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RESEARCH

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The frequency and impact of tramadol addiction on acute aneurysmal subarachnoid hemorrhage: cross-sectional multicenter study

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Abstract

Background Arterial hypertension, cigarette smoking, excessive alcohol abuse and drug addiction such as cocaine all are known risk factors for aneurysmal subarachnoid hemorrhage (SAH). However, there is little information on whether tramadol addiction should also be considered as a risk factor for SAH. The purpose of this study was to investigate the prevalence and the impact of tramadol addiction on the symptomatology of intracranial aneurysmal SAH. We recruited 237 cases with acute aneurysmal ASH with a mean age of 52.3 ± 11.8 ranging from 17 to 86 years old.

Results There were 124 males and 113 females; 43 cases had a history of tramadol addiction (18.1%). Tramadol addicts were significantly younger, more likely to be male (97.7%), and more commonly associated with seizure onset compared with non-addicts. Multiple aneurysms, wide neck, and sizable aneurysms were significantly more common in tramadol than non-tramadol addicts as were dissecting aneurysms. There is a high association of acute aneurysmal SAH with tramadol addiction, especially in young patients.

Conclusions Tramadol addiction might be regarded as modifiable risk factor of aneurysmal ASH and tramadol addicts had a worse presentation than non-tramadol addicts. If this finding is proved, it will be of great importance in managing patients with ruptured and un-ruptured intracranial aneurysms. Tramadol is available over-counter in some countries, more studies are needed.

Keywords Acute aneurysmal subarachnoid hemorrhage, Tramadol addiction, Hess and Hunt staging, Risk factor, Drug addiction

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Background

Aneurysmal subarachnoid hemorrhage (SAH) is associated with high mortality, morbidity, and permanent disability [1, 2] and is one of the main targets of neurocritical care service [3–5]. Aneurysmal SAH had a higher incidence rate than non-aneurysmal SAH (2.08/100,000 versus 0.9/100,000 person-years). In-hospital mortality was 18.2% with no significant difference between aneurysmal SAH and non-aneurysmal SAH subgroups [6].

Approximately half of all survivors cannot back to their previous work, and up to a 25% rely on others for care [7]. Rumalla and colleagues (2023) found that; lack of caregiver support was the only socioeconomic factor associated with an unfavorable outcome at discharge [8]. Possible factors which can cause aneurysm rupture are only partly known.

Some intrinsic and extrinsic factors have been so far identified, including the location, size, surface, and hemodynamic characteristics of the aneurysm [9–16]. Moreover, common cardiovascular risk factors, such as cigarette smoking, alcohol abuse, and arterial hypertension have been found to foster the gradual increase of aneurysm size, finally leading to rupture [17]. Addiction to sympathomimetic drugs such as cocaine and amphetamines has also a direct effect on the outcome of aneurysmal SAH. Remarkably, Howington and colleagues have found that 33% of SAH patients were recent cocaine users [18].

Unfortunately, tramadol abuse has increased in Egypt over the last few years [19]. It is the most popular drug abused among the young and the middle-aged, because it is easily accessible through the black market and can be provided at low cost [19, 20]. In Egypt, and regardless to the order of abuse, cannabis and tramadol are on the top list of the drug/substances used according to statistics of Fund for Drug Control and Treatment of Addiction (FDCTA). Half of the 129,850 people who entered drug rehabilitation in 2007 were addicted to cannabis, while 43% were dependent on opiates of various types. The majority of them are between 15 and 25 years of age. Rising rates of unemployment are said to contribute to the high addiction rates [21–23]. The rates of sub-stance use are increasing markedly with time in Egypt. The group of young adults was the most represented age group among substance users [24]. Mawaheb and colleagues [25] performed a survey of substance abuse on school and young university male students in Fayoum Governorate showed that cannabis was the commonest substance of abuse (40%), tramadol (37%), benzodiazepines (23%), and parkinol (9%). Rabie and colleagues found the percentage for tramadol addiction 1.5% among young adults [26]. We suspected that there were a disproportionate number of tramadol users among patients with aneurysmal SAH in Egypt.

