Hawk and his co-workers[3] confirmed the larger extent of activation of sympathetic nervous system in patients with symptoms of PTSD. Similarly Southwick et al[4]. investigated that overstated noradrenergic activity during recall consolidation is coupled with enhanced memory storeroom and long-term memory in humans. That catecholamine-mediated enrichment of remembrance consolidation for exciting

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and harrowing dealings may perhaps participate in the re-experiencing symptoms of posttraumatic stress disorder [5].

This persistent activation of sympathetic system reflected as exacerbations of urinary Vanillylmandelic Acid(VMA) excretion, preventative nervousness and constant worry might be accountable for these elevations in patients with PTSD. Unsurprisingly stress results in a noteworthy sympathetic excessive activity and raised urinary VMA measurements, which mirror the height of sympathetic activity, may offer helpful biochemical indicator of psychosomatic stress responses[6].

Growing clinical confirmation has exposed that too much endogenous discharge of catecholamine norepinephrine in PTSD patients; amplify the threat of cardiovascular morbidity and mortality[7-9].

The discharge of neurotransmitter is reliant on intracellular calcium and occurs when an action potential reaches the nerve terminal and it triggers adequate incursion of calcium ions. It has newly been exposed that the calcium ions undermine the storage vesicles by interacting with a particular protein, synaptotagmin coupled with the vesicular casing. Blending of vesicular covering with terminal membrane occurs, with the eviction of neurotransmitter [10-16]. As a result interacting through calcium channels, verapamil possibly will trim down the emancipation of neurotransmitter. Though, verapamil by no means been tested in clinical trial for the effectiveness against sympathoadrenal activity in patients with PTSD.

For this reason the study was intended and conducted to evaluate the efficacy and small period toxicity of verapamil in patients with PTSD.

MATERIALS AND METHODS

This study was conducted in the department of Pharmacology, Karachi University, Karachi.

Study population

The Research ethics committee Dow University of Health Sciences permitted this study. Hundred PTSD patients were primarily enrolled in the study, from department of Psychological Medicine Dow University of Health Sciences, Karachi. Following clearing up the confines, permission was obtained from all study participants sooner than enrollment. Every one of the patients was fascinated and gave the written approval to contribute the study. The set of patients established diagnosis according to DSM-IV-RT [17,18]. Patients who were taking drugs identified to effect cortisol, catecholamines, urinary VMA and had a preceding history of chief psychiatric sickness, existing reliance on alcohol or additional drugs of abuse similar to sedative or hypnotic, heart and hepatic diseases were expelled out from study.

The study phase consisted of nine (9) weeks for every patient, with weekly follow up appointment.

Analytical Methods

Subject Reported Measures

The preferred patients were enrolled, data and evolution of patients was recorded. From the start of study i.e. week-0 up to the end of study i.e. week-9, an onlooker accomplished the Stress symptoms questionnaire, which was based on prearranged clinical dialogue intended to evaluate adults for the seventeen symptoms of Posttraumatic Stress Disorder (PTSD) outlined in DSM-IV-TR. Subjects indicated the extent to which they had experienced every one symptom for the duration of past week on a five point scale in which 0 = no symptom, 1 = little symptoms, 2 = fair symptoms, 3 = relatively more symptoms, 4 = tremendous symptoms. The scouring of every item was summed for an entire score [19].

Urine Analysis Measures

Twenty-four hours urinary VMA was determined by way of kit, biosystem Spain. An anionic exchange resin being eluated afterward once the interfering substances are washed away retains VMA. The VMA is quantified spectrophotometrically as Vanilin subsequent to peroidate oxidation under alkaline environment.

The amount of VMA per 24 hours urine was calculated using the following general formula:

$$VMA(mg/L) \times V_{Urine/24\ Hours}(L) = VMA/24\ hours(mg)$$ [19]

Statistical analysis

All results are expressed as means + standard error of the mean (SEM). Differences among means were tested for significance using the paired Student's *t*-test. Data analysis was performed by means of the

Statistical Package for Social Sciences (SPSS). For all analyses, P values less than 0.05 was considered significant.

