



An Association Between Serum Cortisol Levels In Erosive And Nonerosive Oral Lichen Planus Patients

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Abstract

Study objectives: Oral lichen planus (OLP) is a well recognized chronic mucocutaneous disorder which can manifest in the oral mucosa, whose exact pathogenic mechanisms have not been understood. Estimation of serum cortisol in patients with OLP may be helpful in understanding the pathogenesis. Therefore a study was undertaken to analyze the serum cortisol levels in OLP patients. An attempt was also made to evaluate the anxiety and depression levels in these patients.

Design and key methods: A case control study was conducted on 15 cases each of non-erosive oral lichen planus (NEOLP) and erosive oral lichen planus (EOLP) and 10 controls. The serum cortisol levels of all 40 patients were estimated by using electrochemoluminescence. Hospital Anxiety and Depression Score questionnaire was administered to evaluate the psychiatric status of all the patients.

Results: The mean serum cortisol level of the OLP group showed a very highly significant difference ($p=0.001$) from the controls. The mean anxiety and depression scores of the OLP group showed very highly significant difference ($p=0.001$) from the controls. The difference in mean cortisol level between NEOLP group and control was not significant ($p=0.06$), whereas the difference was very highly significant between the EOLP group and controls ($p=0.001$). The difference between the anxiety score between the NEOLP group and EOLP group, but the depression scores between the two groups were not very significant ($p=0.085$).

Conclusion: These findings suggest that psychiatric factors play a vital role in the pathogenesis of OLP and serum cortisol could be a possible indicator for the erosive nature of the lesion.

Introduction

Many systemic diseases manifest in the oral cavity. In

some conditions oral cavity provides the first clue for the detection of underlying systemic disease. Dermatological disorders are one such class of diseases that have oral manifestations. Thus the dentist may be in a position to establish the diagnosis of a dermatologic disease before the cutaneous lesions become apparent. Lichen planus, pemphigus, pemphigoid and psoriasis are a few examples of dermatologic diseases that have oral manifestations.

Lichen planus is a chronic inflammatory mucocutaneous disorder, which can manifest in the oral mucosa. Oral lichen planus affects 0.1-4% of various populations [1]. The disease usually affects middle aged to elderly females. Currently the precise cause of lichen planus is unclear. There have been many investigations, both experimental and epidemiologic, of the forms of lichen planus. Current concepts of pathogenesis include immunologic and genetic factor. In addition to it emotional stress, hepatic disease and drugs also have been implicated as causative factors [2]. Oral lichen planus most often affect the posterior buccal mucosa and tongue and usually have erosive and non-erosive forms. While the non erosive form is often asymptomatic, the erosive forms are commonly sensitive or painful and affect the quality of life [3]. Many patients often report of worsening of the disease during periods of emotional stress [4]. Some patients could recall a stressful situation at the onset of their disease; many others believed that chronic tension aggravated it. Few researches have showed that association exists between emotional stress and erosive disease, but not with asymptomatic variants [5].

Stress is one of the modulating factors that can up regulate the production of cortisol. Cortisol is a 21-carbon glucocorticoid secreted by the adrenal cortex that regulates carbohydrate, protein, fat and water metabolism, maintains vascular reactivity, affects the sensitivity of the nervous system, regulates blood cell numbers, and affects the human stress response [6].

Serum cortisol levels are increased in response to stressful situation is well known fact. Therefore it can be a useful aid in not just understanding the pathogenesis of oral lichen planus but also determining the progression of these lesions. There

have been few studies done in the area of stress as a predisposing factor in oral lichen planus lesions. Thus, there is a great need to understand the etiopathogenesis and progression of these lesion. Whether the cortisol levels in oral lichen planus are altered from those in the normal subjects is also being investigated in this study.

Materials and methods

A case control study involving 40 patients within the age group of 25 to 50 years was carried out in department of Oral medicine, Yenepoya Dental College and Hospital.

Fifteen subjects with clinically non-erosive, histopathologically confirmed oral lichen planus without skin involvement formed group A, whereas fifteen subjects with clinically erosive, histopathologically confirmed oral lichen planus patients without skin involvement formed group B. Ten subjects with no apparent lesions of the oral mucosa and the skin formed the control group C.