This study aimed to investigate the prevalence of tramadol addiction among patients with acute aneurysmal SAH, and to investigate the impact of tramadol addiction on symptomatology of aneurysmal SAH.

Methods

This is a cross-sectional multicenter study (Ain Shams, Cairo, Assiut, and Aswan Universities) was performed for 237 patients with acute aneurysmal SAH during the period from February 2021 to December 2022. As the Egyptian population is distributed all over the country; we selected 4 University hospitals 2 from North (Ain Shams and Cairo), one from Middle (Assiut) and one from South of Egypt (Aswan). A very severe headache of sudden onset combined with meningism was the clinical hallmark of recruited cases of acute aneurysmal SAH. The diagnostic method of choice for demonstrating the presence of blood in the subarachnoid space was computed tomography (CT) of the head in all cases. All subjects gave written informed consent before participation. Inclusion Criteria; Patients ≥ 17 of age, acute aneurysmal SAH within 48 h, with spontaneous ruptured saccular intracranial aneurysm and history of tramadol addiction if present for at least 12 months before admission according to DSM-5 criteria [27]. Exclusion Criteria: patients with fusiform or mycotic aneurysm, tumoral, or AVM-related aneurysm were excluded. Patients receiving anticoagulants, or with a history of blood disease and patients who had serious or life-threatening comorbidity (metabolic dysfunction, psychiatric illness) were also excluded.

Following clinical examination, each patient's history was taken including risk factors (smoking, hypertension, Diabetes Mellitus, drug abuse), Hunt and Hess Score [28], and digital subtraction angiography (Siemens Artis uniplane angiography machine, Siemens Health care GmbH, USA) was performed to determine the type of aneurysm. The aneurysm was described in terms of neck size in mm, neck to dome ratio (aneurysms with wide necks, defined by neck diameters greater than 4 mm or dome-to-neck ratios less than 2 [28], multiplicity, dissection, and site of the aneurysm using 4 vessel angiographies. Size of the aneurysm was measured and considered small-sized if < 7 mm, moderate-sized $> 7 < 20$ mm) and giant-sized > 20 mm [29].

Patients were classified as tramadol and non-tramadol addicts. A patient was considered a tramadol addict if there was a prior history of drug intake for at least 1 year before the episode and/or inability to function normally without the drug for at least 12 months before admission according to DSM-5 criteria [27].

Statistical analysis

Descriptive statistics, crosstabs, and frequency tables were used to describe some of the basic variables. A Mann–Whitney non-parametric test was performed to compare continuous variables, which are expressed as mean ± SD data from the two groups of patients. Categorical variables were compared by Fisher's exact two-tailed test or by Chi-Square test.

Discriminant analysis was used to determine significant discriminating variables between the groups. A multivariate logistic regression analysis was used to estimate the risk (odds ratios) of tramadol dependency, age group, sex, diabetes mellitus (DM), hypertension, and smoking for the presence of single or multiple aneurysms. All statistical analyses were performed using the statistical package for social sciences SPSS 25 (IBM Inc.) and results were considered significant with a p value < 0.05.

Results

We recruited 237 cases of acute aneurysmal SAH. There were no significant differences between the percent of tramadol addict versus non-tramadol addict between the center of recruitment (Tramadol versus non-tramadol addict 30:170, 5:30, 8:37 for North, Middle and South of Egypt, respectively). The mean age was 52.3 ± 11.8 ranging from 17 to 86 years. There were 124 males and 113 females, and 43 cases had a history of tramadol addiction (18.1%). Tramadol addicts were significantly younger than non-tramadol addicts with a mean difference of 12.2, as shown in Fig. 1, and statistically significant difference ($P=0.0001$). In the tramadol addict group, male patients were predominant (97.7%) with a statistically significant difference ($P=0.0001$) (Table 1). The highest prevalence of acute aneurysmal SAH in tramadol addicts was in the age groups 30–39, followed by 40–49 years, while the highest incidence in non-tramadol addicts occurred at 50–59 followed by 60–69 years (0.0001) (Fig. 1).

