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RESEARCH ARTICLE

ASSESSMENT OF ANXIETY AND DEPRESSION IN PATIENTS UNDERGOING SURGICAL REMOVAL OF LOWER THIRD MOLARS UNDER LOCAL ANESTHESIA – A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Aim: The aim is to assess the interplay between anxiety and depression was also assessed by comparing the HAD scales with biochemical serum markers of anxiety and depression, namely cortisol and serotonin during surgical removal of third molar.

Materials & Methods: A prospective randomized study was conducted using 30 healthy patients (male-13, female-17) between 18-45 years, requiring surgical extraction of impacted mandibular third molar were included in the study. Hospital anxiety and Depression Scale (HAD) scale is a questionnaire used to assess levels of Anxiety and Depression. Blood

samples were collected before and after the surgical procedure. The blood samples was analysed for serum cortisol and serotonin, these results were compared with the HAD questionnaire results.

Results: The results were analysed using the Student 't' test and Chi square test. The comparison between the pre and post extraction cortisol (C1 and C2) values suggested that the mean post-operative value was in the higher range of the physiological limits with $p < 0.05$ whereas the pre and post extraction (S1 and S2) was within the normal limits with p value > 0.005 .

Conclusion: The study showed that patients were only anxious but showed no signs of depression after surgical removal of the third molar. Study concludes depression does not co-exist with anxiety in immediate pre and post-operative setting.

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INTRODUCTION

Anxiety & fear of surgical treatment has been always considered as a problem in patient management for many decades. Fear is an emotional, physiological and behavioral response to a recognized external threat. Anxiety is an unpleasant emotional state, the causes of which are less clear³. Depression is a common psychiatric disorder, characterized by a persistent lowering of mood, loss of interest in usual activities and diminished ability to experience pleasure¹. Psychological disorders like depression and anxiety are commonly met in general practice; which are frequently not diagnosed and less treated. It has been estimated that 1 in every 5 patients who consults a dentist experiences clinical symptoms of depression⁵⁷. Majority of patients undergoing elective surgery have increased anxiety.

Stress activates the Hypothalamic-Pituitary-Adrenal axis and produces an immediate sympathetic activation as well as significantly raising anxiety in patients³. Serum Cortisol levels increase due to any type of stress including sepsis, trauma, hypoglycaemia, acute anxiety and heavy exercise. Serotonin has been implicated in the coordination of mood, sleep, motor activity, thermoregulation, sexual activity, aggression, feeding, learning, and memory. Depression is associated with low levels of monoamines, particularly, 5-Hydroxy tryptamine (serotonin) and nor ephedrine. These are the objective methods of assessing anxiety and depression which are reliable. However subjective measurements tools like questionnaires have several advantages as they are quick, inexpensive and non –invasive. Various anxiety & depression scales are developed to measure their levels. The most commonly used questionnaire is the Hospital Anxiety and Depression Scale. HADS is a reliable and valid instrument for assessing anxiety and depression in medical patients. The scale measures separately the Anxiety & Depression as well as both these entities together⁹.

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In this study, we intend to investigate the interplay of anxiety and depression by comparing the HAD scales with biochemical serum markers of anxiety and depression, namely cortisol and serotonin in the immediate pre surgical and post surgical setting.

MATERIALS AND METHODS

This prospective randomized control study was conducted in the Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, Sri Ramachandra University, Chennai. A total of thirty patients with impacted mandibular third molar who reported to the department of Oral and Maxillofacial Surgery, from June 2007 to December 2010, and who satisfied the following criteria, were included in the study. The study protocol was approved by the Hospital Research Ethics Committee. All healthy patients requiring impaction of mandibular third molar for the first time, with age group of 18-45 years were included in the study. Patients on Steroid therapy, or those taking antidepressants/anti-anxiety drugs, medically compromised, with a history of psychiatric problems, previous history of third molar surgery were excluded from the study. A total of thirty healthy patients (male-13, female-17) satisfying the inclusion criteria in the age group between 18-45 years requiring surgical removal of mandibular third molars for prophylactic, symptomatic and orthodontic reasons were included. Preoperative Intra-oral periapical radiographs / Orthopantomograms were taken to assess the type of impaction, position and depth in relation to the second molar. A surgical procedure was planned for removal of impacted mandibular third molars.