Only patients without long term systemic diseases or medications were include in the study. Patients with autoimmune disorders and hepatitis C were excluded from the study. After obtaining consent from the patient, incisional biopsy was performed under local anesthesia from a representative part of the lesion in oral lichen planus patients and sent for histopathological evaluation. 5ml of venous blood was obtained by venipuncture of the median cubital vein under aseptic. The blood samples were obtained between 8.00 - 10.00 A.M. and between 7.00 – 8.00 P.M. They were sent for serum cortisol estimation by the eletrochemoluminiscence method [ELICSYS-1010 (Germany)] within one hour and the mean of the two values was calculated as the serum cortisol level.

Each of the patients was administered a HADS (Hospital Anxiety and Depression Questionnaire). The questions were translated in the regional language for patients unable to read English. Scores were added separately for anxiety and depression and they were assigned as normal (0-7), borderline abnormal (8-10) and abnormal (11-21).

Data was analyzed using the SPSS software (Statistical Package for Social Sciences). Student's *T* test and Tukey's HSD (honestly significant differences) test were applied for statistical evaluation. Level of significance was set at 0.05 and 0.001.

Results

Demographic data analysis of Group A

In this group the age of the subjects ranged from 25 to 50 years. Majority (46.66%) of these cases were within 41-50 years, followed by 31-40 years (33.33%) and least in 21-30 years. Males comprised 73.33% of this group (11/15), while females formed the remaining 26.66% of the group (4/15).

Demographic data analysis of Group B

In this group the age of the subjects ranged from 27 to 50 years. Majority of the patients (60%) were in the age group of 41-50years, followed by 31-40 years age group (26.66%) and the least (13.33%) belonged to 21-30years. Males comprised 60% of this group (9/15) while females comprised the remaining 40% of the group (6/15).

Analysis of demographic data of Group C

Majority of the patients (50%) in this group were in the age group of 41-50 years, followed by the age group of 21-30years (30%) and the least patients (20%) were in the age group of 31-40 years. Males comprised 40% of this group (4/10), while females formed 60% of this group.

Analysis of mean cortisol values, mean anxiety and mean depression scores of

the groups in the study:

Mean cortisol value analysis

The mean cortisol value in Group A calculated to be 9.7133 ± 2.02868 $\mu\text{g/dl}$, was lower than the mean cortisol levels of Group B 14.6067 ± 3.09411 $\mu\text{g/dl}$ but higher than the mean cortisol value of Group C 7.2100 ± 1.62717 $\mu\text{g/dl}$. The combined mean cortisol value of Group A and Group B calculated to be 12.1600 ± 3.5586 $\mu\text{g/dl}$ was higher than that of Group C 7.2100 ± 1.62717 $\mu\text{g/dl}$ [Illustration 1]

Mean anxiety score analysis

The mean anxiety score in Group A calculated to be 10.0667 ± 2.12020 , was lower than mean anxiety score in Group B 14.6000 ± 4.2728 but higher than the mean anxiety score in Group C 6.5000 ± 2.36878 . The combined mean anxiety cores of Group A and Group B 12.3333 ± 4.03718 was higher than that of Group C 6.5000 ± 2.36878 [Illustration 2]

Mean depression score analysis

The mean depression score of Group A calculated to be 4.2000 ± 2.45531 was lower than mean depression score of Group B 6.4000 ± 3.58170 but higher than mean depression score of Group C 1.6000 ± 1.26491 . The combined mean depression score of Group A and

Group B 5.3000 ± 3.21795 was higher than that of Group C 1.6000 ± 1.26491 [Illustration 3]

Combined HADS score of the three groups

The Combined HADS score of Group B was higher than that of group A and group C [Illustration 4]

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ANALYSIS OF STATISTICAL SIGNIFICANCE

Serum cortisol levels

When statistical comparison was made between the three study groups for the serum cortisol levels, a very highly significant statistical difference ($p=0.001$) was noted. [Illustration 5]. When Group A was compared with Group B for serum cortisol levels, it was found to be highly significant ($p = 0.001$). No statistically significant difference was noted between Group A and Group C serum cortisol values ($p = 0.067$). On comparison of Group B with Group C serum cortisol values revealed a very highly statistically significant difference ($p = 0.001$). When comparison of combined mean serum cortisol value of Group A and Group B was done with Group C a very highly statistically significant difference was noticed ($p=0.001$).