Clinical presentation in tramadol addicts

Coma and confusion were significantly higher in tramadol addicts than non-tramadol addict group (58.1%, 25.8%, respectively). Multiple cranial nerve affection was seen more frequently in the tramadol-addict group as compared to the non-tramadol addict group (27.9%, 11.9%, respectively). Onset seizures occurred the near time of initial aneurysm rupture in 30% of cases in the tramadol addict group, while the non-addict group exhibited seizures in only 3.6% of cases. According to Hess and Hunt classification, tramadol-addicts tend to present with poorer grades (VI–V) than non-addicts (46.5%, 26.3%, respectively) with a statistically significant difference ($P=0.008$). As regards risk factors associated with aneurysmal SAH, there was a significantly higher percentage of smokers in the tramadol group, while diabetes mellitus and hypertension were significantly higher in the non-tramadol addict group. Tramadol addicts had slightly higher use of salicylates than non-addicts (Table 1).

The extent and co-existence of other drug abuse in either group were plotted in Tables 2 and 3. Tramadol addiction started at 39 years (mean age) with the mean duration of addition was 5 years. Most cases in tramadol addiction group have severe symptoms according to

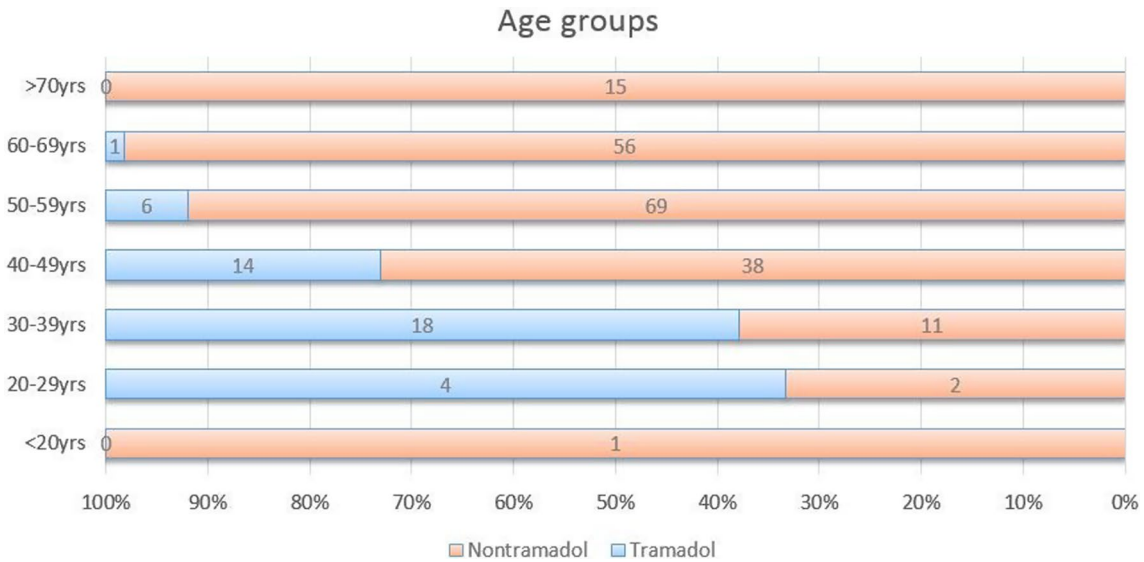

Fig. 1 Age group analysis of our study. Subarachnoid hemorrhage was found to be eminent third and fourth decades than non addicts

Table 1 Demographic data, clinical presentation and risk factors among the studied groups

