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Effect of Tramadol and Heroin on Cardiovascular System

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Abstract: Background: Drug addiction is a worldwide common disorder, problems of substance abuse lead to dramatic costs for all societies in the term of low productivity, transmission of infectious diseases, family and social troubles as well as crimes Tramadol hydrochloride is a synthetic, centrally acting, opiate-like analgesic that is used to treat acute and chronic pain.Heroin is an illegal, highly addictive drug. It is both the most abused and the most rapidly acting of the opiates. **Aim:** The aim of this study was to assess the effect of tramadol and heroin on cardiovascular system; namely: clinical, electrocardiogram (ECG) and transthoracic echocardiography study. **Patients & Methods:** This was a comparative case - control study, it was carried out at Department of Neuropsychiatry, The Centre of Psychiatry, Neurology and Neurosurgery and Department of Cardiology**,** Tanta University Hospitals. The research was conducted during one year period, started from March 2018 through April 2019. Ninety persons were included in this study Patients' groups (Tramadol group:30 patients with tramadol use disorders diagnosed according to DSM-5 criteria) (Heroin group:30 patients with heroin use disorders diagnosed according to DSM-5 criteria) Control group: 30smokers with no cardiac history. **Results:** Tramadol induced hypertension and hypotension with hypertension predominance while heroin induced hypotension. Tramadol induced tachycardia and bradycardia with tachycardia predominance while heroin induced bradycardia.13.3% of heroin addicts had elevated temperature.23.3% of heroin addicts had bradyapnea.40% of heroin addicts had vascular changes (thrombosed veins).Tramadol induced mostly sinus tachycardia, QTc interval prolongation and sinus bradycardia while heroin induced sinus bradycardia. Heroin addiction induced valve abnormalities which tricuspid and mitral valves were the most affected valves.There were no significant differences between vital signs, ECG changes and ECHO findings and the severity of tramadol addiction. There were significant differences between the vital signs of the patients abusing heroin in relation to drug severity index except bradyapnea. There were significant differences between vascular, ECG changes and ECHO findings and the severity of drug abuse in the heroin group. But There was no a significant difference between the diameter of cardiac chambers and the severity of drug abuse in the heroin group. **Conclusion:** There were no significant differences between vital signs, ECG changes and ECHO findings and the severity of tramadol addiction.There were significant differences between the vital signs of the patients abusing heroin in relation to drug severity index except bradyapnea. There were significant differences between vascular, ECG changes and ECHO findings and the severity of drug abuse in the heroin group. But There was no a significant difference between the diameter of cardiac chambers and the severity of drug abuse in the heroin group.

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Key word: Tramadol, Heroin**,** Cardiovascular System

1. Introduction:

Substance abuse, also known as drug abuse, is a patterned use of a drug in which the users consumes the substance in amounts or with methods that are harmful to themselves or others, and is a form of substance-related disorder, anddue to its neurobiological basis, it requires medical intervention to effectively combat the disease**(1).**

Substance abuse in Egypt is a serious public health threat. Recent studies have demonstrated increases in the prevalence of the use of tobacco, illegal drugs and over-the-counter drugs, particularly among youth. Smoking cigarettes and using hashish were the most common practices, and tramadol was the most commonly used pharmaceutical drug**(2).**

Illegal drugs are a major social problem worldwide, the economic crisis has lead the illegal drug users to search for cheaper but potentially more harmful substances[(3)].

Tramadol hydrochloride has been demonstrated in the Egyptian community since 2008. This may be due to the fact that tramadol is easily accessible and readily provided at cheap costs despite of being a scheduled drug[(4)].

Tramadol has a dual mechanism of action: weak μ -opioid receptor agonist and a reuptake inhibitor of serotonin and noradrenalin [(5)].

Heroin is an illegal, highly addictive drug. It is both the most abused and the most rapidly acting of the opiates. Heroin is synthesized from morphine, a naturally occurring substance extracted from the seed pod of certain varieties of Poppy plants[(6)].

Infectious complications are the most frequent cause of medical attention in intravenous drug addicts. One of the most fearful is infective endocarditis, typically involving the tricuspid valve[(7)].

