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Impact of tramadol and heroin abuse on electroencephalography structure and cognitive functions

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Abstract

Background Opioids, defined as medicines that stimulate opioid receptors, are primarily used in the treatment of moderate to severe pain. They induce central nervous system (CNS) adverse effects. This study aimed to assess the effect of opioids on brain electrical activity, the effect of opioids on cognitive functions, and corroborate whether there was any correlation between changes in brain electrical activity and cognitive functions that may do in opioid addicts.

Methods This cross-sectional case–control study was performed on 80 cases (divided into two groups 40 cases with tramadol use disorders and 40 cases with heroin use disorders) and 40 age-/sex-matched healthy control. All subjects were subordinated to neuropsychiatric evaluation, assessment of opioid use complaint through history from the case and his relatives, substance monitoring in urine, medicine abuse screening test (DAST), electroencephalography (EEG), and cognitive assessment by Montreal Cognitive Assessment (MOCA).

Results Opioid dependence convinced global cognitive function impairment, specific cognitive disciplines impairment that included visual-conceptual, visual-motor tracking, visual-constructional skills, language function, attention, memory, and orientation. Additionally, affection of the brain's electrical activities with significant changes compared with control. Comparison of cognitive impairment substantiated by lower cognitive scores in relation to abnormal EEG changes among studied case groups revealed significant differences.

Conclusions Opioid abusers had a significant impairment of cognitive functions and EEG changes with a significant correlation between changes in brain electrical activity and impairment of cognitive functions.

Keywords Tramadol, Heroin, Electroencephalography, Cognition

Introduction

Substance use disorder (SUD) is a treatable mental clutter that influences a person's brain and behavior, driving to their failure to control their utilize of substances like lawful or unlawful drugs, alcohol, or drugs. Manifestations can be moderate to extreme, with addiction being the foremost serious form of SUD [1]. Substance use diseases are serious and significant health problems that bear attention, leading to behavioral and cognitive impairments. In 2015, there were 183 million cannabis abusers, 37 million amphetamine abusers, and 35 million

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opioid abusers [1]. Opioids are an order of substances that mimic morphine in the body, including heroin, which is largely addicting and causes morbidity and mortality [2].

In Egypt, drug addiction is considered one of the genuine issues that stress both individuals and the government. It influences youthful individuals within their productive years. It may lead to numerous issues such as social maladaptation, diminished work efficiency and work misfortune [3]. The changes in lifestyle together with quick financial development in Egypt may too have noteworthy effect on drift of substance utilize in all population positions [4, 5]. Hamdi et al. (2011) found that among the 3842 who were found to utilize substance, 3591 were found to abuse cannabis (93%), 870 were utilizing alcohol (22.6%), 449 were utilizing pharmaceutical drugs (11.7%), 275 were utilizing opiates (7.2%), and 202 subjects were utilizing stimulants (5.3%). Cannabis was the drug for the most part abused within the study taken after by alcohol, pharmaceuticals, opiates, and stimulants [6].

Opioid misuse causes significant changes in the brain, as a result there are numerous studies reporting precious biomarkers for it [1]. Neuroimaging in opiate dependence reveals both brain structural changes, particularly in the anterior cingulate cortex [7, 8], and brain functions affecting the dorsolateral prefrontal cortex and the anterior cingulate cortex [9, 10]. Therefore, opiate dependence is associated with cognitive deficits [11], particularly executive functioning and self-regulatory capacities (impulsivity, decision-making, and hazard-taking) [12].

EEG is an extensively accepted technique for assessing cortical information processing and neurophysiological changes that do during the unconscious and varied conscious states [13]. This is complex, occasionally occurs non-linearly, and is impacted by varied factors such as cranium thickness, cerebrospinal fluid, the distance between electrodes, and age [14]. Electromagnetic techniques similar to EEG can measure brain function and electrical activity on a millisecond scale, delivering precious information about neural abnormalities that cannot be detected by other functional techniques [15]. Thus, EEG can help physicians more understand changes in brain activity during opioid abuse and the effects of pharmacotherapy on functional recovery [16].

Aim of the work

This study aimed to assess the effect of opioids on brain electrical activity, the effect of opioids on cognitive functions, and corroborate whether there was any correlation between changes in brain electrical activity and cognitive functions that may do in opioid addicts.

