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The Effect of Immersive Virtual Reality on Serotonin Levels in Patients Undergoing Subarachnoid Block Anesthesia

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ABSTRACT

Background: Subarachnoid block (SAB) is a commonly used regional anesthesia technique for various surgical procedures. Immersive Virtual Reality (IVR) has demonstrated potential as a non-pharmacological modality to reduce anxiety and enhance perioperative patient comfort. Serotonin, as an important neurotransmitter in mood regulation and stress response, may serve as an objective biomarker for evaluating IVR effectiveness. Objective: This study aimed to analyze the effect of immersive virtual reality administration on serum and salivary serotonin level changes in patients undergoing subarachnoid block anesthesia. Methods: An experimental study with randomized controlled trial design was conducted on 30 patients undergoing surgery with SAB anesthesia, divided into two groups: intervention group receiving IVR (n=15) and control group without IVR (n=15). Serum and salivary serotonin measurements were performed at baseline in the premedication room and at 30 minutes post-SAB procedure using enzyme immunoassay (ELISA) method. Data were analyzed using Paired T-test and Independent T-test. Results: Demographic characteristics of both groups were homogeneous ($p>0.05$). Post-intervention serum serotonin levels in the IVR group (135.15±16.44 ng/mL) were significantly higher compared to the control group (120.15±19.49 ng/mL) with statistically significant difference ($p=0.030$). There was a significant difference between baseline and post-intervention serum serotonin levels in the IVR group (113.22±17.12 vs 135.15±16.44 ng/mL; $p<0.001$). No significant difference was observed in salivary serotonin levels between both groups ($p=0.758$). Conclusions: Immersive virtual reality significantly influences serum serotonin level elevation in patients undergoing subarachnoid block anesthesia, demonstrating the potential of IVR as a non-pharmacological adjuvant modality to enhance perioperative patient comfort.

KEYWORDS: Immersive Virtual Reality, Serotonin, Subarachnoid Block Anesthesia, Neurotransmitter, Perioperative

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INTRODUCTION

Subarachnoid block (SAB) is a medical procedure commonly used to control pain during surgery [1]. This procedure involves injection of local anesthetic medication into the subarachnoid space around the spinal cord, which results in elimination of sensation below the level of anesthesia [2]. Although effective in controlling pain during surgery, subarachnoid block can be an unpleasant experience for many patients [3].

Anxiety before and during medical procedures such as subarachnoid block or during surgery is a common reaction and can have negative impacts on the body's physiological responses, including changes in levels of certain neurotransmitters such as serotonin [4]. Anxiety during surgery in patients undergoing subarachnoid block anesthesia can cause serious complications. High anxiety levels have been associated with increased complications before and after surgery, increased hospitalization, and lower patient satisfaction [5,6]. Patients who will undergo surgery with subarachnoid block anesthesia experience significant preoperative anxiety levels with 48.3% of patients experiencing moderate anxiety and 24.1% experiencing severe anxiety [7].

In several previous studies, it has been shown that anxiety levels in patients undergoing surgery can decrease when they are given information using audiovisual materials [6]. One technology that has attracted attention in reducing anxiety during surgery is Immersive Virtual Reality (IVR). IVR enables patients to interact with a virtual environment audiovisually, thus reducing anxiety [8]. This method works by increasing tolerance to anxiety through inhibition of learning mechanisms as well as interaction and adaptation to virtual situations. Theoretically, anxiety can be suppressed if inhibition of learning mechanisms is achieved with

neurobiological adaptation in the prefrontal motor cortex, amygdala, and hippocampus regions [9].

In this study, the role of serotonin also becomes a concern. Serotonin, as a hormone and monoamine neurotransmitter that works on the central and peripheral nervous systems, has functions related to psychiatric disorders such as anxiety, depression and mania [10]. The highest amount of serotonin is found in enterochromaffin cells of the gastrointestinal tract and in small amounts in the central nervous system and platelets [11]. Several previous studies have reported a direct correlation between levels of 5-hydroxyindoleacetic acid (5-HIAA), which is a metabolite of serotonin, with anxiety [12]. Understanding the mechanism of serotonin in its influence on anxiety can provide further insight into the effects of IVR in managing preoperative anxiety at the neurochemical level.