2. Patients and Methods;

This was a comparative case - control study, it was carried out at Department of Neuropsychiatry, The Centre of Psychiatry, Neurology and Neurosurgery and Department of Cardiology**,** Tanta University Hospitals. The research was conducted during one year period, started from March 2018 through April 2019. Ninety persons were included in this stud **Patients' groups (Tramadol group:30** patients with tramadol use disorders diagnosed according to DSM-5 criteria) **(Heroin group:30** patients with heroin use disorders diagnosed according to DSM-5 criteria) **Control group: 30** smoker persons were taken as a control group matching with patients' groups with no history of heart diseases**.**

The inclusion criteria:

1. All persons included in this study were males.
2. Addicts abusing one substance only either tramadol or heroin
3. Persons aged from 17 to 40 years old.
4. Persons who abused tramadol in a dose 200 mg or more daily orevery other day for at least one year.
5. Persons who abused heroin in a dose 100 mg or more daily or every other day for at least one year.

The exclusion criteria:

1. Addicts abusing other substances with tramadol or heroin.
2. Persons aged less than 17 years and more than 40 years.
3. Patients with past history of cardiac diseases e.g. congenital heart diseases, rheumatic heart diseases, coronary heart diseases and previous cardiac surgery.
4. Patients on drugs that could affect cardiovascular system e.g. Beta blockers.
5. Patients suffering from diseases that could affect cardiovascular system e.g. hypertension, diabetes mellitus, hepatic diseases and renal diseases.

All participants in this study were subjected to the following:

1-History taking.

2-Clinical examination.

3-Investigations:

1- Routine Laboratory investigations e.g. complete blood count and renal function tests

2-Drugs screening in urine for exclusion of polysubstance abuse.

3-The Addiction Severity Index (ASI) scale.

4-Fahmy and El-Sherbini's Social Classification Scale.

5-Resting twelve leads Electrocardiogram (ECG).

6-Transthoracic echocardiography.

Statistical analysis:

The collected data were organized, tabulated and statistically analyzed using SPSS version 19 (Statistical Package for Social Studies) created by IBM, Illinois, Chicago, USA. For numerical values the range mean, median and standard deviations were calculated. The differences between mean values were used analysis of variance (F) and when found significant Bonferroni test was used to compare between each two groups. For categorical variable the number and percentage were calculated and differences between subcategories were tested by Chi square test. When chi square was not found appropriate, Monte Carlo exact test was used. The correlation between two variables was calculated using Pearson's correlation coefficient. The level of significant was adopted at $p<0.05$.

3. Results:

Age: in the present study, all the selected patients were males aged 18 to 40 years old (mean = 29.77+6.15).

Employment: there was a significant difference between the heroin and control group (p= 0.037). Most of heroin addicts were unemployed (60%). This means that heroin addicts were highly affected regarding employment in comparison to other two studied groups as a result of heroin addiction.

Social Status:all patients with different social level were affected. Low and moderate social levels were predominant than high social group in each group with no significant difference.

Marital status: There was no significant difference between the tramadol and control group (P= 0.121) and tramadol and heroin group (P= 0.195)

regarding marital status, while there was significant difference between heroin and control group (p= 0.001).36.7% of heroin addicts were divorced which was significantly higher than control group. This means that heroin addicts were affected regarding marital status in comparison to other two studied groups.

Residence: urban residency was higher in three groups with no significant difference between the tramadol and control group (P= 0.121) and tramadol and heroin group (P= 0.195) regarding residence, while there was a significant difference between heroin and control group (p= 0.019). 70% of heroin addicts were from urban areas. It was found that heroin addiction is more common among urbans compared to rurals.

Table (1): Tramadol induced hypertension in 26.7% oftramadol addicts while induced hypotension in 13.3% of those addicts in comparison with control group which all of the control group had normal blood pressure with significant differences (P= 0.001). While heroin induced hypotension in 36.7% of heroin addicts in comparison with control group which 100% of this group had normal blood pressure with significant differences (P= 0.001). There was significant differences regarding blood pressure between tramadol group and heroin group (P=0.001).

Tramadol induced tachycardia in 43.3% oftramadol addicts while induced bradycardia in 10% of those addicts in comparison with control group which (83.3%) of control patients had normal pulse and (16.7%) of this group had tachycardia with significant differences (P= 0.017). While heroin induced bradycardia in 36.7% of heroin addicts in comparison with control group which 83.3% of control patients had normal pulse and (16.7%) of this group had tachycardia with significant differences (P= 0.001). There was significant differences regarding pulse between tramadol group and heroin group (P=0.017).This means that tramadol induced tachycardia and bradycardia with tachycardia predominance while heroin induced bradycardia.

There was no significant difference regarding temperature between the tramadol group and control group, heroin group and control group and tramadol and heroin group p= (1.000, 0.112 and 1.000 respectively). Most of the patients in the three groups had normal temperature while 13.3% of heroin addicts had elevated temperature. This means that heroin addicts induced elevated temperature but the difference was not significant.