Hospital Anxiety and Depression Questionnaire (HAD)

HAD scale is a questionnaire used by Doctors and various therapists to assess levels of Anxiety and Depression. HADS is a valid tool for assessing anxiety and depression in patients. The HADS comprises of 14 statements. The 14 statements are applicable to either generalized anxiety (7 statements) or depression (7 statements). Even-numbered questions associate to depression and odd-numbered questions associate to anxiety. Each question has 4 possible replies. Responses are measured on a scale from 3 to 0. The maximum score is 21 for depression and 21 for anxiety. A score of 11 or higher indicates the probable presence of the mood disorder with a score of 8 to 10 being just suggestive of the presence of the respective state of disorder. In its current form the HADS is divided into four ranges: normal (0-7), mild (8-10), moderate (11-15) and severe (16-21). A translated version of the HAD scale in the regional language (Tamil) was given to those patients who lacked knowledge of English.

Procedure

Pre Operative

The patients were seated comfortably in the dental chair. Patients were explained about the study and surgical procedure and a verbal and written consent was obtained. HAD questionnaire was filled by the patient.

After completion of the questionnaire, patient's blood sample was collected by venepuncture into vacutainer measuring about 2.5 ml in volume and was kept separately and labelled as A and given a numerical prefix e.g. 1A,2A,3A etc.

Post Operative

The patient was asked to fill the HAD questionnaire on their own after the surgical procedure. After completion of the questionnaire, blood sample was again collected by venepuncture into vacutainer measuring about 2.5 ml in volume and was kept separately and labelled as B and given a numerical prefix e.g. 1B,2B,3B etc.

Method of Collection and Storage of blood

Blood samples were collected from all patients by a single operator. A total of 60 samples were withdrawn from the 30 patients (Pre Operative & Post operative). The blood was collected by venepuncture into vacutainers (Figure 1 and 2) and transferred to pre-rinsed plastic tubes and transported to the lab. To prevent the oxidization of serotonin, a pinch of 0.032M Ascorbic acid was added to the containers. The blood samples were analysed in the Dept of Biomedical Sciences, Sri Ramachandra Medical College & Research Institute. The samples were centrifuged at 4500 x g for 10 minutes to obtain platelet free plasma. Individual serum samples were isolated into two Eppendroff tubes for estimation of serotonin and cortisol (Pre operative – S1 & C1 and Post Operative- S2 & C2). These tubes were kept in deep freezer at -20°C until all the study samples were collected. The serum collected was analyzed by using Enzyme immunoassay to assess Serotonin (Serotonin EIA BA 10-0900, Germany) (Figure 3) and Direct immunoassay to assess the Cortisol (Magiwell SH-101, U.S.A) (Figure 4). All the samples were analysed using BIO RAD ELISA analyser. Results were obtained only for 28 samples out of 30, due to error in detection. Hence only 28 out of 30 patients could be assessed in our study. Analysis was performed to correlate the clinical HAD-A and HAD-D scale and the serum levels of the cortisol and serotonin using Pearson's coefficient of correlation. The mean values were analysed using Student's 't' test (paired sample) using Statistical Package for Social Services (SPSS) Version 15.

RESULTS

Mean value of pre-operative cortisol was observed to be 160.4 ng/dl with a standard deviation of 107.5 for 28 patients. The mean post operative cortisol was observed to be 212.77 ng/dl with a standard deviation of 114.3 for 28 patients. The mean difference between C 1 & C2 was tested using 't'-value = 2.51 which is found to be statistically significant with a p-value of 0.019 as shown in Table 1 and Figure 6. Mean value of pre operative serotonin was observed to be 144.48 ng/dl with a standard deviation of 69.5 for 28 patients. The mean post operative serotonin was observed to be 189.5 ng/dl with a standard deviation of 90.1 for 28 patients. The mean difference between S 1 & S 2 was tested using 't'-value = 2.9 which is found to be statistically significant with a p-value of 0.007 as shown in Table 2 and Figure 7. Mean value of pre-operative HAD-A was observed to be 13.78 with a standard deviation of 2.8 for 28 patients.