Therefore, this study aims to compare serotonin levels in patients undergoing subarachnoid block with the use of IVR during the procedure with patients who do not use IVR. This study will measure serotonin levels in patients' saliva and serum, as indicators of physiological responses to anxiety and stress. It is hoped that this study can provide strong scientific evidence regarding the effectiveness of IVR in managing preoperative anxiety at the neurochemical level, which can support the use of this technology in medical practice.

METHOD

Type and Design of Research

This study is a prospective experimental analytical study using a Randomized Controlled Trial (RCT) design. Participants undergoing surgery with subarachnoid block anesthesia technique will be randomly divided into two groups: the intervention group that will undergo surgery with the use of immersive virtual reality intervention during the procedure, and the control group that does not use immersive virtual reality intervention.

Location and Time of Research

This research will be conducted in the operating room of Airlangga University Hospital Surabaya. The duration of this study will cover a three-month period, starting from April 2025 to June 2025. And this study has received approval from the ethics committee of Airlangga University Hospital Surabaya with Letter No: 028/KEP/2025.

Population and Research Sample

The population that is the focus of this study is patients who will undergo subarachnoid block in the operating room of Airlangga University Hospital Surabaya. The research sample consists of patients who meet the inclusion criteria and give consent to participate in this study. The research sample will be divided into two groups, namely the intervention group and the control group randomly.

This calculation method will follow the formula used in previous research by Sutrisno in 2017 entitled "The effect of reality therapy on the serotonin Level and depression score in cervical cancer patient." The calculation results obtained a total sample size of 24 people. To anticipate lost samples (drop out), a correction factor of 20% is used, so the number of replications becomes: Total sample of all groups = 1.25 x 24 = 30 people.

In this study, inclusion criteria include male and female patients who will undergo surgical procedures with subarachnoid block anesthesia technique, willing to participate in the study, aged 18–45 years, and have a minimum education level of high school or equivalent. In addition, patients do not have a history of epilepsy, psychiatric disorders, or claustrophobia, do not experience visual and/or hearing impairments that can affect the use of Virtual Reality devices, and are included in ASA I–II physical status.

Exclusion criteria include patients with a history of diabetes mellitus, hypertension, and patients with ASA III–V physical status. Meanwhile, drop out criteria in this study are the occurrence of emergency conditions requiring immediate treatment during the procedure, a decision to change the anesthesia technique to another type, failure in the implementation of subarachnoid block, and patients who receive sedation.

Research variables consist of independent variables and dependent variables. The independent variable in this study is the use of Immersive Virtual Reality. Dependent variables include initial and evaluation serum serotonin levels, initial and evaluation saliva serotonin levels, as well as changes (delta) in serotonin levels in serum and saliva.

Data Analysis

1) All demographic characteristic data (age, gender, and others) will be summarized using descriptive statistics with tables. All data obtained from this study will also be displayed first with descriptive statistics. Furthermore, the data in this study will be processed statistically using SPSS application (26.0). All data will be summarized using analytical statistics.
2) Serum and saliva serotonin levels will be analyzed with appropriate statistical methods. Demographic characteristic data, vital sign characteristic data before induction, and comparison data of initial serum and saliva serotonin levels in patients using IVR and without IVR will use independent sample t-test if the data is normally distributed and Mann Whitney U test if the data is not normally distributed. Comparison data of initial and evaluation serum serotonin and saliva serotonin levels in patients using IVR and comparison data of initial and evaluation serum serotonin and saliva serotonin levels in patients without the use of IVR use paired T-test. Comparison data of evaluation serum and saliva serotonin levels in patients using IVR and without IVR use unpaired T-test. Analysis data on the relationship between serum serotonin delta and saliva serotonin delta use Spearman

correlation test.

RESULT

Characteristics of Research Subjects

Demographic characteristics of research subjects

Demographic characteristics in this study, namely based on age, weight, height, BMI, were tested for normality of each variable in both groups. Normal distribution was found in age, weight and height variables. While the BMI variable showed non-normal distribution. Assessment of differences in age, weight, height and BMI variables obtained $p > 0.05$. This means there is no difference in age, weight, height and BMI between the two groups.