Patients and methods

This study was performed on 120 subjects collected from Psychiatry, Neurology, and Neurosurgery Center, Tanta University, from the period March 2017 to September 2019 after approval the ethical commission (code number: 453211117). Informed written consent was attained from all participants in this research after a full explanation of the benefits and pitfalls of the procedure. All cases who met the criteria of opioid use disorder according to DSM-5 criteria were included in the study [17]. Subjects were divided into 2 groups: cases group ($n=80$) and the control group ($n=40$). Cases group included 80 cases divided into two groups: 40 cases of tramadol use disorder and 40 cases with heroin use disorder. Control group included 40 healthy persons matching with the cases.

Cases with a once history of seizures, cases with a family history of epilepsy, any neurological complaint that may draw on seizures (e.g., brain neoplasms, stroke), diseases that may affect cognitive functions (e.g., head trauma), application of other medicines that may bring on seizures (e.g., Benztropine, Methotrexate, and Tarvid), and concurrent abuse of other lawless substances were ruled out from the study.

All cases and control groups were subordinated to the following:

(a) neuropsychiatric evaluation.
(b) Assessment of opioid use disorder through history from the case and his relatives, substance monitoring in urine, and medicine abuse screening test (DAST) [18].
(c) Electroencephalography (EEG): all cases went through EEG using the Neurofax device model Nihon Koden in Psychiatry, Neurology, and Neurosurgery Center, Tanta University. Six montages were done to all cases for 2 min per each using 22 electrodes placed according to a 10–20 system, these montages are external monopolar, parasagittal monopolar, external bipolar, parasagittal bipolar, transverse, and Gastaut [19].

Two provocation tests in the form of exposing the cases for two minutes to photic stimuli for 2 min, hyperventilation for 2 min, and post-hyperventilation for 2 min. The total duration of that EEG record is about 18 min [20].

EEG changes were classified into two changes: normal and abnormal changes. EEG abnormalities were classified into focal, generalized, and focal with secondary generalization. These abnormalities were recorded and statistically assayed.

(d) Cognitive assessment by Montreal Cognitive Assessment (MOCA). MOCA was designed as a rapid

screening instrument for mild cognitive dysfunction. It assesses different cognitive disciplines' attention and concentration, executive functions, memory, language, visuoconstructional skills, abstract thinking, computations, and orientation. The time to administer the MOCA is roughly 10 min. The total possible score is 30 points; a score of 26 or over is considered normal, add one point for an individual who has 12 years or lesser of formal education [21].

Statistical analysis

The collected data were organized, tabulated, and statistically assayed using SPSS interpretation 19 (Statistical Package for Social Studies) created by IBM, Chicago, IL, USA. For numerical values, the range, mean, and standard deviations were calculated. The differences between the two mean values were used using the Mann–Whitney test (*Z*) due to the small sample size in the tested orders that did not guarantee normal distribution. Differences in mean values of cognitive score between studied groups were tested by analysis of friction (F) and the Scheffe test was used to compare between every two groups. For categorical variables, the number and percentage were calculated and differences between subcategories were tested by Monte Carlo exact test. The correlation between the two variables was calculated using Pearson's correlation measure (*r*). The degree of significance was espoused at $p < 0.05$ [22, 23].

Table 1 Distribution of study participants in relation to age in years

Age (years)	Tramadol group ($n=40$)	Heroin group ($n=40$)	Control group ($n=40$)	*P*
Range	18–50	16–44	18–48	0.987
Mean + SD	29.80 ± 9.55	29.90 ± 6.59	30.10 ± 8.68	

Results

Sociographic results

There was no significant difference among the mean age of the three studied groups ($p=0.987$) (Table 1). Besides, all tramadol and heroin groups were males.

Assessment of opioid use disorder results

With respect to the distribution of study participants in relation to the duration of drug abuse, there was no noteworthy difference between the tramadol group and the heroin group ($p=0.102$) (Table 2).

With respect to the distribution of study participants in relation to the amount of drug abuse per day, the highest frequency was for 4–5 gm per day of drug abuse within the tramadol group which represented 45% of the patients in this group and 1–1.5 gm per day of drug abuse within the heroin group which represented 35% of the patients in this group. The mean amount of drug abuse in the day for the tramadol group was 4.20 + 2.04 which was higher than 2.00 + 1.56 for the heroin group, respectively. This difference was highly statistically noteworthy ($p=0.001$) (Table 2).