There was no significant difference between tramadol and control group (P= 0.706) and tramadol and heroin group (P= 0.706) regarding respiratory rate, while there was significant difference between heroin and control group (p= 0.001). 23.3% of heroin addicts had bradyapnea. This means that heroin addicts induced bradyapnea.

Table (1): Comparison of vital signs among studied groups

Vital signs	Tramadol group		Heroin group		Control group		Monte Carlo Exact Test
	n (30)	%	n (30)	%	n (30)	%	
Blood pressure:							1-Tramadol vs Control **P**=0.001*. 2-Heroin vs Control **P**=0.001*. 3-Tamadol vs Heroin **P**=0.001*.
Hypotension	4	13.3	11	36.7	0	0.0	
Normal	18	60.0	19	63.3	30	100.0	
Hypertension	8	26.7	0	0.0	0	0.0	
Pulse:							1-Tramadol vs Control **P**=0.017*. 2-Heroin vs Control **P**=0.001*. 3-Tamadol vs Heroin **P**=0.017*.
Bradycardia	3	10.0	11	36.7	0	0.0	
Normal	14	46.7	19	63.3	25	83.3	
Tachycardia	13	43.3	0	0.0	5	16.7	
Temperature:							1-Tramadol vs Control **P**=1.000. 2-Heroin vs Control **P**=0.112. 3-Tamadol vs Heroin **P**=1.000.
Normal	30	100.0	26	86.7	30	100.0	
Elevated*	0	0.0	4	13.3	0	0.0	
Respiratory rate:							1-Tramadol vs Control **P**=0.706. 2-Heroin vs Control **P**=0.001*. 3-Tamadol vs Heroin **P**=0.706.
Brady apnea	0	0.0	7	23.3	0	0.0	
Normal	25	83.3	23	76.7	27	90.0	
Tachypnea	5	16.7	0	0.0	3	10.0	

Table (2): There was no significant difference between the tramadol and control group regarding vascular changes (P= 1.000) while there was significant difference between heroin and control group (P= 0.001) and tramadol and heroin group (P= 0.001). 40% of heroin addicts had vascular changes (thrombosed veins). This means that heroin addiction induced vascular changes (thrombosed veins) while no vascular changes was observed in the tramadol and control groups.

Table (2): Comparison of vascular changes among studied groups

Vascular changes	Tramadol group		Heroin group		Control group	
	n (30)	%	n (30)	%	n (30)	%
None	30	100.0	18	60.0	30	100.0
Thrombosed veins	0	0.0	12	40.0	0	0.0
Monte Carlo ExactTest	**1**-Tramadol group vs Control group **P**=1.000. **2**-Heroin group vs Control group **P**=0.001*. **3**-Tamadol group vs Heroin group **P**=0.001*.					

Table (3): 43.3% of tramadol addicts had sinus tachycardia, 10% had sinus bradycardia and 10% had long QTc interval in addicts in comparison with control group which 80% of this group had normal ECG, 16.7 % had sinus tachycardia and one patient had ischemic changeswith significant differences (P= 0.001). 63.3% of heroin addicts had normal ECG and the rest of this group (36.7%) had sinus bradycardia in comparison with control group which 80% of this group had normal ECG, 16.7% had sinus tachycardia and one patient had ischemic changes with significant differences (P= 0.001). There was significant differences regarding ECG changes between tramadol group and heroin group (P=0.001). This means that tramadol induced mostly sinus tachycardia, QTc interval prolongation and sinus bradycardia while heroin induced sinus bradycardia.

Table (3): Comparison of ECG changes among studied groups

ECG changes	Tramadol group		Heroin group		Controlgroup	
	n (30)	%	n (30)	%	n (30)	%
Normal	11	36.7	19	63.3	24	80.0
Sinus bradycardia	3	10.0	11	36.7	0	0.0
Sinus tachycardia	13	43.3	0	0.0	5	16.7
Ischemic changes	0	0.0	0	0.0	1	3.3
Long Qtc interval	3	10.0	0	0.0	0	0.0
*Arrhythmias	0	0.0	0	0.0	0	0.0
Monte Carlo ExactTest	**1**-Tramadol group vs Control group **P**=0.001*. **2**-Heroin group vs Control group **P**=0.001*. **3**-Tamadol group vs Heroin group **P**=0.001*.					