	Total number of patients (*n* = 237)	Tramadol addict (*n* = 43)	Non-tramadol addict (*n* = 194)	p value
Age (years) mean ± SD years	52.3 ± 11.8	40.1 ± 9.7	55.1 ± 10.4	< 0.0001*
Range	17–86	23–62	17–86	
Sex number (%)				
Male	124 (52.3%)	42 (97.7%)	82 (42.3%)	< 0.0001*
Female	113 (47.7%)	1 (2.3%)	112 (57.7%)	
Clinical presentation number (%)				
Headache, neck pain, neck stiffness	233 (98.3%)	43 (100%)	190 (97.9%)	0.33
Confusion, coma	75 (31.6%)	25 (58.1%)***	50 (25.8%)	< 0.0001*
Multiple cranial nerve palsy	35 (14.8%)	12 (27.9%)*	23 (11.9%)	0.0076*
Seizure onset	20 (8.4%)	13 (30.2%) ***	7 (3.6%)	< 0.0001*
Hess and Hunt staging				
I–III	166 (70.0%)	23 (53.5%)	143 (73.7%)	0.008*
VI–V	71 (30.0%)	20 (46.5%)	51 (26.3%)	
Hypertension	145 (61.2%)	7 (16.3%)	138 (71.1%)	< 0.0001*
Normotensive	92 (38.8%)	36 (83.7%)	56 (28.9%)	
Diabetes mellitus				
Diabetic	100 (42.2%)	3 (7%)	97 (50%)	< 0.0001*
Non-diabetic	137 (57.8%)	40 (93%)	97 (50%)	
Smoking number (%)				
Smokers	110 (46.4%)	40 (93.0)	70 (36.1%)	
Non-smokers	127 (53.6%)	3 (7.0%)	124 (63.9%)	< 0.0001*
Use of acetylsalicylic acid number (%)				
Yes	18 (7.6%)	8 (18.6%)	10 (5.15%)	
No	219 (92.4%)	35 (81.4%)	184 (94.85%)	0.03*

* Significant *p* value

Table 2 Extent of addiction in tramadol addict group

Age at onset	
Mean ± SD	39.7 ± 5.36
Range	20–60
Duration of use (years)	
Mean ± SD	8.85 ± 4.7
Range	(3–9)
Average daily use (mg)	
Mean ± SD	1020.64 ± 525
Range	(50–2700)
DSM-5 severity	
Severe (≥ 6 symptoms)	29 (67.44)
Moderate (4–5 symptoms)	13 (30.23)
Mild (2–3 symptoms)	1 (2.3)

DSM-5 diagnostic and statistical manual of mental disorders

DSM-5 criteria (Table 2). Cannabis and alcohol usage were the most common co-existence drug abuse and mostly related to tramadol addiction with a statistically significant difference (< 0.05), Table 3.

Table 4 shows the morphological characters of aneurysms among the studied groups. Multiplicity, wide neck, and sizable aneurysms were significantly more common in tramadol addicts than non-addicts as were dissecting aneurysms with a statistically significant difference as shown in Table 4.

The variable of aneurysm's site was homogenously distributed in both groups across all locations (*p* value > 0.05) except for posterior communicating artery aneurysms which showed a statistically significant difference (0.006), where 57% of them were allocated in the tramadol-addicts group (Table 5).

Multivariate logistic regression analysis showed that only tramadol addiction was considered as a significant risk factor for the presence of multiple aneurysms, as shown in Table 6. The odds ratio (OR) of tramadol addiction for multiple aneurysms was 21.167 (95% CI, 4.35 to 4.13).