With respect to the drug abuse screening test, the highest frequency for the score of + ve items was 15 in both groups, representing 50% of the patients within the tramadol group and 60% within the heroin group. The mean score of drug abuse screening test + ve items for the tramadol group was 17.80 + 3.94, slightly less than 18.00 + 2.68 for the heroin group. This difference was not statistically noteworthy ($p=0.791$) (Table 2). The cut-off point for that test was 6 or more + ve items.

Table 2 Distribution of study participants in relation to duration and amount of drug abuse and also in relation to drug abuse screening test

	Tramadol group ($n=40$)		Heroin group ($n=40$)		*P*
Duration of drug abuse in years	5.85 ± 2.83		4.65 ± 3.61		0.102
Z	1.774				
Amount of drug abuse gm/day	4.20 ± 2.04		2.00 ± 1.56		0.001*
Median	5		3.75		
Z	3.409				
Drug abuse screening test (number of + ve items)	*N*	%	*N*	%	0.791
More than 6 and less than 15	9	22.50	3	7.50	
15–	20	50.00	24	60.00	
20–	11	27.50	13	32.50	
Mean + SD	17.80 ± 3.94		18.00 ± 2.68		
Z	0.395				

*significant at $p<0.05$

Cognitive assessment results

With respect to the comparison of the whole score of cognitive functions as evaluated by MOCA among examined groups. The highest score on the normal cognitive function test was found within the control group, 82.50% of the control group had a normal cognitive function, on the other hand, 85% of tramadol and 87.50 of the heroin group had impaired cognitive function. Statistical analysis utilizing the Scheffe test revealed that the control group was significantly different from tramadol and heroin groups, as the mean score of the cognitive function test for the control group was 26.85 + 1.27, which was higher than 20.80 + 4.53 and 20.60 + 5.06 for tramadol and heroin groups, respectively ($p = 0.001$) (Table 3). This meant that addicts of heroin and tramadol had noteworthy cognitive impairment compared to control.

A comparison of subitems of cognitive functions among examined groups evaluated by MOCA was outlined in Table 4. The addicts of heroin and tramadol had noteworthy cognitive impairment in sub-items of alternating trail making, cube drawing, naming, attention, sentence repetition, verbal fluency, and orientation compared to control. In the meantime, there was no noteworthy difference with respect to sub-items of clock drawing, abstraction, and delayed recall between addicts of heroin and tramadol and control.

Correlation between drug abuse screening test, cognitive scoring on the one hand and age in years, duration, and amount of abuse on the other hand in patients group

With respect to the correlation between cognitive scoring, drug abuse screening test results on the one hand and age in years, duration, and amount of abuse on the other hand within the patient groups, there was no noteworthy difference in the correlation between cognitive scoring, drug abuse screening test results and age of the drug abuser in years, duration of the abused substance in years and the amount of drug abused by mg per day in addicts of heroin and tramadol groups (Table 5).

EEG assessment results

EEG within the examined groups revealed the following: tramadol group: 52.50% showed abnormalities in EEG, in the heroin group: 32.50% showed abnormalities in EEG and control group: 20% showed abnormalities in EEG which was statistically noteworthy ($p = 0.029$), This meant that opioid abusers had noteworthy EEG changes (Table 6) (Fig. 1).

The comparison according to EEG changes revealed that there was no statistically noteworthy difference between the three groups with respect to EEG changes ($p = 0.268$). The number of patients who had generalized high amplitude paroxysmal slow activity was 8 within the control group, 15 within the tramadol group, and 11 within the heroin group. The number of patients who had no paroxysmal activity was 32 within the control group, 19 patients within the tramadol group, and 25 patients within the heroin group. Only four patients had focal paroxysmal slow activity, they were from the heroin group. That means that there was no specific EEG change within the examined groups (Table 7) (Fig. 1).

There was a significant relation between the EEG abnormalities and cognitive deficits within the tramadol and heroin groups (0.002) (Table 8).

Discussion

Opioids are composites that act by binding to specific opioid receptors in the central and peripheral nervous systems and interceding their effects through the opioid system. These receptors are substantially mu, kappa, and delta [24]. Current exploration showed that all medicine addicts were male. This was harmonious with the findings of Sattari M and associates, who interpreted this finding because men were generally more at the hazard of medicine dependence than women, conceivably because they were more curious, preferring further different and less tolerant of social or social conditions, family stress related to women [25].