Fig. 2. Labelling of blood sample



Fig. 1. Armamentarium for blood sample collection



Fig. 3. Serotonin elisa kit



Fig. 4. Cortisol elisa kit



Fig. 5. Bio rad Elisa analyser

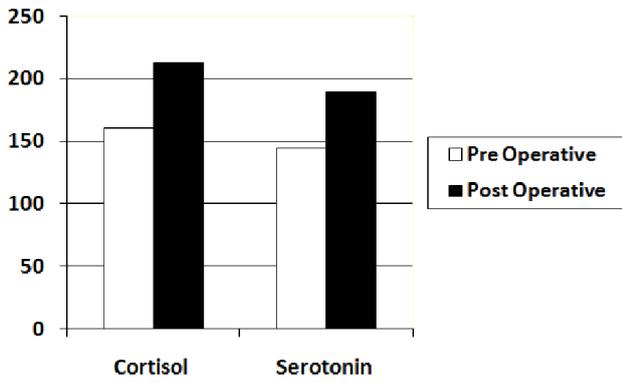


Figure 6. Bar Chart showing the preoperative and post-operative cortisol and serotonin levels

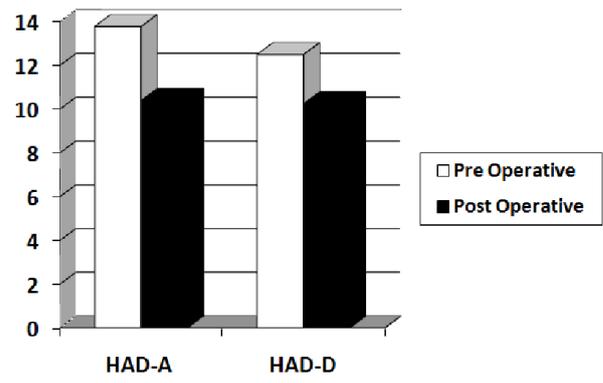


Figure 7. The comparison between the preoperative and post-operative cortisol and serotonin levels

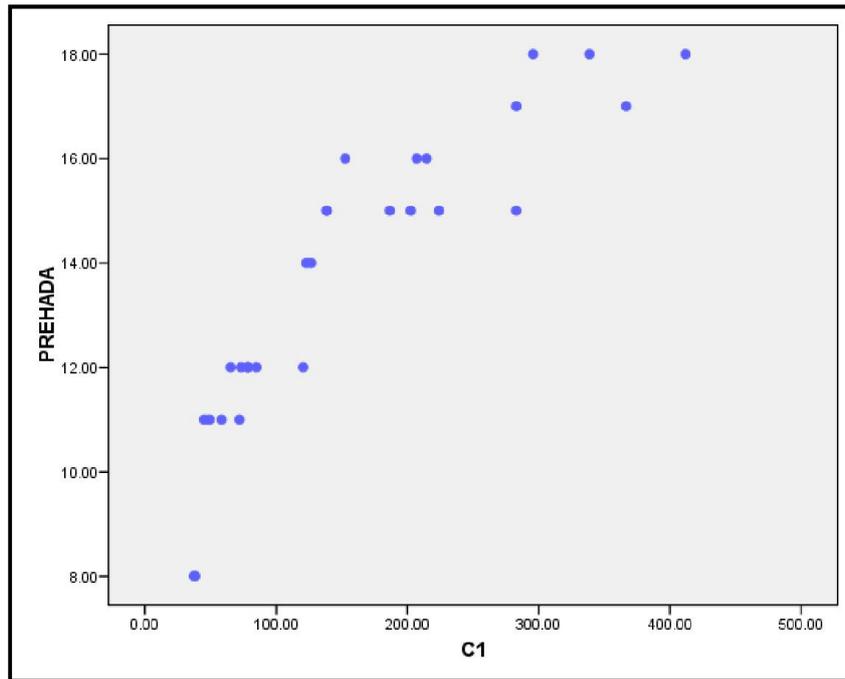


Figure 8. Comparison between the Mean Pre op Cortisol C1 and Mean Pre Operative HAD -A