Table 1: Demographic characteristics of research samples

Subject Characteristics	Group		Total	p-value
	Intervention with IVR (n = 15)	Control without IVR (n = 15)		
Age (years) (Mean ± SD)	31.07 ± 8.75	30.07 ± 8.91	30.57 ± 8.69	0.759 [a]
Body Weight (kg) (Mean ± SD)	62.47 ± 7.53	63.13 ± 7.28	62.80 ± 7.29	0.807 [a]
Height (cm) (Mean ± SD)	160.53 ± 7.71	163.47 ± 7.70	162.00 ± 7.72	0.307 [a]
BMI (kg/m^2) Median (min-max)	24.70 (17.40-32.90)	23.70 (21.40-28.80)	24.04 ± 3.36	0.213 [b]

[a] independent sample T test
[b] Mann Whitney - U test

Vital sign characteristics before induction

Normality tests were conducted on SBP, DBP, MAP, pulse and temperature variables and obtained normally distributed data, while SpO2 variable data was not normally distributed. So the difference test on SBP, DBP, MAP, pulse and temperature variables uses independent sample T test. While the SpO2 variable uses the Mann Whitney test.

Table 2: Vital sign characteristics before induction

Subject characteristics	Group		p-value
	Intervention with IVR (n = 15)	Control without IVR (n = 15)	
TDS (mmHg) (Mean ± SD)	116.40 ± 10.02	115.07 ± 12.82	0.753[a]
TDD (mmHg) (Mean ± SD)	77.67 ± 9.04	75.93 ± 8.83	0.600[a]
MAP (mmHg) (Mean ± SD)	90.53 ± 7.09	89.07 ± 8.72	0.617[a]
Pulse (times per minute) Median (Min - Max)	75.80 ± 1.14	75.93 ± 1.28	0.766 [a]
Pulse oxymetri (%) Median (Min - Max)	99.00 (97-99)	98.00 (97-99)	0.270[b]
Temperature (°C) (Mean ± SD)	36.96 ± 0.30	36.993 ± 0.27	0.756[a]

[a] independent sample T test
[b] Mann Whitney - U test

The mean initial systolic blood pressure characteristics in the intervention and control groups were 116.40 ± 10.02 mmHg and 115.07 ± 12.82 mmHg and statistically did not have a significant difference (p=0.753). The mean initial MAP in the intervention group was higher than the control group, the mean initial pulse rate in the intervention group was the same as the control group, but all vital sign parameters were not statistically different.

Comparison of Initial and Evaluation Serum and Saliva Serotonin Levels in Patients Using IVR

Initial serum serotonin samples and initial saliva serotonin samples were taken in both groups in the premedication room. After that, research participants were fitted with monitors including blood pressure, ECG, respiratory rate, SpO2, and temperature.

Table 3: Comparison of initial and evaluation serum and saliva serotonin levels in patients using IVR

Sample	Measurement	Mean ± Std	Mean difference	P value
Serum	Initial	113.22 ± 17.12	21.93	<0.001
	Evaluation	135.15 ± 16.44		
Saliva	Initial	1.007 ± 0.109	0.005	0.326
	Evaluation	1.012 ± 0.104		

A normality test was conducted on initial and evaluation serum serotonin levels with IVR use and obtained normally distributed data. Likewise, normality tests on initial and evaluation saliva serotonin levels obtained normally distributed data.
Based on table 3 above, we can see the comparison of initial and evaluation serum serotonin levels in the IVR group analyzed using paired T-test. The mean initial and evaluation serum serotonin levels in the group using IVR showed different numbers, the initial group was 113.22 ng/mL and the evaluation group was 135.15 ng/mL with an average difference in the two groups of 21.93 ng/mL, statistically both groups had a significant difference (p<0.001).
Based on table 5.3 above, we can see the comparison of initial and evaluation saliva serotonin levels in patients using IVR analyzed using paired T-test. The mean initial and evaluation saliva serotonin levels in the group using IVR showed different numbers, the initial group was 1.007 ng/mL and the evaluation group was 1.012 ng/mL with an average difference in the two groups of 0.005 ng/mL, statistically both groups did not have a significant difference (p=0.326).