Anxiety scores

When an intergroup comparison was made between the three groups for the anxiety scores, a very highly statistically significant difference ($p = 0.001$) was noted [Illustration 6]. On comparison of Group A and Group B a very high statistical significant difference was noticed ($p=0.001$). A statistically significant difference was observed between Group A and Group C when anxiety scores were compared ($p=0.023$). On comparison of the mean anxiety scores of group B with Group C a very highly statistically significant difference ($p=0.001$) was detected. When comparison of combined mean anxiety scores of Group A and Group B was done with Group C a very highly statistically significant difference was noticed ($p=0.001$).

Depression scores

When an intergroup comparison was done for the depression score between the three groups in the study, a very highly significant difference ($p=0.001$) was noted [Illustration 7]. No statistically significant difference ($p=0.085$) was observed between the mean depression scores between Group A and Group B. Similarly no significant difference ($p=0.065$) was noticed when Group A was compared to Group C. But when Group B scores were compared to Group C a very highly significant difference ($p=0.001$) was observed. When comparison of combined mean depression scores of Group A and Group B was done with Group C a very highly statistically significant

difference was noticed ($p=0.001$).

Discussion

In this study an attempt was made to analyze the anxiety, depression levels and the serum cortisol levels in erosive, and non-erosive oral lichen planus patients. Also an attempt was made to compare these parameters between oral lichen planus patients and normal patients. The study was performed by dividing the patients into three groups, two groups of oral lichen planus patients of erosive and non-erosive types, the third group served as controls.

Analyzing the results of our study, it can be noted that both in Group A (non erosive) & Group B (erosive) majority of the patients (46.66% & 60% respectively) were within the age range of 41 to 50 yrs. The age distribution was similar as in most of the studies [7, 8].

The gender distribution in the present study for Group A and Group B was 7:3 & 6:4 (males: females) respectively. This ratio was opposite to that seen in studies by Silverman S Jr et al and Brown JS et al [7, 9].

The mean serum cortisol analysis between oral lichen planus patients (Group A & Group B combined) and controls (Group C) revealed a significant difference. Similar results were found by Prolo P et al Ivanoski K et al [10, 11]. Both these studies showed that there was a significant alteration in the CD4/CD8 ratios. They suggested that altered CD4/CD8 ratios could be an effect of alterations in the serum cortisol levels. In the present study we have not taken into consideration of the CD4/CD8 ratios but this could probably be the factor linking the altered serum cortisol levels with oral lichen planus.

Few studies have reported no significant difference in the cortisol levels between controls and oral lichen planus patients [12, 13]. One of the research group conducted a study by determining the salivary cortisol levels in patients under stressful conditions, while the other had conducted a study determining the average plasma cortisol and 24-hr urine cortisol in oral lichen planus patients. They stated that their study results do not support the hypothesis that environmental factors like stress have an influence on the neuro-endocrine system through cortisol levels.

Prolo P et al found that more than half of the patients, in their study who had elevated serum cortisol levels had erosive oral lichen planus [10]. The non-erosive types had serum cortisol levels similar to that of controls. Similar results were found in our study, a very highly statistically significant between the erosive

group and control but no significant difference between the non-erosive group and controls. The mean cortisol levels in all three groups – non erosive, erosive and controls were marginally higher in the present study compared to Prolo P et al.

Ivanoski K et al measured serum cortisol levels by using radio immuno-assay [11]. In their study they found that the serum cortisol levels in the controls and non-erosive lichen planus patients was 248.7 ± 10.7 Nmol/L and 250.3 ± 11.1 Nmol/L respectively, while in the erosive group the serum cortisol level was 536.0 ± 55.6 Nmol/L. The results matched our study wherein the mean cortisol value in control group was calculated to be 7.2100 ± 1.62717 μ g/dl and the mean serum cortisol value in non-erosive group was calculated to be 9.7133 ± 2.02868 μ g/dl whereas the mean cortisol levels erosive lichen planus group was 14.6067 ± 3.09411 μ g/dl. Although a different method of estimation of serum cortisol in the present study compared to the one used by Ivanoski K et al the outcome was similar.