RESULTS

Throughout the study it was observed that mean age of all participants of either sex was 35.1 (Range 25-45 years). They had a mean of 1.5 months precedent history of traumatic incident (Range 1-3 months). Each and every one had subjective symptoms of Post Traumatic Stress Disorder and mean symptom severity score was 60.5 ± 1.73, their urine specimens showed optimistic outcome when tested for 24 hours urinary VMA. Management compliance was excellent and no irregularity was observed in complete blood counts or in kidney and hepatic function tests following treatment by means of placebo as well as verapamil. Whereas the drug associated adverse effects observed in verapamil group were constipation (10%) and headache (8%).

As it is revealed in Table-1, following 9 weeks of two treatment methods, there were statistically noteworthy reductions in urinary VMA excretion (P < 0.000 1), but this reduction was additional in verapamil group (49.2%) than placebo group (12.9%).

Table1 Effects of verapamil and placebo on urinary VMA excretion before and after treatment (Mean ± SEM)

Urinary VMA	Before Treatment	After Treatment	P value	Reduction
Placebo(n = 50)	6.21 ± 0.34	5.41 ± 0.24	< 0.000 1	12.9 %
Verapamil(n = 50)	5.14 ± 0.17	2.53 ± 0.11	< 0.000 1	49.2 %

DISCUSSION

This is the opening study to our information, to explore the effects of calcium channel blocker verapamil on sympathetic activity in patients with PTSD. In elucidation of study's outcome, it is significant to note the conclusion that paying attention on an increase of sympathetic nervous system bustle, which manifested itself through an intensified 24-hour's urinary VMA concentration.

24-hour urinary VMA levels were assessed as an indicator of activity in the sympathetic limb of the autonomic nervous system, the segment of nervous system that would trigger the supposed hyperarousal in the PTSD. In the present study, excretion of VMA was straightly interrelated with PTSD findings and symptom severity amongst the patients. These findings are consistent with biopsychological study by Yehuda [20], which verified the sympathetic hyperarousal in PTSD. These results prop up the proposition that enhanced noradrenergic activity throughout reminiscence consolidation is coupled with improved long-termed memory in humans.

On the other hand, Cui et al [21]. has investigated the problem, who observed augmented urinary VMA concentrations in stroke-prone impulsively hypertensive rats, that were identified to have sympathetic hyperactivity to a variety of stimuli. Additionally, this is in absolute conformity with our consequences; yet this study incorporated an investigation of urinary excretion of norepinephrine (NE) and vanillylmandelic acid (VMA), in addition to the plasma levels of norepinephrine in association with cold stress, regrettably we did not approximate urinary or plasma levels of norepinephrine. This is one of the confines of our study.

Epidemiological and experimental studies have linked sever acute and, less recurrently, chronic life anxiety to cardiovascular diseases. In addition, animal models recommend that psychological stress may perhaps cause atherosclerosis, almost certainly by escalating sympathetic activation [22]. The present conclusions of this research are reliable with confirmation that inhabitants with PTSD are at the elevated hazard of cardio-vascular disorders, for the reason of amplified activity of noradrenergic system, which is the foremost risk issue of arteriosclerosis and vascular accidents[23, 24].

The present results recommend an opportunity to expand insights as to the probable utilization of verapamil in psychiatric remedy. We found that placebo and verapamil treatment showed a significant turn down in excretion of urinary VMA, but this cutback was additional in verapamil group than placebo group. The improvements in placebo group were might be a natural diminution and a role of time,

which is forever probable among all psychiatric disorders.

Furthermore, verapamil treatment helps to lessen the cardiovascular risk in psychiatric patients. So this treatment dampens on the whole threat to cardiovascular well being, in patients with PTSD.

CONCLUSION

Posttraumatic stress disorder exacerbates the foremost cardiovascular risk in alliance with sympathetic nervous system over activity, as indicated by corresponding augment in the excretion of VMA. Verapamil have been reported as secure and effectual management for the patients with PTSD. It has a capacity to condense as well as ameliorates cardiovascular threat.

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