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Research Article

The Effect of Hypnoanesthesia on Serotonin

Ihyan Amri[1], Abdul Hafid Bajamal[2,*], David S. Perdanakusuma[3]

ABSTRACT

Background: Every minor and major surgical procedure requires anesthesia to relieve pain during surgery. The neuro-biomolecular mechanism of pain relief in hypnoanesthesia remains uncomprehended. **Objective**: This study aims to observe the effect of hypnoanesthesia on several neurotransmitters, including serotonin, glutamic acid, and substance P, which play a role in the mechanism of pain. **Methods**: The study subjects included patients with benign soft tissue tumors consisting of 40 people who were divided into two groups, namely treatment and control groups. Minor surgery with hypnoanesthesia was performed in the treatment group, whereas in the control group, minor surgery was performed with 2% lidocaine local anesthetic. Pain in both groups was measured by FPS (Face Pain Scale) and monitored by a vital sign monitor. The processes of the study were recorded with a camcorder. Changes in serum levels of excitatory (glutamic acid and substance P) and inhibitory (serotonin) neurotransmitters before and after the intervention were analyzed using ELISA (Enzym-Link Immunosorbent Assay) in both groups. **Results**: The control and treatment groups had the same end result, which was pain relief. The results of regression and ANOVA analysis indicated that serotonin simultaneously had a significant effect on substance P at 98.4% and glutamic acid at 98.2%. **Conclusion**: There was no statistically significant change in serotonin levels before and after hypnoanesthesia. Serotonin, as an inhibitory neurotransmitter, simultaneously has a significant effect on both excitatory neurotransmitters, namely Glutamate Acid and Substance P, in the mechanism of nociceptive pain relief with hypnosis.

Key words: Hypnoanesthesia, Serotonin, Glutamate Acid, Substance P.

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INTRODUCTION

Every minor and major surgical procedure requires anesthesia to relieve pain during surgery. An anesthetized state achieved through hypnosis is called hypnoanesthesia, which was first utilized in the field of medicine by James Esdaille (1808-1859), a Scottish surgeon, in both minor and major surgical procedures. All explanations regarding hypnosis cover only hypnotic techniques and clinical applications in the field of surgery or other medicine. Several studies on hypnoanesthesia related to the neurophysiology of pain have been conducted, but previous studies only discussed several variables of molecular markers in separate studies. Therefore, the neuro-biomolecular mechanism of pain relief in hypnoanesthesia has not been fully revealed.[1,2-4]

Serotonin is a monoamine neurotransmitter synthesized in serotonergic neurons in the central nervous system and enterochromaffin cells in the digestive tract.[5] Serotonin plays a role in pain control and anesthesia. Serotonin modulates pain perception and nociceptive processing at multiple levels in the central and peripheral nervous systems. In localized inflamed tissues at the periphery, serotonin release causes an increase in the sensitivity of peripheral nerve fibers that carry nociceptive information to the central nervous system. Serotonin in brain neurons sends signals down to the spinal cord that modulates incoming nociceptive information. Serotonin, which is synthesized by the raphe nuclei in the brainstem, also sends signals to the cortical and limbic areas to inhibit pain in the pain modulation.[6-8]

The correlation between hypnoanesthesia and serotonin expression is essentially a continuation of the biological cascade between hypnoanesthesia and the expression of beta-endorphins and enkephalins, which we discussed in one of our studies as part of this study. The activation of the prefrontal cortex of the pituitary causes the pituitary to stimulate the raphe nuclei in the brainstem, which subsequently produce 5-hydroxytryptamine (5-HT).[9,10] Serotonin or 5-HT is widely perceived to contribute to feelings of well-being and happiness and modulate cognition, appreciation, learning, memory, and various other physiological processes.[5]

The 5-HT produced will stimulate 5-HT receptors, which will then decrease glutamate and Substance P activities.[11] The increased production of enkephalins ultimately stimulates δ-opioid activities, which subsequently decreases glutamate and Substance P activities.[12] The activation of Beta Endorphins due to POMC stimulation will lead to the activation of μ-opioid.[13] Ultimately, the activation of the μ-opioid will reduce glutamate and Substance P activities.[14] Glutamate is a stimulating neurotransmitter and is abundant in the central nervous system (brain and spinal cord). Meanwhile, substance P acts as a neurotransmitter and neuromodulator.[15,16]

Studies on hypnoanesthesia have been extensively performed and discussed.[1,17] However, the mechanism of pain relief found in hypnoanesthesia for minor surgery remains uncomprehended.[2-4] This study is part of our other studies and aims to observe the effect of hypnoanesthesia on serotonin, a neurotransmitter that plays a role in the mechanism of pain, in a comprehensive manner.