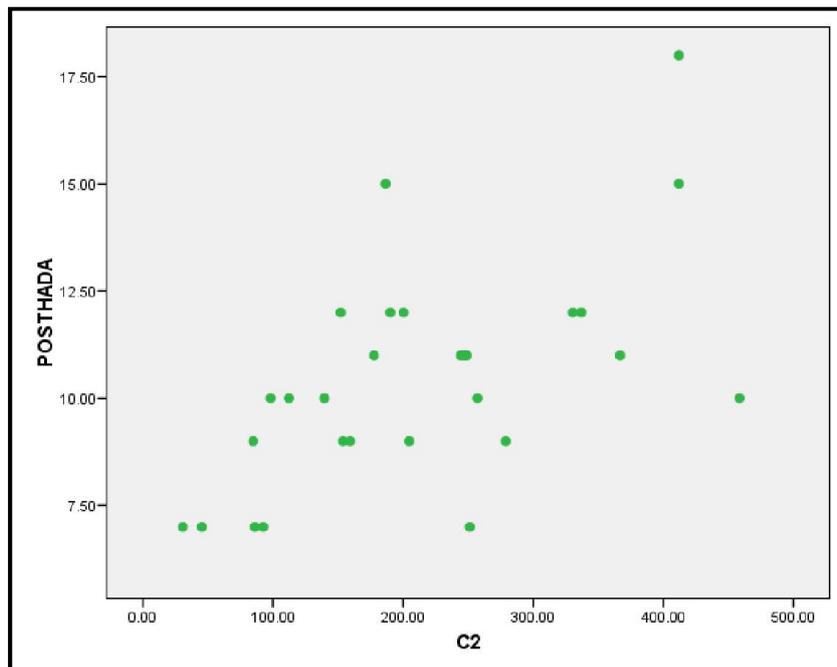


Figure 9. Comparison between the Mean Post-Operative Cortisol C2 and Mean Post-Operative HAD -A

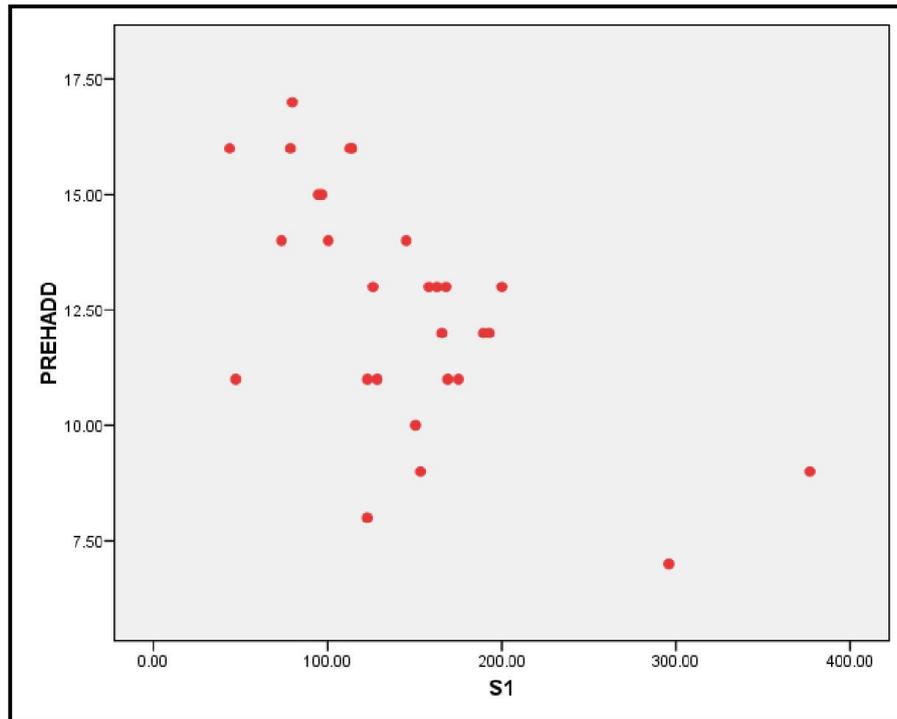


Figure 10. Comparison between the Mean Pre Operative Serotonin S1 and Mean Pre Operative HAD -D