Table 3 Comparison of total score of cognitive functions among studied patients and control groups assessed by MOCA

	Tramadol group ($n = 40$)		Heroin group ($n = 40$)		Control group ($n = 40$)		*P*
Cognitive function test	*N*	%	*N*	%	*N*	%	0.001*
Abnormal	34	85.0	35	87.50	7	17.50	
Normal	6	15.0	5	12.50	33	82.50	
Mean ± SD	20.80 ± 4.53		20.60 ± 5.06		26.85 ± 1.27		
F	15.867						

*significant at $p<0.05$

Table 4 Comparison of subitems of cognitive functions among studied patients and control groups assessed by MOCA

Cognitive function test	Tramadol group ($n=40$)		Heroin group ($n=40$)		Control group ($n=40$)		$\chi 2$	p
	N	%	*n*	%	*n*	%		
Alternating trail making:							24.646	0.001*
0	26	65.0	27	67.5	0	0.0		
1	14	15.0	13	32.50	40	100.0		
Cube drawing							34.29	0.001*
0	33	82.50	32	80.0	0	0.0		
1	7	17.50	8	20.0	40	100.0		
Clock drawing							MCET	0.250
0	5	12.50	8	20.00	0	0.0		
1	5	12.50	12	30.00	10	25.0		
2	23	57.50	9	22.50	20	50.0		
3	27	67.50	11	27.50	10	25.0		
Naming:							MCET	0.001*
1	0	0.0	2	5.00	0	0.0		
2	21	52.5	25	62.50	0	0.0		
3	19	47.50	13	32.50	40	100.0		
Attention:							13.029	0.001*
2–4	14	35.0	15	37.50	0	0.0		
5	10	25.0	9	22.50	25	62.50		
6	16	40.0	16	40.00	15	37.50		
Sentence repetition:							MCET	0.033*
0	9	22.50	10	25.0	0	0.0		
1	21	52.50	22	55.0	18	45.0		
2	10	25.00	8	20.0	22	55.0		
Verbal fluency:							13.678	0.001*
0	35	87.50	28	70.0	27	67.50		
1	7	17.50	12	30.0	13	32.50		
Abstraction:							MCET	0.050
0	7	17.50	3	7.50	0	0.0		
1	9	22.50	9	22.50	0	0.0		
2	24	60.00	28	70.00	40	100.0		
Delayed recall:							5.740	0.300
0–3	15	37.50	12	30.0	7	17.50		
4	13	32.50	8	20.0	15	37.50		
5	12	30.00	20	50.0	18	45.00		
Orientation:							MCET	0.001*
0–4	10	25.0	13	32.50	0	0.0		
5	22	55.0	17	42.50	6	15.0		
6	8	20.0	10	25.00	34	85.0		

*significant at $p<0.05$

Our study showed that people addicted to heroin and tramadol endured significant cognitive impairment compared with the control group. This agreed with Bassiony and associates, who set up in their study that tramadol abusers ($n=100$) were roughly three times more likely to witness cognitive impairment than subjects control. In addition, cases who abused pure tramadol ($n=24$) were 2 times more likely to have cognitive impairment than control subjects [26]. Estimates of the frequency of cognitive impairment in cases with substance use diseases varied extensively and ranged from roughly 30 to 80% in the Zickler P study [27]. Meanwhile, Allan and associates [28] estimated the frequency of cognitive decline in a group of medicine inpatients in rural Australia. They reported that

Table 5 Correlation between drug abuse screening test and cognitive scoring on the one hand and age in years, duration, and amount of abuse on the other hand in patients group

Variables	Drug abuse screening test			
	R		*P*	
Age in years	−0.047		0.723	
Duration of abuse by years	0.119		0.463	
Amount of drug abuse by gm per day	0.094		0.562	
Variables	Cognitive score			
	Tramadol group (*n* = 40)		Heroin group (*n* = 40)	
	r	*P*	*R*	*P*
Age in years	0.184	0.437	0.380	0.098
Duration of abuse by years	0.006	0.981	0.185	0.435
Amount of drug abuse by mg per day	0.193	0.416	−0.193	0.416

12% to 40% of the cases had moderate to severe or mild to moderate cognitive impairment, respectively. These differences in the frequency of cognitive impairment may be due to the use of different assessment tools in different settings for cases taking different substances.