Table (4): There was significant difference between heroin and control group (p= 0.001). 20% of heroin addicts (n=6 patients) had tricuspid valve affection (vegitations) and one patient had mitral valve affection while tramadol and control groups had no valve abnormalities. This means that Heroin addiction induced valve abnormalities which tricuspid and mitral valves were the most affected valves.There was no significant differences regarding diameter of cardiac chambers between the tramadol group and control group, heroin group and control group and tramadol and heroin group p= (1.000, 0.237 and 1.000 respectively). There were no significant differences regarding mitral regurge findings between tramadol and control group, heroin and control group and tramadol and heroin group p= (0.488, 0.500 and 0.731 respectively). There were no significant differences regarding tricuspid regurge findings between tramadol and control group, heroin and control group and tramadol and heroin group p= (0.317, 0.350 and 0.067 respectively). There were no significant differences regarding pulmonary arterial systolic pressure (PASP) between tramadol and control group, heroin and control group and tramadol and heroin group p= (1.000, 0.183 and 1.000 respectively).

Table (5): There was a significant difference between hypotension and the severity of drug abuse in the heroin group (P=0.001). This means that the more the severity of heroin addiction, the more hypotensive patients were.There was a significant difference between bradycardia and the severity of drug abuse in the heroin group (P=0.001. This means that the more the severity of heroin addiction, the more the occurrence of bradycardia.There was a significant difference between elevated temperature and the severity of drug abuse in the heroin group (P=0.003). This means that the more the severity of heroin addiction, the more feverish patients were.There was no a significant difference between respiratory rate and the severity of drug abuse in the heroin group (P=0.400). Heroin addicts who had bradyapnea were not related to the severity of heroin addiction.

Table (4): Comparison of ECHO findings among studied groups

ECHO findings	Tramadol group		Heroin group		Controlgroup		Monte Carlo Exact Test
	n (30)	%	n (30)	%	n (30)	%	
Valve abnormalities							1-Tramadol vs Control **P**=1.000. 2-Heroin vs Control **P**=0.001*. 3-Tamadol vs Heroin **P**=1.000.
Normal	30	100.0	23	76.7	30	100.0	
Tricuspid	0	0.0	6	20.0	0	0.0	
Mitral	0	0.0	1	3.3	0	0.0	
Aortic	0	0.0	0	0.0	0	0.0	
Pulmonary	0	0.0	0	0.0	0	0.0	
Mitral regurge:							1-Tramadol vs Control **P**=0.488. 2-Heroin vs Control **P**=0.500. 3-Tamadol vs Heroin **P**=0.731.
Normal	26	86.7	26	86.7	24	80.0	
Mild	4	13.3	3	10.0	6	20.0	
Severe	0	0.0	1	3.3	0	0.0	
Tricuspid regurge:							1-Tramadol vs Control **P**=0.317. 2-Heroin vs Control **P**=0.350. 3-Tamadol vs Heroin **P**=0.067.
Normal	28	93.3	21	70.0	25	83.3	
Mild	2	6.7	4	13.3	4	13.3	
Moderate	0	0.0	2	6.7	1	3.3	
Severe	0	0.0	3	10.0	0	0.0	
Pulmonary arterial systolic pressure:							1-Tramadol vs Control **P**=1.000. 2-Heroin vs Control **P**=0.183. 3-Tamadol vs Heroin **P**=1.000.
Normal	30	100.0	25	83.3	29	96.7	
Mild	0	0.0	3	10.0	1	3.3	
Moderate	0	0.0	1	3.3	0	0.0	
Severe	0	0.0	1	3.3	0	0.0	
Cardiac chambers dimensions							1-Tramadol vs Control **P**=1.000. 2-Heroin vs Control **P**=0.237. 3-Tamadol vs Heroin **P**=1.000.
Normal	30	100.0	27	90.0	30	100.0	
Dilated Lt atrium	0	0.0	0	0.0	0	0.0	
Dilated Lt ventricle	0	0.0	0	0.0	0	0.0	
Dilated both Rt atrium and ventricle	0	0.0	3	10.0	0	0.0	

Table (5): Comparison of vital signs among patients abusing Heroin in relation to Drug Severity Index (drug abuse scale).