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METHOD

This quasi-experimental study applied a randomized control group pretest-posttest design conducted at Dr. Moh. Soewandhie Regional Public Hospital, Surabaya. The inclusion criteria for the sample population of this study included male or female patients (18-60 years) who were able to communicate in Indonesian (not deaf-mute) and were cooperative with a minimum education level of a six-year elementary school. Surgical excisions were performed for clinically benign tissue tumors located on the ventral part of the patient's body, and surgical excisions in a supine position were performed for benign tumors no more than 5 cm in size. Meanwhile, patients who did not reach the optimal degree of anesthesia when hypnoanesthesia was performed and/or those who experienced abreaction were included in the exclusion criteria.

Based on the above criteria, it was found that the control group and treatment group amounted to 20 people, so the overall size of the study subjects in the two groups was 40 people. This study received an Ethical Eligibility Letter No.001/KE/KEPK/2020 dated October 27, 2020, from the Clinical Research Ethics Commission. Prior to the procedure, sample patients signed an informed consent form to participate in the study process. Then, the measurement of the pain scale and the first vital sign was conducted by tweezing the area subjected to the surgical procedure and the area around it using a tweezer. Furthermore, blood samples were collected by the laboratory nurse from peripheral blood intravenously to check serotonin, glutamic acid, and substance P levels before the surgery.

Local anesthesia was performed in the control group with 2% lidocaine in the area subjected to surgical procedure until the anesthetic level was reached. As for the treatment group, hypnoanesthesia was performed (the script is attached) in the area subjected to surgical procedures. An indicator of achieving the required level of hypnoanesthesia was obtained by tweezing the area subjected to surgical procedures and the area around it using a tweezer. Pain relief and pain scale (Face Pain Scale) determinations in the patients were carried out using the reference in Figure 1. The level of anesthesia was achieved when the patients reached a scale value of 0. In addition, pain in both groups was monitored with a vital sign monitor. The study processes were recorded with a camcorder.

The surgical procedures were performed by the operator while maintaining the level of hypnoanesthesia and monitored by a vital sign monitor during the operation until the surgical procedure was completed. Then, after the 10-minute incision, a pain scale and vital sign measurement, as well as a second intravenous blood sampling, was carried out to examine the serotonin, glutamate acid, and substance P levels and recorded on the Hypnoanesthesia Study Form. Data on the results of the first and second blood sampling were analyzed by ELISA test at the Laboratory of Dr. Soetomo Regional Public Hospital. The data collected was processed manually and using SPSS 17. The significance level of the statistical test applied in this study was 0.05.

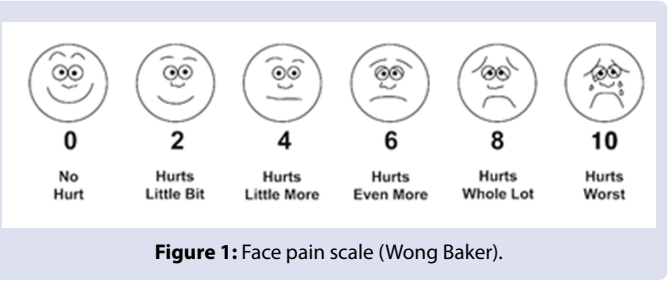

Figure 1: Face pain scale (Wong Baker).

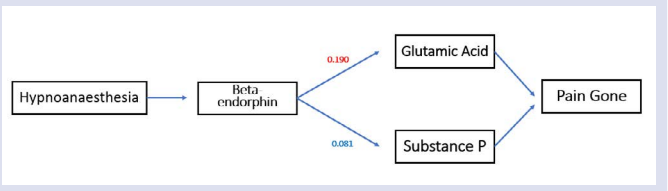

Figure 2: Path analysis model.

RESULTS

Table 1 below presents the characteristics of the subjects in this study.

The results of the Shapiro-Wilk test showed that the difference in the data (the table is attached) of serotonin and glutamic acid levels of the two groups was normally distributed ($p > 0.05$), whereas the difference in the data of Substance P of the two groups was not normally distributed ($p < 0.05$). Differences in the data before and after the treatments in each group, where the difference data were normally distributed, were analyzed using the paired t-test. Meanwhile, if the difference data were not normally distributed, the Wilcoxon test was utilized. The difference in serotonin and glutamic acid differences of the groups were analyzed using the 2-sample t-test. Meanwhile, when the data were not normally distributed, the Mann-Whitney test was used.