Table 3 Other drug addiction

	Total number of patients (*n* = 237)	Tramadol addict (*n* = 43)	Non-tramadol addict (*n* = 194)	*p* value
Alcohol	11 (4.64%)	6 (13.95%)	5 (2.57%)	0.0014*
Cannabis	14 (5.88%)	12 (27.9%)	2 (1.03%)	< 0.0001*
Cocaine	1 (0.42%)	1 (2.325%)	0 (0%)	–
Ecstasy	1 (0.42%)	1 (2.325%)	0 (0%)	–
Amphetamine	2 (0.843%)	2 (4.65%)	0 (0%)	–
Benzodiazepines	3 (1.26%)	3 (6.975%)	0 (0%)	–
Heroin	1 (0.42%)	0 (0%)	1 (0.515%)	–

* Significant *p* value

Table 4 Morphological characters of aneurysms among the studied groups

	Total number of patients (*n* = 237)	Tramadol addict (*n* = 43)	Non-tramadol addict (*n* = 194)	*p* value
Multiplicity of aneurysm				
Single	214 (90.3%)	28 (65.1%)	186 (95.9%)	0.0001*
Multiple	23 (9.7%)	15 (34.9%)	8 (4.1%)	
Neck of aneurysm				
Narrow neck	142 (59.9%)	5 (11.6%)	137 (70.6%)	0.0001*
Wide neck	95 (40.1%)	38 (88.4%)	57 (29.4%)	
Dissecting aneurysm				
No	220 (92.8%)	32 (74.4%)	188 (96.9%)	0.0001*
Yes	17 (7.2%)	11 (25.6%)	6 (3.1%)	
Size of aneurysm				
Small-sized (< 7 mm) 172 (72.6%)	172 (72.6%)	24 (55.8%)	148 (76.3%)	
Moderate-sized (> 7 < 20 mm) 61 (25.7%)	61 (25.7%)	18 (41.9%)	43 (22.2%)	0.02*
Giant-sized (> 20 mm) 4 (1.7%)	4 (1.7%)	1 (2.3%)	3 (1.5%)	

* Significant *p* value

Table 5 Multivariate logistic regression analysis for aneurysmal multiplicity

Variables	*B*	SE	WALD	*df*	Sig	OR	95% CI for OR	
							Lower	Upper
Tramadol addiction	3.052	0.807	14.31	1	0.000*	21.167	4.353	102.933
Age group	0.126	0.360	0.123	1	0.726	1.134	0.561	2.296
Sex (male)	1.198	0.872	1.89	1	0.169	3.314	0.600	18.296
Diabetes mellitus	− 0.245	0.685	0.128	1	0.720	0.783	0.205	2.995
Hypertension	0.051	0.885	0.003	1	0.954	1.052	0.186	5.961
Smoking	− 0.754	0.820	0.847	1	0.357	0.470	0.094	2.345

Adjusted for tramadol addiction (yes = 1 or no = 0), age group (1 = ≤ 20; 2 = ≤ 30; 3 = ≤ 30; 5 = ≤ 60; 6 = ≤ 70 years), Sex (female = 0 or male = 1), Diabetes mellitus (yes = 1 or no = 0), Hypertension (yes = 1 or no = 0), Smoking (yes = 1 or no = 0), *B* correlation coefficient, *CI* confidence interval, *OR* odds ratio, *SE* standard error, *Wald* Wald statistics for logistic regression analysis; *Significant *p* value

Discussion

Substance abuse is a rising public health concern in Egypt [26, 30–32]. Tramadol is one of the most common abused substances in Egypt. It is readily available, relatively cheap, causes euphoric sensation, and allegedly improves sexual performance. The working class seems to be particularly severed by the uprising tramadol epidemic which could end up in an economic and public health crisis [33].