Vital signs	Mild		Moderate		Severe		Extreme		p
	n (11)	%	n (12)	%	n (6)	%	n (1)	%	
Blood pressure:									0.001*
Hypotension	2	18.2	3	25.0	5	83.3	1	100	
Normal	9	81.8	9	75.0	1	16.7	0	0.0	
Pulse:									0.001*
Bradycardia	1	9.1	4	33.3	5	83.3	1	100	
Normal	10	90.9	8	66.7	1	16.7	0	0.0	
Temperature:									0.003*
Normal	11	100	11	100	3	50.0	0	0.0	
Elevated	0	0.0	0	0.0	3	50.0	1	100	
Respiratory rate:									0.400
Brady apnea	2	18.2	2	16.7	3	50.0	0	0.0	
Normal	9	81.8	10	83.3	3	50.0	1	100	

Table (6): There was a significant difference between vascular changes and the severity of drug abuse in the heroin group. (P=0.033). This means that the more the severity of heroin addiction, the more the occurrence of venous thrombosis.

Table (7): There was a significant difference between ECG changes (sinus bradycardia) and the severity of drug abuse in the heroin group (P=0. 001).This means that the more the severity of heroin addiction, the more the patients who had sinus bradycardia.

Table (6): Comparison of vascular changes among patients abusing heroin in relation to Drug Severity Index (drug abuse scale).

Vascular changes:	Mild		Moderate		Severe		Extreme	
	n (11)	%	n (12)	%	n (6)	%	n (1)	%
None	9	81.8	8	66.7	1	16.7	0	0.0
Thrombosed veins	2	18.2	4	33.3	5	83.3	1	100
P	0.033*							

Table (7): Comparison of ECG changes among patients abusing heroin in relation to Drug Severity Index (drug abuse scale).

ECG changes	Mild		Moderate		Severe		Extreme	
	n (11)	%	n (12)	%	n (6)	%	n (1)	%
Sinus bradycardia	1	9.1	4	33.3	5	83.3	1	100
Normal	10	90.9	8	66.7	1	16.7	0	0.0
P	0.001*							

Table (8): There was significant differences between valve abnormalities and the severity of drug abuse in the heroin group (P=0. 033) as the heroin addicts had tricuspid mass (thrombus formation) (total n=6) were affected moderately 8.3% (n=1), severe 66.7% (n=4) and extremely severe 100% (n=1), while one patient had mitral mass (thrombus formation) was affected severely. This means that the more the severity of heroin addiction, the more tricuspid and mitral valves were affected regarding mass. Tricuspid valve was affected more than mitral valve.There was no a significant difference between the diameter of cardiac chambers and the severity of drug abuse in the heroin group (P=0.233).There was no a significant difference between the mitral regurge (total n=4) and the severity of drug abuse in the heroin group (P=0.333).There was a significant difference between the tricuspid regurge (total n=9) and the severity of drug abuse in the heroin group (P=0.001). This means that the more the severity of heroin addiction, the more the severity of tricuspid regurge.There was a significant difference between elevated PASP (total n=5) and the severity of drug abuse in the heroin group (P=0.001). This means that the more the severity of heroin addiction, the more the severity of PASP.

Table (8): Comparison of ECHO findings among patients abusing Heroin in relation to Drug Severity Index (drug abuse scale).

ECHO findings	Mild		Moderate		Severe		Extreme		P
	n (11)	%	n (12)	%	n (6)	%	n (1)	%	
Valve abnormalities									
Normal	11	100	11	91.7	1	16.7	0	0.0	0.033*
Tricuspid	0	0.0	1	8.3	4	66.7	1	100	
Mitral	0	0.0	0	0.0	1	6.7	0	0.0	
Mitral regurge:									
Normal	10	90.9	10	83.3	5	83.3	1	100	0.333
Mild	1	9.1	2	16.7	0	0.0	0	0.0	
Severe	0	0.0	0	0.0	1	16.7	0	0.0	
Tricuspid regurge:									
Normal	11	100	9	75.0	1	16.7	0	0.0	0.001*
Mild	0	0.0	2	16.7	2	33.3	0	0.0	
Moderate	0	0.0	0	0.0	1	16.7	1	100	
Severe	0	0.0	1	8.3	2	33.3	0	0.0	
Pulmonary arterial systolic pressure:									
Normal	11	100	10	83.3	4	66.7	0	0.0	0.001*
Mild	0	0.0	2	16.7	1	16.7	0	0.0	
Moderate	0	0.0	0	0.0	1	16.7	0	0.0	
Severe	0	0.0	0	0.0	0	0.0	1	100	
cardiac chambers dimensions									
Normal	11	100	11	91.7	4	66.7	1	100	0.233
Dilated both Rt atrium and ventricle	0	0.0	1	8.3	2	33.3	0	0.0	

4. Discussion:

In our study, all the selected patients were males with an age range from 18 to 40 year with mean + SD (29.77+6.15). **Niaz et al., 2005**[8]revealed that 71.5 % of the drug abusers were less than 35 years of age with the highest proportion in the 20-30 years age.