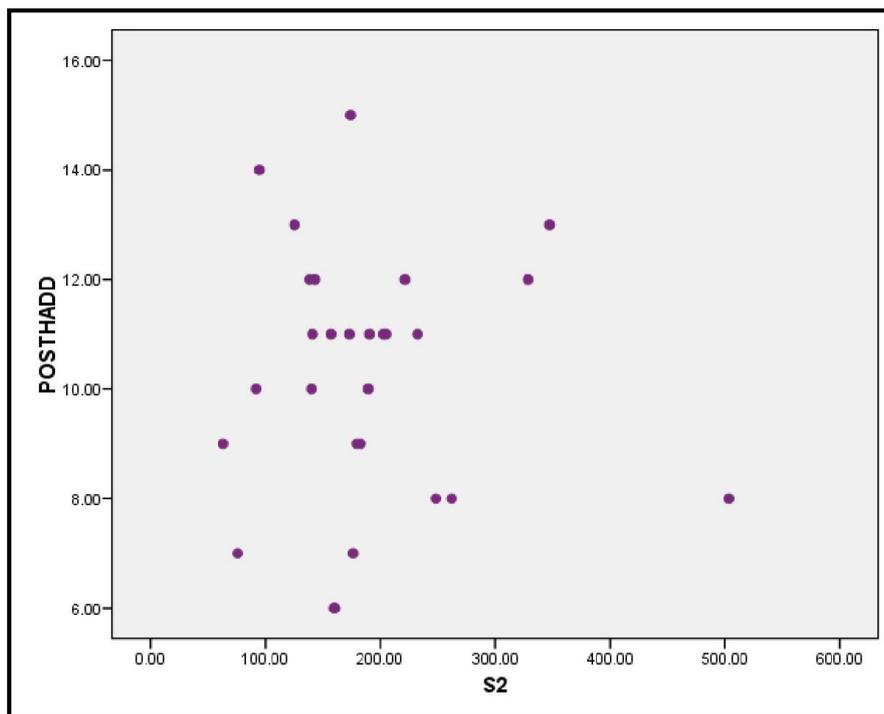


Figure 11. Comparison between the Mean Post Operative Serotonin S2 and Mean Post Operative HAD -D

Table 1. The preoperative and post operative cortisol levels

| Cortisol | N | X- Mean | SD | t-value | P-value |
|-------------------|----|---------|-------|---------|---------|
| Pre Operative C1 | 28 | 160.47 | 107.5 | 2.51 | 0.019 |
| Post Operative C2 | 28 | 212.77 | 114.3 | | |

Table 2. The comparison in the preoperative and post operative serotonin levels

| Serotonin | N | X- Mean | SD | t-value | p-value |
|--------------------|----|---------|------|---------|---------|
| Pre Operative S 1 | 28 | 144.48 | 69.5 | 2.90 | 0.007 |
| Post Operative S 2 | 28 | 189.51 | 90.1 | | |

Table 3. The preoperative and post operative HAD-A levels

| HAD A | N | X- Mean | SD | t-value | P-value |
|----------------|----|---------|-----|---------|---------|
| Pre Operative | 28 | 13.78 | 2.8 | 6.10 | 0.00 |
| Post Operative | 28 | 10.4 | 2.6 | | |

Table 4. The preoperative and post operative HAD-D levels

| HAD-D | N | X- Mean | SD | r-value | P-value |
|----------------|----|---------|------|---------|---------|
| Pre Operative | 28 | 12.5 | 2.60 | 4.86 | 0.00 |
| Post Operative | 28 | 10.25 | 2.31 | | |

Table 5. Comparison between the Mean Pre op Cortisol C1 and Mean Pre Operative HAD -A

| | N | X- Mean | SD | r-value | P-value |
|-----------|----|---------|-------|---------|---------|
| Pre C 1 | 28 | 160.47 | 107.5 | 0.89 | 0.000 |
| Pre HAD A | 28 | 13.78 | 2.82 | | |

Table 6. Comparison between the Mean Post Operative Cortisol C2 and Mean Post Operative HAD –A

| | N | X- Mean | SD | r-value | P-value |
|------------|----|---------|-------|---------|---------|
| Post C2 | 28 | 212.7 | 114.3 | 0.6 | 0.001 |
| Post HAD A | 28 | 10.4 | 2.6 | | |

Table 7. Comparison between the Mean Pre Operative Serotonin S1 and Mean Pre Operative HAD -D

| | N | X- Mean | SD | r-value | P-value |
|-----------|----|---------|------|---------|---------|
| S 1 | 28 | 144.48 | 69.5 | -0.612 | 0.001 |
| PRE HAD D | 28 | 12.5 | 2.60 | | |

Table 8. Comparison between the Mean Post Operative Serotonin S2 and Mean Post Operative HAD –D

| | N | X- Mean | SD | r-value | P-value |
|------------|----|---------|-------|---------|---------|
| S 2 | 28 | 189.5 | 90.19 | -0.03 | 0.869 |
| POST HAD D | 28 | 10.25 | 2.31 | | |