In addition, Lyvers and Yakimoff set up that opioids caused deficits in cognitive inflexibility [29]. Likewise, Ornstein and his associates set up this; habitual heroin users showed deficits in a range of cognitive skills, including fluency, pattern recognition, planning, and the capability to shift attention from one frame of mind to another. other frame of reference [30]. Soyka and associates stated that long-term exposure to opiates, similar to heroin, has been shown to compromise cognitive function [31].

Current exploration showed that heroin and tramadol addicts endured significant cognitive impairment in the sub-components of interspersing path generation, drawing shapes, naming, attention, sentence repeat, fluency, and control orientation. Meanwhile, there were no significant differences in clock drawing, abstraction, and delayed recall subtypes between heroin and tramadol addicts and controls. This was harmonious with Bassiony and associates, who set up statistically significant differences between cases and control subjects in all cognitive disciplines assessed on the MOCA scale. This impairment ranged from 23% in exposure to 96% in cases with delayed recall (total cases and pure tramadol), while in control subjects it ranged from 4% acquainted to 54% in case of slow recall. The areas most constantly affected in total cases and cases with tramadol abuse only were memory (delayed recall), spatial image processing (clock drawing), language (language fluency), and speech [26]. No studies have examined the relationship between long-term tramadol use, abuse or dependence, and cognitive decline worldwide.

An experimental study by Hosseini-Sharifabad and associates set up that a single dose or diurnal administration of tramadol for 21 successive days caused memory impairment in rats. Opioids have convinced cognitive impairment through their effects on the structure of the hippocampus and prefrontal cortex. These medicines have been shown to enhance apoptosis and inhibit neurogenesis [32].

In this study, there was no significant correlation between cognitive scores and abuse levels in the heroin-using group, the tramadol group, and the each-abuse group. This was harmonious with Bassiony and associates [26], who set up no association between tramadol dose and cognitive impairment, and this finding confirms an earlier study by Mintzer and associates [33], which reported no difference between the high dose (800 mg) and the low dose (400 mg) of tramadol in all cognitive disciplines except balance.

Our study showed that opioid addicts showed significant EEG changes compared with the control group. This was harmonious with the study by Iranmanesh et al., which showed that further than half of tramadol abusers had EEG abnormalities, although seizure waves were seen in only about 20 of cases [34]. Another cross-sectional study by Boostani R, Derakhshan S showed that 43% of tramadol cases had EEG changes on day 1, but abnormalities were only 3.5% a week latterly in control EEGs [35]. In addition, Shadnia, S. reported that tramadol abuse was frequently associated with common electroencephalogram (EEG) abnormalities [36]. There had been many studies of EEG changes in people using tramadol. There was a significant correlation between EEG abnormalities and cognitive deficits in the tramadol and heroin groups. This finding was in agreement with the findings of Davydov DM, Polunina AG, who stated that it should also be considered that resting EEG properties in tramadol and heroin addicts may be affected by ongoing cognitive

Table 6 EEG in the studied groups

	Tramadol group (*n* = 40)		**Heroin group (*n* = 40)**		**Control group (*n* = 40)**		**χ2**	***P***
	N	**%**	***N***	**%**	***N***	**%**		
Normal	19	47.50	27	67.50	32	80	7.059	0.029
Abnormal	21	52.50	13	32.50	8	20		