Regarding employment, there was a significant difference between heroin and control group group (P =0.037), while there were no significant differences between tramadol and control group and tramadol and heroin group. **Loffredo et al., 2015**[(2)]found that substance use was often described by youth as a formof self-medication to overcome psychological stress andfrustration, helping them to forget unpleasant things orovercome physical pain which occur during working.

On the contrary, **Amr et al., 2014**[(9)] found that there was no statistical significant difference regarding employment (P= 0.100).

Regarding social status, there were no significant differences between the three groups. This can be explained by; addicts of high social classes search for more enjoyment and addicts of low socioeconomic class escape from socioeconomic stress by using drugs. On the contrary, **Fawzi et al., 2010**[(4)]revealed that tramadol addicts being with low socioeconomic status.

This comes in agreement with**Amr et al., 2014**[(9)]who found that that being younger, unmarried, male sex and unsatisfactory income were significant risk factors of substance abuse.

In our study, we found that (63.3%) of tramadol group were married.This comes in agreement with **Saleem et al., 2008** [(10)] whorevealed that the alleged usages of tramadol contributed greatly to its popularity and massive use especially among youth and middle-aged groups as a remedy for premature ejaculation and for extended orgasm and to increase sexual potency as promoted in many online drug stores and media.

Our study is in agreement with **El-Sawyet el., 2010** [(11)]who found that there was significant difference regarding residence with urban predominance (P= 0.002).

In contrast, **Mohamed et al., 2015**[(12)] who found that no statistically significant association between the residence and the use of substance, this may be due to availability of substance of abuse in rural and urban areas and also due to urbanization of rural areas.

There were significant differences between the three groups regarding blood pressure. Hypotension only was observed in heroin group may be due to heroin (diacetylmorphine) is rapidly hydrolysed to 6-monoacetylmorphine (half-life, 9 minutes), which in turn is hydrolysed to morphine (half-life, 9 minutes)[(13)]**.** Morphine in healthy individuals does not cause significant changes in the cardiovascular system. The effect of morphine induces peripheral vasodilation and orthostatic hypotension[(14)].

Our study revealed that tramadol induced hypertension and hypotension with hypertension predominance.This may be due to tramadol acts as both a serotonin and norepinephrine reuptake inhibitor[(15)] .

Spiller et al., 1997 [(16)] mentioned thathypertension has also been reported, the least tramadol dose that has resulted in hypertension and agitation is 500mg.Also **Ghamsari et al., 2016**[(17)]stated that unlike opioids, tramadol overdose leads to irritability, increased deep tendon reflexes, tremor, and hypertension.

Moghadam et al 2016 [(18)] reported that hypotension, especially affecting SBP and sinus tachycardia are the cardiac complications resembling findings caused by other opioids.

There were significant differences between the three groups regarding pulse. Bradycardia only was observed in heroin group, may be due to heroin acts directly on the vasomotor center to increase parasympathetic activity and also reduces sympathetic tone as well as stimulates the release of histamine from mast cells. These effects on the cardiovascular system are likely to produce bradycardia and hypotension. **(Pavlidis et al., 2016)**[(19)]as well as (**Lubana et al., 2015)**[(20)].

In our results we observed that tachycardia in a significant number of patients in the tramadol group more than bradycardia. Although sinus tachycardia is usually non-specific for opioids, and bradycardia is a more common finding with other opioids **(Afshari et al., 2011)**[(21)] **(Chen et al., 2015)**[(22)] , our findings are in line with some other studies focusing on tramadol this may be through fast blockade of sodium and potassium channels (**Ghamsari et al., 2016)** [(17)]**(Spiller et al., 1997)**[(16)] , while few cases had tachycardia in the control group may be due to anxiety.

There were no significant differences between the three group regarding temperature, elevated temperature was observed only in heroin group may be due to drug contaminants and nonsterile injection methods provide a ready source of infection to the intravenous drug user, in addition, constitutional abnormalities in addicts such as malnutrition, transient bacteraemia**(Joseph et al., 1973)**[(23)]**.**

There was a significant difference between heroin and control group (P =0.001), while there were no significant differences between tramadol and control group and tramadol and heroin group. Patients had bradyapnea (23.3%) were observed only in heroin group (n=7) may be due to heroin induced respiratory depression. Opioid analgesics are generally associated with respiratory depression. This is mediated through a decrease in the sensitivity of the respiratory centre to CO2 which results in a decrease in respiratory rate and tidal volume **(Scott et al., 2000)**[(24)] **,** while there were few patients had tachyapnea in the tramadol group and

control group was observed may be due to the anxiety associated with examination.