Comparison of Initial and Evaluation Serum and Saliva Serotonin Levels in Patients Without the Use of IVR

Table 4: Comparison of initial and evaluation serum and saliva serotonin levels in patients without the use of IVR

Sample	Measurement	Mean ± Std	Mean difference	P value
Serum	Initial	114.97 ± 16.91	5.18	0.001
	Evaluation	120.15 ± 19.49		
Saliva	Initial	1.020 ± 0.095	0.004	0.442
	Evaluation	1.024 ± 0.095		

A normality test was conducted on initial and evaluation serum serotonin data in the group without IVR, and obtained normally distributed data. Likewise, initial and evaluation saliva serotonin data in the group without IVR obtained normally distributed data.
Based on table 4 above, we can see the comparison of initial and evaluation serum serotonin levels in patients not using IVR analyzed using paired T-test. The mean initial and evaluation serum serotonin levels in the group without the use of IVR showed different numbers, the initial group was 114.97 ng/mL and the evaluation group was 120.15 ng/mL with an average difference in the two groups of 5.18 ng/mL, statistically both groups had a significant difference (p=0.001).
Based on table 4 above, we can see the comparison of initial and evaluation saliva serotonin levels in patients not using IVR using paired T-test. The mean initial and evaluation saliva serotonin levels in the group without the use of IVR showed different numbers, the initial group was 1.020 ng/mL and the evaluation group was 1.024 ng/mL with an average difference in the two groups of 0.004 ng/mL, statistically both groups did not have a significant difference (p=0.442).

Comparison of Initial Serum and Saliva Serotonin Levels in Patients Using IVR and Without IVR

Table 5: Difference in initial serum and saliva serotonin levels in IVR and non-IVR patients

Serotonin	Treatment	Mean ± Std Median (min-max)	P value
Serum	IVR	112.00 (92-138)	0.756[b]
	Non IVR	119.90 (91-139)	
Saliva	IVR	1.007 ± (0.109)	0.726[a]
	Non IVR	1.020 ± (0.095)	

[a] independent sample T test
[b] Mann Whitney - U test

A normality test was conducted on initial serum serotonin data in the group using IVR and without IVR and obtained non-normally distributed data. While the normality test on initial saliva serotonin data in the group using IVR and without IVR was normally distributed.
Based on table 5 above, we can see the comparison of initial serum serotonin levels in patients using IVR and without IVR analyzed using Mann Whitney U test. Statistically both groups did not have a significant difference (p=0.756). While the comparison of initial saliva serotonin levels in patients using IVR and without IVR analyzed using independent sample T test, statistically did not have a

significant difference (p=0.726).

Comparison of Evaluation Serum and Saliva Serotonin Levels in Patients Using IVR and Without IVR

Table 6: Difference in evaluation serum and saliva serotonin levels in IVR and non-IVR patients

Serotonin	Treatment	Mean ± Std	Mean difference	P value
Serum	IVR	135.15 ± (16.44)	15	0.030
	Non IVR	120.15 ± (19.49)		
Saliva	IVR	1.012 ± (0.104)	0.012	0.758
	Non IVR	1.024 ± (0.095)		

A normality test was conducted on evaluation serum serotonin level data in the group using IVR and without IVR and obtained normally distributed data, likewise the normality test on evaluation saliva serotonin levels in the group using IVR and without IVR obtained normally distributed data.

Based on table 6, evaluation serum serotonin levels in the group using IVR were higher when compared to the group not using IVR. The mean evaluation serum serotonin level in the group using IVR was 135.15 ng/mL while in the group not using IVR it was 120.15 ng/mL. The mean difference between the two groups was 15 ng/mL. Statistical testing using unpaired T-test obtained a value of p=0.030 (p<0.05) which indicates that there is a difference in serum serotonin levels in both groups.

Based on table 6, the mean saliva serotonin level in the group using IVR was lower than the group not using IVR. It was found that the mean saliva serotonin level in the group using IVR was 1.012 ng/mL while in the group not using IVR it was 1.024 ng/mL.

The mean difference between the two groups was 0.012 ng/mL with statistical testing using unpaired T-test obtaining a value of p=0.758 (p<0.05) which indicates that there is no difference in evaluation saliva serotonin between the two groups.

Analysis of the Relationship between Delta Serum Serotonin and Delta Saliva Serotonin

Table 7: Relationship between delta serum serotonin and delta saliva serotonin

Variable	p
Delta Serum and Saliva Serotonin	0,372

Before conducting correlation analysis, first a normality test was conducted to determine the appropriate type of statistical test. Normality test results showed that delta serotonin group data was not normally distributed in both the delta serum serotonin group and the delta saliva serotonin group with values of p = 0.006 and p = 0.000 (p < 0.05), so Spearman correlation test was chosen as a non-parametric analysis method.