The mean post operative HAD-A was observed to be 10.4 with a standard deviation of 2.6 for 28 patients. The mean difference between pre operative HAD-A & post operative HAD-A was tested using 't'- value = 6.1 which is found to be statistically significant with a p –value of 0.000 as shown in Table 3. Mean value of pre operative HAD- D was observed to be 12.5 with a standard deviation of 2.60 for 28 patients. The mean post operative HAD-D was observed to be 10.25 with a standard deviation of 2.31 for 28 patients. The mean difference between pre operative HAD-A & post operative HAD-A was tested using 't'- value = 4.68 which is found to be statistically significant with a p –value of 0.000 as shown in Table 4. Mean value of pre-operative cortisol was observed to be 160.4 ng/dl with a standard deviation of 107.5 for 28 patients. The mean pre operative HAD-A was observed to be 13.78 with a standard deviation of 2.82 for 28 patients. The Pearson's Coefficient of correlation (r-value) was found to be 0.89 with a P-value of 0.000 which is found to be statistically significant as shown in the Table 5 and Figure 8. Figure 9 shows the scatter plot diagram depicting the comparison of post-operative cortisol (c2) levels and HAD A. Mean value of post-operative cortisol was observed to be 212.7 ng/dl with a standard deviation of 114.3 for 28 patients. The mean post operative HAD-A was observed to be 10.4 with a standard deviation of 2.6 for 28 patients. The Pearson's Coefficient of correlation (r-value) was found to be 0.6 with a P-value of 0.001 which is statistically

significant as shown in Table 6. Figure 10 depicts the scatter plot diagram depicting the comparison of pre-operative serotonin levels and pre-operative HAD-D. Mean value of pre-operativeserotonin was observed to be 144.48 ng/dl with a standard deviation of 69.5 for 28 patients. The mean pre operative HAD-D was observed to be 12.5 with a standard deviation of 2.60 for 28 patients. The Pearson's Coefficient of correlation (r-value) was found to be -0.61 with a P-value of 0.001 which is statistically significant as shown in Table 7. Figure 11 depicts the scatter plot diagram depicting the comparison of of post-operative serotonin levels and post-operative HAD -D. Mean value of post-operativeserotonin was observed to be 189.5 ng/dl with a standard deviation of 90.1 for 28 patients. The Mean Post operative HAD -D was observed to be 10.25 with a standard deviation of 2.31 for 28 patients. The Pearson's Coefficient of correlation (r-value) was found to be negative (-0.03) with a very low magnitude & P-value of 0.869 which is not statistically significant.

Inference

Outcome of comparison between the pre operative Cortisol C1 and post operative Cortisol C2 values suggested that the mean post operative value was in the higher range of the physiological limits. Outcome of comparison between the pre operative Serotonin S1 and post operative Serotonin S2 values

indicated a normal mental status before and after the third molar procedure.

Outcome of comparison between the pre operative HAD-A and post operative HAD-A suggested that patients were moderately anxious before and after the surgical procedure. Outcome of comparison between the pre operative HAD -D and post operative HAD-D seemed to indicate that the patients showed signs of moderate depression preoperatively and the post operative score suggested signs of mild depression. Outcome of comparison between the Pre operative Cortisol C1 and Pre Operative HAD -A showed that there is a good correlation between the two, indicating that patients are moderately anxious. Outcome of comparison between the post operative Cortisol C2 and post operative HAD -A showed that there is a good correlation between the two, suggesting that patients are mildly anxious. Outcome of comparison between the Pre Operative Serotonin S1 and Pre Operative HAD -D showed that though the subjective and objective correlation was statistically significant, there seemed to be no corresponding decrease in the serum serotonin levels in comparison to the subjective assessment of patients which seemed to indicate that the patients showed signs of moderate depression.

Outcome of comparison between the Post Operative Serotonin S2 and Post Operative HAD -D showed that the patients, subjectively or objectively show no signs of depression established by the fact that there was no statistically significant correlation between the serum post operative Serotonin and the clinical Post operative HAD-D questionnaire.