40% of the patients in the heroin group had thrombosed veins, this may be due to drug contaminants and nonsterile injection methods provide a ready source of infection to the intravenous drug user, this comes in agreement with **(Joseph et al., 1973)** [(23)] that as more readily accessible veins become sclerosed and difficult to puncture, the long-term addict resorts to using smaller, more distal vessels for drug injection. The veins of the hand, especially on the dorsal aspect, are ideal for intravenous injection (mainlining). These fragile veins rapidly thrombose or rupture, allowing local subcutaneous infiltration of toxic substances with extensive tissue destruction.

Another opinion argues that heroin induced infective arteritis or vasculitis fromdrug adulterants**. (Kumar et al., 2015)**[(25)].

Only One heroin addict had lower limb gangrene may be due to arterial system affection and this in concordance with **Joseph et al., 1973** [(23)]who reported that intra-arterial injection of drugs in the addict, either accidental or intentional، can result in transient arterial ischemia in the peripheral vessels from micro embolism of particulate materials or thrombosis.

In our results we observed that sinus tachycardia in a significant number of patients in the tramadol group more than bradycardia (explanation as discussed before), while three patients had Long QTc interval. QTc prolongation is the primary ECG manifestation of potassium channel blockers **(Lionte et al., 2012)**[(26)].

While one control patient had ischemic changes in the ECG due to the effect of smoking, this patient had severe smoking index in comparison with other patients. The association between smoking and acute myocardial infarction has been reported by **(Auer et al., 2002)**[(27)]**.**

There were no significant differences between the three groups regarding cardiac dimension, but there were three patients in the heroin group had dilated right side of the heart may be a consequence of tricuspid valve destruction and severe tricuspid regurgitation with right sided volume overload, chamber dilatation, and right heart failure. In agreement with **Moss et al., 2003**[(28)]who found that extensive valve destruction with failure of leaflet co-optation and severe tricuspid regurgitation is a common sequel to tricuspid endocarditis.

There was a significant difference between heroin and control group regarding valve abnormalities (p=0.001), while there were no significant differences between tramadol and control group and tramadol and heroin group. This comes in agreement with **Pons Llado et al., 1992**[(7)]who found that the morphologic abnormalities of the valves that could be detected by echocardiography were: (1) mitral and tricuspid valvular focal thickening, defined as a small echogenic protruding mass distorting the valve contour and eliciting a distinctive signal by M mode examination and (2) mitral or tricuspid valve prolapse.

No apparent abnormalities were observed at the aortic or pulmonary valves **(Joseph et al., 1973)**[(23)]**.**

We found that 13.3%, 10% and 20% of the tramadol group, heroin group and control group respectively had mild mitral regurge, while 6.7%, 13.3% and 13.3% of the tramadol group, heroin group and control group respectively had mild tricuspid regurge which may be normal findings in echocardiography and this was going with **Yoshida et al., 1988**[(29)] who revealedthat the presence of mild valvular regurgitation detected by Doppler imaging in normal persons is well known. Its prevalence was increased slightly in control group than patients groups in which mild valve regurgitation was not limited to those with echocardiographic valvular abnormalities. Another opinion argues in favour of a drug-induced valvularabnormalites that, in some patients with Doppler regurgitations but without echocardiographic abnormalities, could be subtle enough not to be detected by echocardiography.

The moderate to severe valve regurgitation in heroin group could be explained by endocarditis which causes extensive valve destruction with failure of leaflet co-optation leading to moderate to severe regurgitation **(Moss et al., 2003)**[(28)]. While one patient had moderate tricuspid regurge in the control group, this could be explained by ischemic changes in the ECG with ejection fraction (30%).

There were significant differences between the vital signs of the patients abusing heroin in relation to drug severity index (drug abuse scale). The more the severity of heroin addiction, the more the occurrence of hypotension, bradycardia and elevated temperature. There was no significant difference between respiratory rate and the severity of drug abuse in the heroin group (P=0.400). Heroin addicts who had bradyapnea were not related to the severity of heroin addiction. However, the difference was not significant may be due to small sample size.

In contrast, **Tress et al., 1980** [(30)] revealed that there were no significant differences in vital signs in included subjects as regard to high and low dose heroin dependence.