Numerous studies showed that significantly higher stress, anxiety and depression levels were found in the oral lichen planus patients when compared to the controls [4-18]. This feature was also noticed in the present study with the lichen planus group showing significantly higher anxiety scores (12.3333 ± 4.03718) and depression scores (5.3000 ± 3.21975) when compared to the anxiety scores (6.5000 ± 2.36878) and depression scores (1.6000 ± 1.26491) of the controls. Allen et al and McCartan BE found that there was no statistically significant difference of the anxiety and depression scores between oral lichen planus patients. Allen et al however noticed that anxiety levels were elevated in 50% of their cases while depression scores, both measured on HAD scale were low in all but a few. In the present study both the anxiety and depression scores were elevated in oral lichen planus patients compared to that of controls. Lundquist EN et al observed that depression, anxiety and stress were more common in patients with erosive lichen planus than in a control group. Similar features were noticed in our study wherein both anxiety and depression scores were higher in the erosive group when compared to the control group.

A study suggested that patients with erosive lichen planus exhibited higher depression scores than patients with non-erosive lichen planus [18]. In our study we found that there was no significant difference in the depression scores between the non-erosive and erosive lichen planus groups. Ivanoski K et al observed that a very highly significant difference was noticed between the (combined erosive and

non-erosive) and the controls when anxiety scores and depression scores were taken into consideration. But there was not much difference between the anxiety and depression scores when an intercomparison was done between the erosive and non-erosive group. In the present study a significant difference between the anxiety and depression scores of the erosive and non-erosive groups unlike the observation of Ivanoski K et al.

Most of the drug trial and studies have all stated that corticosteroids are one of the most effective treatment modality available for the treatment of oral lichen planus. Corticosteroids have at times been used in the systemic form for the treatment of severe forms of erosive lichen planus [21-35].

Prolo P et al Ivanoski K et al and the present study have concluded that the serum cortisol levels increase during the erosive phase of oral lichen planus. But than the logic of administering corticosteroids in treating lichen planus is questionable. Ivanoski K et al have stressed on the role the psycho-neuro-immunological model for the possible solution to the above mentioned question. The stressful situation causes the HPA-axis to release corticosteroids; simultaneously there are psycho-neuro-immunologic interactions at the nerve terminals with the lymphocytes and haemopoetic system. An altered lymphocytic state is produced which is directly linked to the occurrence of lichen planus. The corticosteroids released by the body control the immune response. However they act selectively inhibiting the non-activated lymphocytes while the activate cells continue to produce pro-inflammatory cytokines. This warrants the use of an external source of corticosteroids in the treatment of oral lichen planus.

Although the cortisol levels tested in this study represents only one possible mechanism for psycho-neuro-immune interactions, these data suggest that cortisol and psychological status may play a role in the pathogenesis of OLP, especially in the erosive forms of the disease. Taken together, these may represent possible avenues by which the psychological status of an individual may impact on immune system homeostasis during onset and progression of lichen planus.

Conclusion

The following conclusions can be drawn from the study: Oral lichen planus was more commonly observed in the middle age group of 40-50 years.

Serum cortisol levels were significantly higher in the oral lichen planus patients compared to controls. The anxiety scores of oral lichen planus patients were significantly higher than that of the controls. The depression scores of the oral lichen planus patients were significantly higher than that of the controls. This highlights the fact that anxiety and depression may have a role in the pathogenesis of lichen planus. There was no significant difference in the serum cortisol levels between non-erosive oral lichen planus and that of controls. The serum cortisol levels of erosive lichen planus patients were significantly higher than the serum cortisol levels of the controls. The serum cortisol levels of the erosive oral lichen planus patients were significantly higher than that of non-erosive oral lichen planus patients. This finding suggests that serum cortisol may be a predictor for the erosive nature of oral lichen planus. The anxiety score of the erosive group was very significantly higher than that of the anxiety scores of the controls. The anxiety scores of the non-erosive group marginally higher than the anxiety scores of controls. This suggests that stress may be an aggravating factor of oral lichen planus. The depression scores of the oral lichen planus patients are significantly higher than that of the controls. There is no significant difference between the depression scores of the non-erosive oral lichen planus group compared to the depression scores of the erosive oral lichen planus group.

The overall results suggest that changes in serum cortisol levels correlates with changes in the stress levels and the clinical presentation of oral lichen planus.