Correlation analysis using Spearman test was conducted to evaluate the relationship between delta (change) in serum serotonin levels with changes in saliva serotonin levels in all research subjects. Analysis results showed a value of p = 0.372 which is greater than 0.05. This finding indicates that there is no statistical relationship between delta serum serotonin levels and delta saliva serotonin.

DISCUSSION

Characteristics of Research Subjects

This study involved 30 patients undergoing surgery with subarachnoid block anesthesia. In general, there is homogeneity of age, body weight, height and BMI variables in both intervention groups. The mean age in both groups was 30.57 ± 8.69 and the mean BMI was 24.04 ± 3.36. These results show that the research subjects are young adults with an ideal body mass index level. In this study, it was found that age and BMI data between individuals did not have a significant difference.

Vital sign characteristics were also assessed in this study and also showed homogeneity in blood pressure, MAP, pulse rate, temperature and oxygen saturation (pulse oximetry) variables in both groups. Although the initial study MAP was found to be higher in the intervention group than the control group at 90.53 ± 7.09 and 89.07 ± 8.72, it was still within the normal value range. Characteristic assessment provides homogeneous results, thus researchers can ensure that comparisons between groups for SBP, DBP, MAP, pulse, pulse oximetry and temperature measurements are not biased by significant variance differences that can affect research results.

Comparison of Initial and Evaluation Serum and Saliva Serotonin Levels in Patients Using IVR

In this study, comparison of initial and evaluation serum serotonin levels in patients using IVR showed an increase. The mean initial serum serotonin level was 113.22 ng/mL and at evaluation was 135.15 ng/mL with an average difference in the two groups of 21.93 ng/mL, statistically both groups had a significant difference (p<0.001). Comparison of initial and evaluation saliva serotonin levels also increased. The mean initial saliva serotonin level was 1.007 ng/mL and at evaluation was 1.012 ng/mL with an average

difference of 0.005 ng/mL, but statistically both groups did not have a significant difference (p=0.326).

Serotonin (5-HT) is a monoamine neurotransmitter synthesized from the amino acid tryptophan. This hormone is mainly produced in the raphe nuclei in the brainstem and released tonically or pulsatilely depending on physiological and environmental stimuli. After synthesis, serotonin is distributed through nerve pathways, mainly to areas including the hippocampus, amygdala, basal ganglia, prefrontal cortex, and hypothalamus, where it plays a key role in regulating mood, cognition, and various physiological functions [13].

Salivary serotonin reflects peripheral serotonergic activity and has been associated with mood dysregulation in depression. Although peripheral serotonin is different from central serotonin, changes in salivary serotonin concentration may correlate with central serotonin dysfunction, thus offering a minimally invasive method to monitor treatment response [13].

Saliva is a biofluid that provides clinical information and is used for new approaches in diagnosis, monitoring, and management of patients with systemic diseases. Although the exact mechanism of how serotonin enters the oral cavity is not clear, it appears to be largely influenced by blood serotonin levels. Previous experiments have sought noninvasive surrogate markers of central serotonin, including serotonin in whole blood, plasma, platelets, saliva, and urine [14].

A previous study showed a positive relationship between the level of recovery from depressive symptoms and increased circadian amplitude of salivary serotonin secretion in depressed patients after clinical treatment. This suggests that salivary serotonin may be useful for assessing serotonergic function [15].

Similar results were found in Zaki's 2024 study, where his research assessed anxiety from cortisol levels in serum and saliva. Serum cortisol levels were found to be lower in patients receiving IVR compared to the control group. However, salivary cortisol levels also decreased in the IVR group [16]v.

Research by Arifin et al showed a significant decrease in perioperative anxiety levels was observed in the VR group compared to the control group. Patient satisfaction levels were also significantly higher in the VR group compared to the control group. This was reflected in the decrease in mean salivary cortisol values in the IVR group compared to the non-IVR group (p value 0.036) and the decrease in mean plasma cortisol values in the IVR group compared to the non-IVR group (p value 0.023). Subjects' perception according to the computer-generated virtual environment during surgery with regional anesthesia technique was considered as a factor influencing these results [17].