Table 6 Frequency of aneurysm location among studied groups

Site of aneurysm	Total number of patients (*n* = 237)	Tramadol addict (*n* = 43)	Non-tramadol addict (*n* = 194)	*p* value
Anterior communicating artery	87 (36.7%)	13 (30.2%)	74 (38.1%)	0.330
Middle cerebral artery	38 (16%)	8 (18.6%)	30 (15.4%)	0.611
Posterior communicating artery	32 (13.5%)	5 (11.6%)	27 (13.9%)	0.313
Supraclinoid artery	27 (11.4%)	3 (6.9%)	24 (12.4%)	0.961
Ophthalmic artery	3 (1.3%)	0 (0%)	3 (1.5%)	0.411
Internal carotid artery	12 (5.6%)	3 (6.9%)	9 (4.6%)	0.527
Anterior cerebral artery	10 (4.2%)	2 (4.6%)	8 (4.1%)	0.876
Posterior cerebral artery	7 (2.95%)	4 (9.3%)	3 (1.5%)	0.006*
Basilar artery	13 (5.5%)	2 (4.6%)	11 (5.7%)	0.790
Posterior inferior cerebellar artery	4 (1.7%)	0 (0%)	4 (2.1%)	0.342
Vertebral artery	4 (1.7%)	2 (4.6%)	2 (1%)	0.095

* Significant p value

To the best of our knowledge, no previous publication has discussed the effects of tramadol on aneurysmal SAH. The main findings of the present study first 18.1% of patients with acute aneurysmal SAH were recorded as tramadol addicts and tramadol addicts were significantly younger than patients without a history of tramadol addiction and predominantly male (97.7%). Second, tramadol addicts had a worse clinical presentation of SAH than non-tramadol addicts as coma and confusion, multiple cranial nerve affection, seizure onset and poorer grades of Hess and Hunt classification were significantly higher in tramadol addicts than non-addicts. Thirdly: Tramadol addicts are more commonly associated with multiple aneurysms, wide neck, and sizable aneurysms than non-tramadol addicts.

In the present study we try to estimate the prevalence of tramadol addiction in patients with acute SAH, the impact of tramadol on symptomatology of SAH and explain why tramadol may be considered as a risk factor for SAH. and possible mechanism of tramadol in developing aneurysms and their rupture.

Our data suggest that tramadol abuse correlates with chance of early aneurysmal rupture, perhaps by weakening the wall of the aneurysm and should be taken into account during the management of patients with intracranial aneurysms. Medetov and colleagues (2022) found that the youngest age group had higher percentage of rupture intracerebral aneurysm and explained such observation as it might be due to the slower blood flow rate, and calcification of arterial walls among older one [34].

In the current study tramadol addict patients had a worse clinical presentation of SAH and poorer grades of Hess and Hunt classification than non-tramadol addicts. As tramadol abuse can result in stroke either by causing direct damage to cerebral vessels or indirectly, by affecting other organs, such as the heart or the liver (affecting blood coagulation pathways), thus negatively affecting cerebral circulation [35, 36]. Tramadol has a sympathomimetic effect, and other sympathomimetic such as cocaine increase the incidence of SAH and worsen its prognosis [18]. Studies on cocaine showed that it decreases both nitric oxide (NO) production, endothelial No-synthase (eNOS) expression, and endothelial adhesion of monocytes [37]. It also was found that cerebral vessels, predominantly those of small caliber, are infiltrated in a transmural and perivascular fashion by inflammatory cells and promote neutrophils and other monocytes to cross the blood–brain barrier causing cerebral vasculitis and SAH [38]. Further studies are required to probe if tramadol has a similar sympathomimetic effect as potent as cocaine.

Interestingly, a case report published recently of a female patient 32 years came to the hospital with deep coma after massive tramadol ingestion with prolonged high plasma concentrations, a serial imaging showing progressive extension of ischemic edema the author hypothesized a cerebral vasospasm as mechanism of severe brain injury [39]. Cattaneo and colleagues (2023) found that patients with a higher Hunt and Hess score, a lower initial Glasgow Coma Scale score and received a higher median norepinephrine dose developed had more frequent vasospasms [40]. In the present study tramadol addict patients had higher Hunt and Hess scores than non-tramadol addicts with a higher risk for developing vasospasm. Interestingly, most tramadol addict patients (81.4%) were also smokers (nicotine dependence) and few studies have shown that nicotine and opioids modulate each other's [41]. Since smoking is one of the important risk factors for aneurysm rupture, tramadol may

enhance its effect and facilitate rupture. Cigarette smoking has been shown to increase the risk for aneurysmal SAH in several case–control and cohort studies [42–45]. However, the involved mechanisms by which smoking increases this risk remain elusive. Cigarette smoking can also be a crucial risk factor for subsequent rupture of an un-ruptured aneurysm [42–45]. Therefore, long-term smoking can induce the formation of an aneurysm as well as lead to an increase in its size by weakening the vessel walls of the cerebral arteries.