DISCUSSION

Laskin⁴⁸ posed the question; "We are experts in dealing with the physical care of the traumatized patient, but what are we doing to treat the psychological effects of traumatic facial injury?" In the study by Melanie Girona *et al*⁵⁸ clearly showed immediately after any oral surgical procedures involving jaw fracture, depressive symptoms increased. This rise in depressive symptoms is associated with patient's pain and quality of life during recovery. In accordance to the revised monoamine hypothesis, the rate of serotonin synthesis is significantly decreased in depressed patients. A decrease in serotonin synthesis also results in depression, depression in turn causes in reduction in serotonin synthesis, or a third factor may be responsible for not only lowering serotonin synthesis rates but also triggering depression⁵⁴. The body responds to stress first by releasing the catecholamine hormones like epinephrine and nor epinephrine, and the glucocorticoid hormones like cortisol and cortisone. Cortisol is the principal glucocorticoid. Its secretion is predominately from zona fasciculata of the adrenal cortex under the control of Adrenocorticotrophic hormone from anterior pituitary. Serum Cortisol levels rise in response to almost any type of stress (physical / psychological) including trauma, sepsis heavy exercise, hypoglycemia and acute anxiety. In psychotic patients there is found to be higher cortisol levels (plasma, salivary, & urinary) and abnormal circadian cortisol. Stress appears to have a major influence on the prefrontal cortical serotonergic system. Both stress and glucocorticoids

exert major role on the expression of pre synaptic 5-Hydroxytryptamine 1A (5HT1A) and post synaptic 5Hydroxytryptamine 2A (5HT2A) receptors. It is known that 5HT1A receptor expression is under constant inhibition by adrenal steroids in the hippocampus and other parts in the brain where mineralocorticoid (type 1 glucocorticoid receptors) are expressed. Weakened HPA response in depression may be associated with a glucocorticoid dependent sub-sensitivity of the postsynaptic 5HT1A receptor or a defective postsynaptic signaling pathway⁴⁹. As per monoamine hypothesis, depressed individuals are likely to have decreased levels of these neurotransmitters due to the intake of various antidepressant drugs⁴⁷. The finding that the rate of serotonin synthesis may be reduced in depressed patients can be briefed in multiple ways. A reduction in serotonin synthesis may result in depression, depression may result in a reduction in serotonin synthesis, or a third factor may be responsible for both lowering serotonin synthesis rates and triggering depression⁴⁹. Serotonin is an inhibitory neurotransmitter that originates in raphe nuclei & terminates in the hypothalamus, exerts a circadian influence on pituitary adrenal function by stimulating hypothalamic corticotrophin-releasing hormone. Serotonin has both facilitatory and inhibitory actions on the axis and also through the hippocampal negative feedback regulation of the HPA axis causing disinhibition of the axis and a rise in Cortisol levels. This biogenic amine serotonin occurs primarily in serotonergic neurons in the brain, in the enterochromaffin cells of the intestine, and in blood platelets⁵.

Serotonin plays an important role in the pathophysiology of depression. Michael Owens *et al*⁵⁹ found the decreased cerebrospinal fluid concentrations of 5-hydroxyindoleacetic acid, reduced concentrations of 5-Hydroxytryptamine and 5-hydroxyindoleacetic acid in postmortem brain tissue of depressed and suicidal patients and decreased plasma tryptophan concentrations in depressed patients. Patients see advice for dental treatment commonly show fear and anxiety⁷⁵. Dental anxiety is most commonly provoked by treatment involving anaesthetic injection, use of the drill, and/or tooth removal. In accordance with this, surgical removal of a lower third molar also aggravates anxiety²⁷. Different factors have been found in the aetiology of dental anxiety, including trauma, congenital problems and the traumatic experiences of family and friends²⁸.

Oral surgery is reported to cause the highest level of anxiety of all dental procedures. There have been some studies of anxiety and fear in patients about to undergo minor oral surgery⁵¹. Shannon *et al*⁷⁸ reported that the expectation of oral surgery produced a significant rise in steroid levels compared with those of healthy patients not receiving any dental treatment. Anxiety of local anaesthesia administration and oral surgery, can both cause rise in cortisol in patients undergoing oral surgical procedures. Some of these studies have found about the high levels of pre-operative anxiety. Anxiety produces emotional disturbance, and it may also inflame patient behaviour that hinders surgery, in some patients prolonging the intervention and obscure post operative recovery⁵¹. Philips *et al*⁶⁷ found that patients who are psychologically distressed before surgery reported a higher recovery burden with more physical and social discomfort after surgery. Kiyak *et al*.⁴⁵

found that depressive symptoms peaked immediately after surgery and were associated with extensive pain, post surgical discomfort, and problems with oral function.