Comparison of Initial and Evaluation Serum and Saliva Serotonin Levels in Patients Without the Use of IVR

Comparison of initial and evaluation serum serotonin levels in patients without the use of Immersive Virtual Reality also showed a significant increase. The mean initial serum serotonin level was 114.97 ng/mL and at evaluation was 120.15 ng/mL with an average difference of 5.18 ng/mL with a value of ($p<0.001$). Similar to the IVR group, the mean initial and evaluation saliva serotonin levels in the group without the use of IVR showed an increase but was not statistically significant. The mean initial saliva serotonin level was 1.020 ng/mL and at evaluation was 1.024 ng/mL with a value of (p=0.442). Both of these results in both the IVR group and the control group show that serotonin levels contained in serum are higher than serotonin levels in saliva.

Research by Egri analyzing correlations between salivary serotonin levels and empathy trait subscales (perspective taking, personal distress, and fantasy). The results showed a significant negative correlation between salivary serotonin concentration and perspective taking scores (perspective taking, personal distress, and fantasy). Furthermore, researchers calculated correlations between salivary serotonin levels and happiness in hypothetical life events. Salivary serotonin levels correlated negatively with happiness in positive-self conditions [$r(183) = -0.194$, $p < .01$] [14].

In this study, there was a significant increase in evaluation serum serotonin compared to initial in the group without IVR.

Comparison of Initial Serum and Saliva Serotonin Levels in Patients Using IVR and Without IVR

The mean initial serum serotonin levels showed numbers that were not much different in both groups. In the intervention group it was 113.22 ng/mL and in the control group it was 114.97 ng/mL, statistically both groups did not have a significant difference (p=0.775). The mean initial saliva serotonin levels also showed similar results. In the intervention group it was 1.007 ng/mL and in the control group it was 1.020 ng/mL, with a value of (p=0.726).

These results show that serotonin levels contained in serum are higher than serotonin levels in saliva, but serotonin levels in both groups were found with almost the same results. Data from the literature shows that serum serotonin levels below 100 µg/L can be associated with depressive syndrome. In Egri's study assessing correlations between salivary, platelet and central serotonin levels in children, the results showed that salivary serotonin levels were lower than platelet and central serotonin [14].

Comparison of Evaluation Serum and Saliva Serotonin Levels in Patients Using IVR and Without IVR

In this study, evaluation serum serotonin levels in patients using IVR were higher compared to the control group. The results showed that evaluation serum serotonin levels in patients with the use of IVR were higher compared to the control group. In the intervention group it was 135.15 ng/mL while in the control group it was 120.15 ng/mL. The mean difference in evaluation serum serotonin levels in the intervention group and control group was 15 ng/mL with a significance value of ($p=0.030$ ($p<0.05$) which indicates that there is an influence of Immersive Virtual Reality on serum serotonin levels in patients using subarachnoid block anesthesia technique with Immersive Virtual Reality.

While the mean evaluation saliva serotonin level in the intervention group was 1.012 ng/mL while in the control group it was 1.024

ng/mL with a mean difference of 0.012 ng/mL with a significance value of p=0.758 (p>0.05) which indicates that there is no influence of Immersive Virtual Reality on saliva serotonin levels in patients using subarachnoid block anesthesia technique with Immersive Virtual Reality.

These results are comparable to Zaki's 2024 study which measured plasma cortisol levels to assess the effectiveness of IVR in patients post subarachnoid block. The results showed that mean plasma cortisol levels 30 minutes after SAB were lower in the IVR group compared to non-IVR. In the IVR group it was 300.13 + 68.79 nmol/L while in the non-IVR group, plasma cortisol level was 355.13 ± 68.14 nmol/L [16].

In this study, changes in initial and post-intervention saliva serotonin levels provided different results. Although there was an increase in both groups, statistically it did not show a significant difference. In the IVR group there was an increase in saliva serotonin from 1.007 ng/mL to 1.012 ng/mL with an average difference of 0.005 ng/mL, (p=0.326). In the control group there was an increase in saliva serotonin from 1.020 ng/mL to 1.024 ng/mL, with a value of (p=0.442).

Virtual reality (VR) offers new solutions in healthcare and has been gradually applied in medical education, rehabilitation, and management of mental health and chronic pain. VR is believed to create an immersive experience that can limit the mind from processing acute pain and has been proven superior to simpler distraction methods in reducing pain scores for inpatients [18]

These results are comparable to Zaki's 2024 study which measured plasma cortisol levels to assess the effectiveness of IVR in patients post subarachnoid block. The results showed that mean plasma cortisol levels 30 minutes after SAB were lower in the IVR group compared to non-IVR. In the IVR group it was 300.13 + 68.79 nmol/L while in the non-IVR group plasma cortisol level was 355.13 ± 68.14 nmol/L [16].