Another cause for the worse clinical presentation of SAH in tramadol addict patients is the high incidence of seizure onset (8.6%) as seizures can be a major neurological complication of tramadol addiction [46], Moreover, 13 (30.2%) tramadol addicts in our study had seizures which were significantly higher than non-addicts (3.6%). We suggest that epileptic threshold in young adults with a suspected history of tramadol abuse is much lowered than non-addicts with aneurysmal SAH [47–49].

Supporting this result Khedr and colleagues found hyperexcitability of the motor cortex coupled with inhibitory deficits in tramadol dependent patients [46]. Lagard and colleagues (2022) strongly suggested a tramadol-induced allosteric change of the benzodiazepine-binding site of GABAA receptors. Epilepsy is based on abnormal neuronal activities that have been suggested to arise from an excess of excitation (glutamatergic drive) and a defect of inhibition (GABAergic activity) [50] and management of tramadol-poisoned patients should take into account that tramadol-induced seizures are mainly related to a GABAergic pathway [51].

SAH on its own is a devastating presentation of intracerebral aneurysms but with tramadol addiction, the added risk of a younger age of presentation; the multiplicity of the aneurysm, as well as dissection worsens the clinical presentation. Zhang and colleagues found an association between the young age and morphological features that lead to rupture, like the presence of daughter and irregular domes, larger flow angle [52]. Liberato found that four aneurysm factors: size ≥ 5 mm, narrow neck, irregular shape, and anterior cerebral/anterior communicating artery location, associated with rupture status [53].

There were several limitations in this study. First, small sample size may not reflect the required subjects to build up a statistically sound conclusion. Second, screening for tramadol addiction lacks either severity classification or even classification into sole drug abuse or part of multiple substances abuse. Third, screening of tramadol abuse is lacking laboratory confirmation of it (serum level of tramadol) or combination of other substance. Finally, functional outcome at discharge was too difficult to be estimated either due to missing data provided or transfer of patients to be more specialized endo/cerebrovascular centers outside the governorates. Further studies should be encouraged to elaborate a cohort study on the impact of tramadol usage and incidence of subarachnoid hemorrhage with strictly designed protocols preliminarily.

Conclusions

There is a high association of acute aneurysmal SAH with tramadol addiction, especially in young patients. Tramadol addiction might be regarded as modifiable risk factor if this finding is proved; it will be of great importance in managing patients with ruptured and unruptured intracranial aneurysms. Further studies on tramadol addiction should, therefore, be performed, since tramadol is available to the public in several countries, some as an over-the-counter drug.

Abbreviations

SAH	Subarachnoid hemorrhage
CSF	Cerebrospinal fluid
FDCTA	Fund for Drug Control and Treatment of Addiction
NO	Nitric oxide
eNOS	Endothelial NO-synthase
DCI	Delayed cerebral infarction
GABAA	γ-Aminobutyric acid type A
DM	Diabetes mellitus

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Author contributions

AE, EMK, AH, OR HA contributed to study concept and design, acquisition of data, draft and revision of the report, statistical analyses, and interpretation of data. RKS, AS, AA contributed to case recruitments, acquisition of data and statistical analyses. 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 available from corresponded on request.

Declarations

Ethics approval and consent to participate.

The study received ethical approval from the Aswan Universities faculty of medicine's institutional review boards with NB (Aswn\580/1/21) on January 2021. All participants gave their written informed consent to participate in the study. All participants' personal details were be kept confidential, and all patients' personal data were anonymized immediately after data collection. We confirmed that all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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