Our results showed that the more the severity of heroin addiction, the more feverish patients were. This may be due to repeated non sterile intravenous drug injection which made addicts were moresusceptible to infectious complications such as infective endocarditis **(Joseph et al., 1973)**[(23)]**.**

The results of our study reported that vascular changes (thrombosed veins) are statistically significant

among high doses group, and this can be explained by repeated injection in the veins induced thrombosed veins, this made patients to search for another veins **(Joseph et al., 1973)**[23]or may be due to heroin induced vasculitis **(Kumar et al.,2015)**[25]**.**

Our study reported that ECG changes of heroin addicts are statistically significant among high doses group. This means that the more the severity of heroin addiction, the more the patients who had sinus bradycardia (As discussed before).

Regardingthe ECHO findings of the patients abusing heroin in relation to drug severity index (drug abuse scale), tricuspid and mitral mass (vegitations) with regurgitationwere significantly higherin the high doses heroin addicts,and this can be explained by damage to the rightand left sided valves which results from repeated injected particulate matter as well as injected bacterial loads, while subtle abnormalities of immune function may also have a role in pathogenesis for a long time **(Moss et al., 2003)**[28].

Regarding the pulmonary arterial systolic pressure (PASP) of the patients abusing heroin in relation to drug severity index (drug abuse scale). The more the severity of heroin addiction, the more the severity of PASP. The main mechanism is unknown also, **Ghuran et al., 2000**[31] revealed that pulmonary hypertension can also occur with cocaine and amphetamine misuse, although the underlying mechanism also remains unknown. This need for further investigation and evaluation in the future studies.

Conclusions:

We came to the conclusion that:

1-Heroin addiction inversely affects employment and marital status. All patients with different social and educational levels were affected with no significant differences. Heroin addiction is more common among urbans compared to rurals.

2- There was significant difference between tramadol and control group as regards blood pressure, tramadol induced hypertension and hypotension with hypertension predominance. There was significant difference between heroin and control group, heroin induced hypotension. Hypotension was significantly higher in heroin group than tramadol group.

3-There was significant difference between tramadol and control group as regards pulse, tramadol induced tachycardia and bradycardia with tachycardia predominance. There was significant difference between heroin and control group, heroin induced bradycardia. Bradycardia was significantly higher in heroin group than tramadol group.

4-heroin addicts induced elevated temperature but the difference was not significant in comparison with other two groups.

5-Heroin addiction induced bradyapnea and the difference was significant between the heroin and control groups.

6-Heroin addiction induced vascular changes (thrombosed veins and gangrene) with significant differences when compared with other two groups, while no vascular changes was observed in the tramadol and control groups.

7- There was significant difference between tramadol and control group as regards ECG changes, tramadol induced mostly sinus tachycardia, QTc interval prolongation and sinus bradycardia. There was significant difference between heroin and control group, heroin induced sinus bradycardia. Sinus Bradycardia was significantly higher in heroin group than tramadol group.

8- There was significant difference between heroin and control groups. Heroin addiction induced valve abnormalities (vegitations) which tricuspid and mitral valves were the most affected valves. Tricuspid valve was affected more than mitral valve.

9-Heroin addiction induced dilated right side of the heart in comparison with other two groups, but the differences were not significant.

10-Heroin addiction induced valve regurgitation including mitral and tricuspid regurge with no significant diffrences when compared to other two groups.

11-Heroin addiction induced elevated pulmonary arterial systolic pressure but with no significant differences when compared with both tramadol and control groups.

12-There was no significant difference regarding Ejection fraction between the three groups.

13-There were no significant differences between vital signs, ECG changes and ECHO findings and the severity of tramadol addiction.

14- There were significant differences between the severity of heroin addiction and vital signs. The more the severity of heroin addiction, the more the occurrence of hypotension, bradycardia and elevated temperature.

15-There was significant difference between ECG changes (sinus bradycardia) and the severity of heroin addiction.

16-There were significant differences between ECHO findings (valve abnormalities, valve regurgitation and PASP) and the severity of heroin addiction.

Recommendations

1. We recommend another study with muchlarger sample to confirm the results of this study.

2. Follow up the patients for several years to detect other cardiovascular problems of addicts which may appear after a long time.
3. Psychoeducation programmes for GP, primary care physicians and Family doctors should be established to allow early detection of Substance related disorders.
4. We recommend routine ECG and ECHO for addicts.
5. Integration between the addiction unit in the Neuropsychiatry Department and the Cardiology Department for management addicts with cardiovascular problems.
6. We need to make the same research on female addicts for tramadol and heroin.
7. We recommend arterial and venous duplex for heroin addicts to detect the vascular changes.

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Conflicts of interest
There are no conflicts of interest.

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