The results of the paired t-test indicated no significant difference in serotonin levels before and after the intervention ($p > 0.05$), both in the control and treatment groups (Table 3).

The results of the t-test for two independent samples revealed no significant differences between the serotonin and glutamic acid levels of the groups ($p > 0.05$), while the results of the Mann-Whitney test showed that Substance P levels in the groups were not significantly different ($p > 0.05$).

The Model Summary table of the regression test presents that the R square reached 0.982; thus, the path coefficient ε (variable outside the model) is 0.134 (Table 5).

$$_{Y5\varepsilon} = \sqrt{(1 - 0.982)} = \sqrt{0.018} = 0.134$$

Meanwhile, the ANOVA test coefficient table shows that the Serotonin path coefficient reached 0.19. It indicates that serotonin does not correlate significantly with glutamic acid (Table 6).

The Summary Model table of the Regression Test shows that the R square reached 0.984. Thus, the path coefficient ε (variable outside the model) is 0.126 (Table 7).

$$_{Y5\varepsilon} = \sqrt{(1 - 0.984)} = \sqrt{0.016} = 0.126$$

Meanwhile, the Serotonin pathway coefficient reached 0.081, indicating that serotonin does not correlate with Substance P (< 0.05) (Table 8).

The correlation between serotonin and glutamic acid is indicated with red correlation numbers with a magnitude of 0.190. Meanwhile, the correlation between serotonin and substance P is indicated with blue correlation numbers with a magnitude of 0.081 (Figure 2).

DISCUSSION

The results of this study and the statistical tests in this study indicated no significant difference in serotonin level changes as an inhibitory neurotransmitter ($p > 0.05$) before and after the hypnoanesthesia intervention. There was no statistically significant difference, but it turned out that empirically, the subjects experienced pain relief after being given hypnoanesthesia (the data sourced from the video recordings of this study). Suggestions for pain relief or numbness through visual, sound, and/or touch stimuli are received by the sensory organs and then passed on to the thalamus. After breaking through the Reticular Activating System (RAS) alert system in Formatio

Table 1: **Characteristics of the subjects.**

Characteristics	Control (n = 20)	Treatments (n = 20)
Age		
Mean ± Standard Deviation	30.4 ± 13.220	28.15 ± 12.076
Sex [n(%)]		
Male	12 (60%)	5 (25%)
Female	8 (40%)	15 (75%)
Education [n(%)]		
Elementary School	2 (10%)	2 (10%)
Middle School	1 (5%)	3 (15%)
High School	14 (70%)	14 (70%)
Bachelor's degree	3 (15%)	1 (5%)
Pain Scale		
Before	10	10
After	0	0
Systolic Blood Pressure		
Before	137.45 ± 27.810	133.60 ± 19.672
After	132.70 ± 23.622	130.75 ± 20.047
Diastolic Blood Pressure		
Before	77.80 ± 15.419	71.80 ± 13.320
After	76.55 ± 14.376	69.90 ± 9.597
Pulse rate (x/minute)		
Before	92.15 ± 20.399	84.85 ± 16.813
After	82.95 ± 18.894	81.30 ± 15.755
Respiratory Rate (x/min)		
Before	23.35 ± 2.084	21.05 ± 3.103
After	20.60 ± 1.465	20.00 ± 1.864
Conciousnes level before/after		
CM	20 (100%)	20 (100%)

Table 2: **Normal distribution test.**

Variables	p-value	
	Control (n = 20)	Treatment (n = 20)
Differences in serotonin levels	0.551	0.696
Differences in glutamic acid levels	0.068	0.537
Differences in Substance P levels	0.031	0.023

Table 3: **Differences in serotonin levels before and after intervention.**

Groups		n	Mean Standard Deviation	Mean Standard Deviation of the Differences	p-value
Control	Before	20	82.98 ± 42.217	4.06 ± 14.990	0.241
	After	20	87.04 ± 36.900		
Treatments	Before	20	98.69 ± 116.094	2.48 ± 23.136	0.638
	After	20	101.16 ± 121.807		

Table 4: **Change differences in serotonin, glutamate acid, and substance P levels of the two groups.**

Variables	Groups	n	Mean ± Standard Deviation Median (min–max)	p-value
Serotonin	Control	20	4.06 ± 14.990	0.799
	Treatments	20	42.48 ± 23.136	
Glutamic Acid	Control	20	0.04 ± 0.160	0.937
	Treatments	20	0.035 ± 0.230	
Substance P	Control	20	-8.7 (-56,3–113.9)	0.507
	Treatments	20	0.05 (-135–156)	

Table 5: **Regression test of serotonin against glutamic acid.**

Model	R	R Square	Adjusted R Square	Standard Deviation Error of the Estimate
1	0.991[a]	0.982	0.978	0.4067

Description: a. Predictors: (Constant), serotonin.