Anxiety prior to oral surgical procedures is most commonly measured using different questionnaires and rating scales. In assessment of fear, questionnaires have several advantages. They are easy to score, quick and inexpensive. Secondly, they have good face validity, making them suitable tasks for patients and research subjects to be assessed⁷⁴. Various anxiety & depression scales are developed to measure their levels. The various examples of such are The Hospital Anxiety & Depression Scale, Hamilton Depression Rating Scale, Beck Depression Inventory, Duke Anxiety-Depression Scale (DUKE-AD). The Hospital Anxiety & Depression Scale (HADS) was developed by Zigmond and Snaith in 1983 identify caseness (possible and probable) of anxiety disorders & depression among patients in non-psychiatric hospital clinics⁸⁵. To measure stress response, salivary cortisol samples have found to be accurate and efficient³⁴. During measurement, salivary samples can be contaminated by blood from the operative site, therefore we chose to estimate the serum levels of cortisol. Serotonin is present in blood, plasma, serum, cerebrospinal fluid, urine, platelets but not in saliva¹⁵. Different methods have been advocated in the estimation of serotonin and cortisol like Radioimmunoassay, Spectrofluorometry and High pressure liquid chromatography with each analysis method having their respective advantages and disadvantages. Connolly *et al.*¹⁸ described radioimmunoassay as a simple and rapid method to estimate cortisol. Govindankutty *et al.*³¹ reported on a rapid, sensitive, and reproducible assay for determination of platelet serotonin. Since radio immunoassay is a rapid, sensitive method with its sensitivity being similar to high pressure liquid chromatography and more cost effective, we therefore used radioimmunoassay as the method of estimation of serum serotonin and cortisol.

In the present study, the mean pre operative HAD-A score (13.78) shows that patients were moderately anxious which is not surprising because of the impending surgery. However the mean post operative HAD-A score (10.4) shows that the patients were mildly anxious due to their coming out of the stressful environment. The pre operative analysis of the mean HAD-D score (12.5) indicates that the patients showed signs of moderate depression whereas the mean post operative HAD-D score (10.25) indicates that the patients showed signs of mild depression, but the exact cause of depression has to be investigated because depression is multifactorial. In other words, whether the thought of losing a tooth or fear of surgery or any other factor remains to be investigated. On analysis of the mean pre operative cortisol level (160.47 ng/dl) and the mean post operative cortisol (212.77 ng/dl) values, it was found that the mean post operative cortisol level was in the higher range of physiological limits (50-230 ng/dl)¹³. This correlated well with the subjective finding of decrease score on postoperative HAD-A scale. This is in accordance to normal response to stressful situation as supported by the study by C.M.Hill *et al.*³⁴. On analysis of the mean pre operative serotonin level (144.48 ng/dl) and mean post operative serotonin level (189.51 ng/dl) values, it was found that the mean post operative serotonin level was in the higher range of

the physiological limits (50-200 ng/dl)¹³. The phenomenon of desensitization of the serotonin receptors (5HT1A) is explained in the flow chart on page 4 thereby causing an increase in the serum serotonin levels. But whether this has any bearing in circumstances of acute stress could be a matter for further investigation. The intergroup (cortisol and the questionnaire) for anxiety when analysed using Pearson's Coefficient was positively correlating. The analysis of the intergroup between serum marker and questionnaire for depression when analysed using Pearson's Coefficient, was not correlating. Finally, the results of the study showed that depression does not co-exist with anxiety in the immediate pre and post operative settings. This is in contrast to the findings of the study by Melanie Girona *et al.* which clearly showed that depressive symptoms increase for jaw fracture in oral surgery. However theirs was a subjective assessment of the depressive symptoms. Of particular note is their explanation, base line depression is not associated with follow up depression suggesting, a specific psychological morbidity of depression in the 1 month period after surgery that is not strongly related to one's psychological state in hours immediately after the traumatic injury.

In this regard, our study can be developed further by:

Collecting the blood samples after the cessation of the effects of local anesthesia; in which case pain becomes a significant modulator. Study can also be repeated at intervals of 1 week and 1 month to assess whether other modulators such as complicated wound healing and prolonged discomfort would elicit a different subjective and objective outcomes.

Conclusion

During this study, significant observations came to light. They are, Subjectively patients were anxious and depressed preoperatively. Subjectively patients were neither anxious nor depressed post operatively Objectively patients were neither anxious nor depressed preoperatively. Objectively patients were only anxious but showed no signs of depression following immediate post operative setting. In conclusion, depression does not co-exist with anxiety in immediate pre and post operative setting.

Ethics approval

SRU Ethical committee Approval obtained

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