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Illustrations

Illustration 1

Graph showing mean serum cortisol values of the three groups

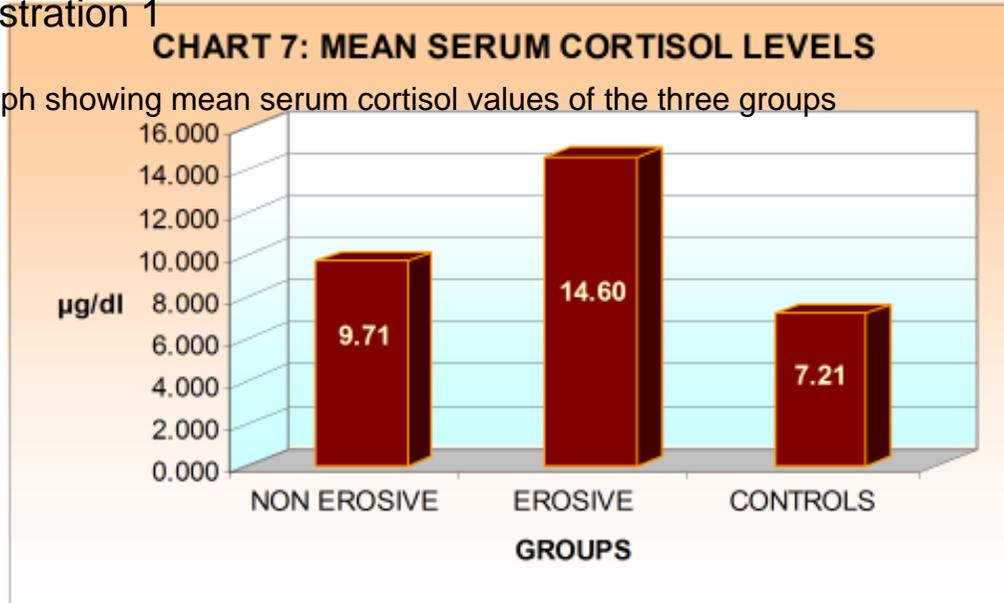


Illustration 2

CHART 8: MEAN ANXIETY SCORES

Graph showing the anxiety scores of the three groups

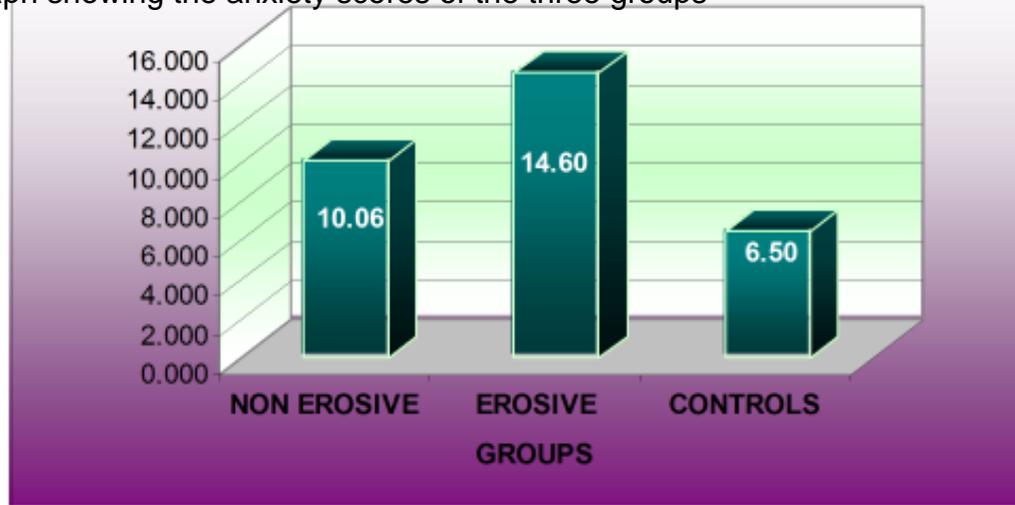


Illustration 3

CHART 9: MEAN DEPRESSION SCORES

Graph showing the depression scores of the three groups

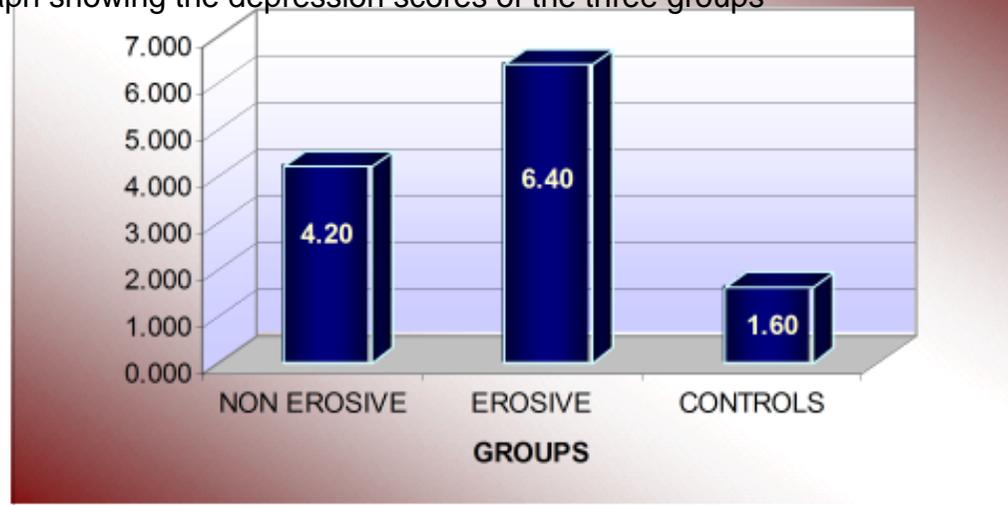


Illustration 4

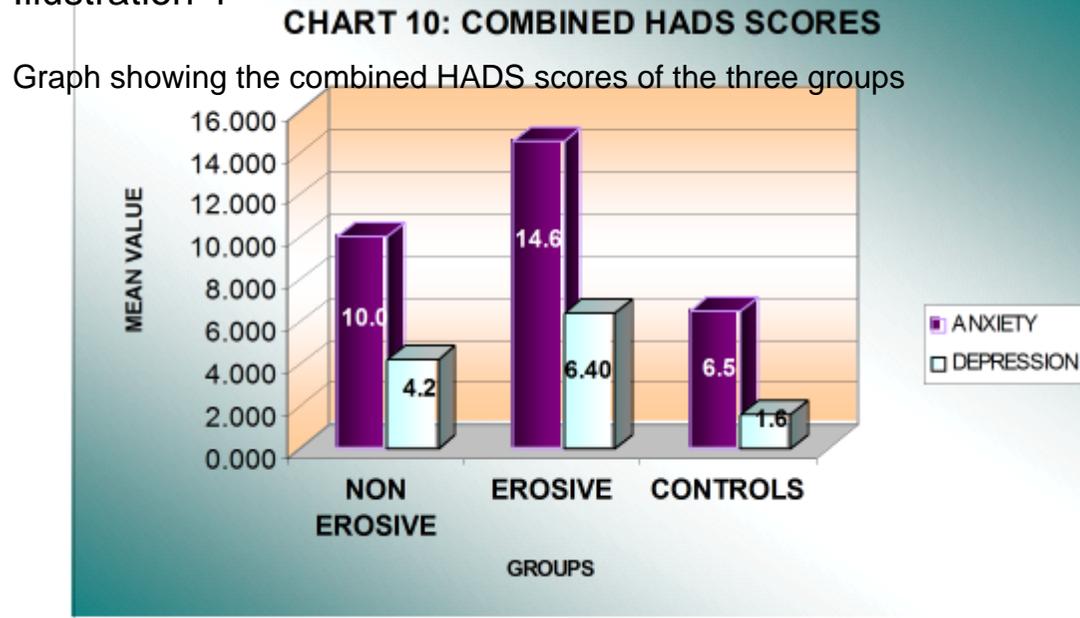


Illustration 5

INTERGROUP COMPARISON OF THE MEAN CORTISOL LEVELS

GROUPS	n	MEAN	STANDARD	F	p value
GROUP A	15	9.7133	2.02868		
GROUP B	15	14.6067	3.09411		
GROUP C	10	7.2100	1.62717	31.20	.001VHS

Illustrations	n	MEAN	STANDARD	F	p value
INTERGROUP COMPARISON OF MEAN AND DELTA SCORES					
GROUP A	15	9.7133	2.02868		
GROUP B	15	14.6067	3.09411		
GROUP C	10	7.2100	1.62717	31.20	.001VHS

Illustration	n	MEAN	STANDARD	F	p value
GROUP A	15	4.2000	2.45531		
GROUP B	15	6.4000	3.58170		
GROUP C	10	1.6000	1.26491	9.24	.001VHS

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