Table 6: **ANOVA test of serotonin against glutamic acid.**

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Standard Deviation Error	Beta		
a	(Constant)	-0.588	0.777		-0.757	0.46
	Serotonin	0.004	0.006	0.19	0.701	0.493

Table 7: **Regression test of serotonin against substance P.**

Model	R	R Square	Adjusted Square	R Standard Deviation Error of the Estimate
1	0.992[a]	0.984	0.981	73.4711

Table 8: **ANOVA test of serotonin against substance P.**

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Standard Deviation Error	Beta		
a	(Constant)	54.243	140.427		0.386	0.704
	Serotonin	0.358	1.103	0.081	0.325	0.750

Reticularis, they are passed on to the Dorso Lateral Prefrontal Cortex as a new perception, namely a perception of pain relief.[18] This pain relief perception is stored in the Ventro-Medial Prefrontal Cortex.

The mechanism of pain in the control group is the inhibition of the transduction process in minor surgical procedures by the intervention of local anesthetic administration with 2% lidocaine; thereby, the pain is not passed on to the transmission, modulation, and perception processes so that the pain is not felt.[19,20] It is consistent with the results of the t-test in the control group, proving that the control and treatment groups have the same end result, namely pain relief (Table 2). It means that hypnoanesthesia can replace local anesthesia in situations and conditions where there are contraindications to local anesthetic drugs.

The results of the regression and ANOVA analysis found that serotonin simultaneously had a significant effect on Substance P at 98.4% and glutamic acid at 98.2% (Table 7). Thus, the study hypothesis is fulfilled, but not completely. These results are consistent with the Gate Control Theory, which states that ascending pain signals delivered by excitatory neurotransmitters (Glutamate Acid and Substance P) interact with descending signal barriers by the inhibitory neurotransmitter serotonin.[21]

CONCLUSION

Empirical nociceptive pain relief occurred in patients who underwent minor surgery under hypnoanesthesia, and statistically, there was no significant change in serotonin levels before and after hypnoanesthesia. In addition, serotonin as an inhibitory neurotransmitter simultaneously has a significant effect on the excitatory neurotransmitters, namely glutamate acid and substance P, in the mechanism of nociceptive pain relief with hypnoanesthesia.

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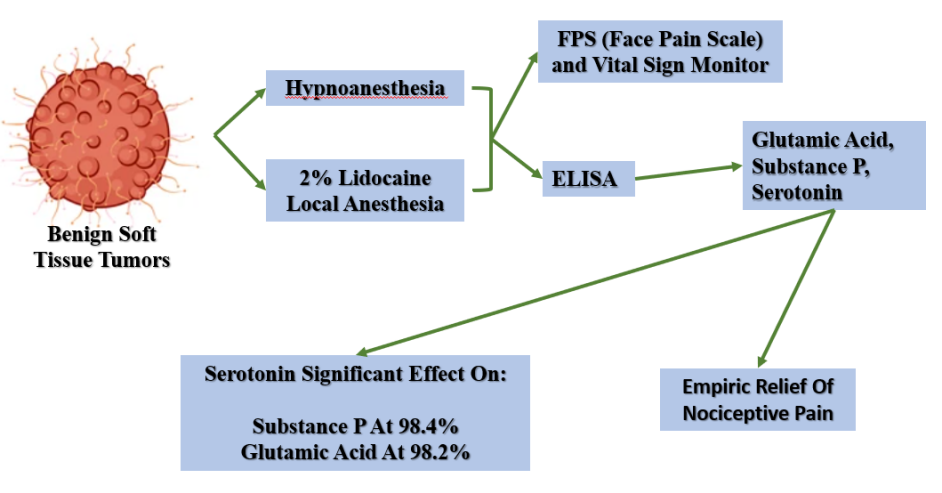
GRAPHICAL ABSTRACT



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