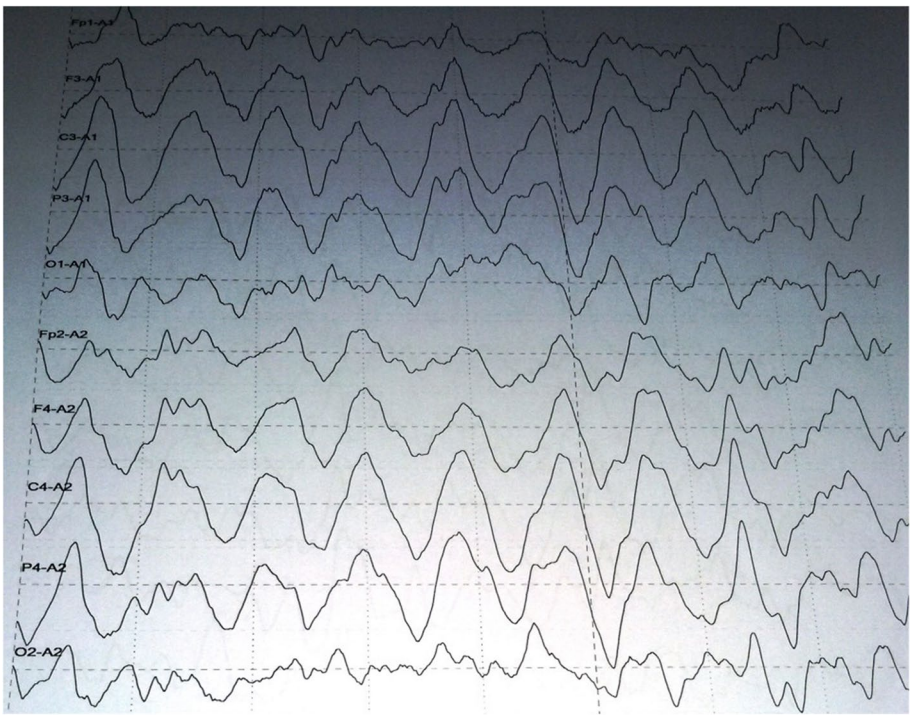

Fig. 1 EEG study samples from tramadol, heroin abusers patients with upper panel generalized high amplitude polymorphic delta activity. The second panel showing scattered central theta activity, and the third panel showing focal polymorphic delta activity (original images from patients enrolled in the study)

Table 7 Distribution of EEG findings among studied patients and control groups

	Tramadol group ($n=40$)		Heroin group ($n=40$)		Control group ($n=40$)		χ2	Df	*p*
	No	%	No	%	No	%			
No paroxysmal activity	19	47.50	25	62.50	32	80	12.3	10	0.268
Generalized high amplitude paroxysmal slow activity	15	37.50	11	27.50	8	20			
Focal paroxysmal slow activity	0	0.00	4	10.00	0	0			
Scattered central delta theta activity	3	7.50	0	0	0	0			
Paroxysmal fast beta activity	1	2.50	0	0	0	0.0			
Polymorphic activity	2	5.00	0	0.0	0	0.0			

Table 8 Comparison of cognitive score in relation to EEG -changes among studied patients groups

EEG changes	Tramadol group	Heroin group	*P*
Normal	21.71 + 5.85	21.19 + 3.94	0.108
Abnormal	20.31 + 4.01	17 + 8.45	0.002*
Z	0.756	0.949	

*significant at $p<0.05$

processes similar to memory processes, habitual cravings, medicine use, and emotional states of objects. In addition, cognitive dysfunction in heroin addicts was associated with abnormal EEG results [37].

The strength of the present paper lies in its comparative profile when a control group is applied, which we consider pivotal for relating cognitive and EEG abnormalities due to opioid abuse for proper management. In addition, follow-up of our cases and assessment of the long-term effects of abuse on cognitive aspects and our studied EEG were performed.

Conclusion

Opioid abuse induced global cognitive function impairment, specific cognitive domains impairment that included visual-conceptual, visual-motor tracking visuo-constructional skills, language function, attention, memory, and orientation. Besides, affection of the brain electrical activities with significant changes with a significant correlation between changes in brain electrical activity and impairment of cognitive functions that should be detected early, tracked with follow-up for proper management and possible prevention.

Abbreviations

DAST	Drug abuse screening test
EEG	Electroencephalography
MOCA	Montreal Cognitive Assessment

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Authors' contributions

FE conceptualized the study. EG, AM, YE, AI, AB, and MB have given inputs in the study design. FE collected the data. MB analyzed the data and wrote the first draft of the handwriting and all co-authors contributed to a critical review of data analysis and handwriting notation. MB will act as patron for this paper. All authors have read and approved the handwriting. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published composition (and its supplementary information lines).

Declarations

Ethics approval and consent to participate

The study protocol followed was reviewed, and approved by the Research Ethics Committee of the Faculty of Medicine, Tanta University, and has therefore been performed in agreement with the ethical morals laid down in the 1964 Declaration of Helsinki. A detailed explanation of the study was given by the top investigator after which they handed concurrence for publication. All the cases included in this study gave written informed consent to publish the data contained within this study.

All ethical morals were maintained. Any unexpected hazards that appeared during the study will be clarified to the subjects and the ethical commission on time. There were respectable measures to keep the privacy of sharers and the confidentiality of the data. Ethics approval code: 453211117.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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