In this study, changes in initial saliva serotonin levels and evaluation serotonin levels provided different results. Although there was an increase in both groups, statistically it did not show a significant difference. In the group using IVR there was an increase in saliva serotonin from 1.007 ng/mL to 1.012 ng/mL with a difference of 0.005 ng/mL, (p=0.326). In the group not using IVR there was also an increase in saliva serotonin from 1.020 ng/mL to 1.024 ng/mL with a value of p=0.442.

The application of IVR as a non-pharmacological anxiolytic and peri-analgesic technique has developed over the last decade. The mechanism of action of IVR is not fully understood, but is thought to be related to IVR's ability to divert attention. MRI studies show that IVR significantly reduces pain-related brain activity in the anterior cingulate cortex, primary and secondary somatosensory cortex, thalamus, and insula and shows that IVR can provide analgesia equivalent to hydromorphone. IVR reduces procedural anxiety by diverting patients' attention to a computer-generated world, as IVR "moves" patients from the clinical environment to another 'reality'. The application of IVR has been proven to lower diastolic blood pressure, heart and respiratory rate, temperature, muscle tension, temperature, skin conductance, and serum carbon dioxide levels [19].

A systematic review by Li et al, 2025 from as many as 35 randomized clinical trials (RCTs) with 3341 patients. Compared with usual care, virtual reality-based interventions showed substantial benefits in reducing preoperative anxiety in patients undergoing elective surgery ([SMD] 0.65, 95% CI 0.37-0.92; P<.001). Regarding subgroup analysis, IVR-based interventions showed significant but moderate effects on preoperative anxiety in pediatric populations (SMD 0.77, 95% CI 0.32-1.22; P<.001) compared to adult populations (SMD 0.58, 95% CI 0.23-0.93; P=.001). The distraction approach showed more significant effects (SMD 0.73, 95% CI 0.24-1.21; P=0.004) on preoperative anxiety compared to the exposure approach (SMD 0.61, 95% CI 0.27-0.95; P<0.001). Patients undergoing elective surgery with anesthesia can benefit from IVR as a new alternative to reduce preoperative anxiety, especially pediatric patients through the distraction approach [20].

Relationship between Delta Serum Serotonin Levels and Delta Saliva Serotonin Levels

Statistical analysis results showed no relationship between delta serum serotonin and delta saliva serotonin in both groups with p value > 0.05.

Research by Egri et al, 2019 showed that there was no correlation between serotonin levels in serum and serotonin in CSF (Pearson correlation coefficient- PCC: 0.010) or between salivary serotonin and CSF serotonin (PCC: 0.258). There was no correlation between salivary serotonin and serum serotonin (PCC: -0.679). These findings suggest that salivary serotonin measurement is not an accurate noninvasive marker to represent serum serotonin [14].

Several things that can be bias in serotonin measurement that have been previously reported that may often not be taken into account in measurement are: first, a diet rich in tryptophan (bananas, chocolate, pineapple, plums, and nuts) will increase plasma serotonin levels and second, sample collection time is important, because the highest serotonin levels in the morning are in plasma [14].

CONCLUSION

This study shows that in patients undergoing subarachnoid block anesthesia with or without the use of immersive Virtual Reality (IVR), there is a significant difference between initial serum serotonin levels and evaluation serum serotonin levels, while saliva serotonin levels do not show differences between the two measurement times. There is no difference in serum or saliva serotonin levels at initial measurement between the IVR group and the non-IVR group. However, at evaluation measurement, serum serotonin levels in the IVR group increased significantly compared to the control group, while saliva serotonin levels remained no different between the two groups. In addition, no relationship was found between changes (delta) in serum serotonin levels and delta saliva

serotonin levels, both in the group with IVR and without IVR.

Based on these findings, further research is recommended not to use saliva serotonin as a substitute for serum serotonin measurement, as well as to correlate serotonin measurement with standardized anxiety scales before, during, and after surgery. Further research also needs to consider the use of CSF samples, comparison of IVR with sedative medication, as well as evaluation of the influence of IVR on other physiological and clinical parameters that are monitored continuously. The limitations of this study include limited measurement time, short duration of IVR intervention, the non-involvement of CSF and objective anxiety scales, as well as the influence of subjective responses and psychological factors of patients on research results.

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