Gastrointestinal, hepatic and biliary sequelae of frequent ketamine use: a prospective observational study

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Final Research Report

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Background

Recreational use[1] of inhalational ketamine is emerging as a major global social and health issue [1, 2]. While ketamine, a N-methyl D-aspartate receptor antagonist, has medical uses in anesthesia and chronic pain control, its highly addictive nature has led to a massive increase in recreational consumption worldwide. Due to the ease of production and low cost, the non-medical use of ketamine is especially increasing in East and South East Asia, with its lifetime prevalence in the general population ranging from 0.3% to 2.0% [United Nations 3], comprising up to 39.7% of total recreational drug users in these regions [4]. The self-reported use of recreational ketamine in Western countries, including the United Kingdom, Australia and Canada, is also increasing [5, 6]. From 2008 to 2014, law enforcement seizures of ketamine worldwide has increased by more than threefold [3].

Long-term heavy use of ketamine is associated with different medical problems, including cognitive impairment and psychological issues [7]. Inhalation of ketamine could result in hallucinations, out-of-the-body experiences and psychological dissociation. One of the well-known side effects of ketamine is bladder dysfunction, which is seen in one-quarter of chronic ketamine users [8]. Damage to the urological system is also well-documented, with many ketamine users developing a large variety of urinary problems, ranging from lower urinary tract symptoms and bladder incontinence to hydronephrosis, renal impairment and papillary necrosis [8, 9]. Urinary tract damage seemed reversible in a proportion of patients who ceased ketamine use [10].

Ketamine has also been known to be associated with gastrointestinal symptoms. Colicky epigastric / abdominal discomfort in ketamine users, known as “K-cramps”, has been reported in 33.3% of frequent ketamine users [11], and is the second-most common symptom of presentation (21%) among ketamine users in the emergency department [12], more common than symptoms related to bladder dysfunction [12]. Nonetheless, the underlying etiology resulting in this abdominal discomfort remains poorly defined. A possible etiology is intestinal motility disorders, since ketamine interferes with gastric

[1] Recreational use refers to non-prescribed use irrespective on the frequency of use

motility [13]. Ketamine-related liver dysfunction is seen in 16% of ketamine users [12], and is associated with mitochondrial liver injury and liver fibrosis [14, 15]. Another associated condition is ketamine-related cholangiopathy, which has been described in both Asia [16] and Europe [17]. This is postulated to be related to the increase of flow resistance across the sphincter of Oddi [18], with biliary anomalies ranging from common bile duct dilatation [19] to intra-hepatic beading and strictures [16]. The anatomical description of biliary anomalies had been limited to small case series; a detailed depiction of different cholangiopathic patterns and their correlation with clinical characteristics, as well as any potential reversibility of biliary anomalies after ketamine cessation, remains lacking.

Studies aimed at recruiting recreational drug users are hampered by high default rates [20], rendering the arrangement of investigations and longitudinal follow-up difficult. As ketamine continues to be a drug of widespread recreational use, it is imperative to further understand its effects on the biliary system, the patterns of clinical and radiological presentation, and possible clinical sequelae. To address this important issue, we have established a territory-wide community network of non-government charitable service organizations actively tackling substance abuse in Hong Kong to enroll recreational ketamine users in their assessment of gastrointestinal conditions.

Aim

Primary

To determine the underlying etiology of abdominal discomfort among frequent ketamine users

Secondary

- To describe the prevalence of different gastrointestinal, liver and biliary pathologies among frequent ketamine users.
- To describe the long-term clinical outcomes of different gastrointestinal, liver and

biliary pathologies in frequent ketamine users.

Methods

Subjects

We planned to recruit subjects from ketamine users with the aid of different non-profit charitable service organizations that were providing medical and social support to recreational drug users in Hong Kong. Participating charitable organizations included Barnabas Charitable Service Association Limited, CROSS Centre Tung Wah Group of Hospitals, Lutheran Social Service Centre, Hong Kong Christian Service PS33 Centre and Hong Kong Children and Youth Services. We also invited substance abuse clinics in Kwai Chung Hospital and Pamela Youde Nethersole Eastern Hospital to refer eligible participants.

Following standard criteria [21, 22], ketamine users can be divided into two groups:

Primarily ketamine group - defined as use of ketamine with frequency at least twice per month over 6 months within the last 2 years with no other illicit psychotropic drug use up to once per month over 6 months within the last 2 years.

Ketamine poly-drug group - defined as use of ketamine and, together with other illicit psychotropic drugs, e.g. ecstasy and/or methamphetamine, with frequency at least twice per month over 6 months within the last 2 years.

Inclusion criteria

- Use of ketamine or ketamine mixed with other psychotropic drugs with frequency of at least twice per month over 6 months within the last 2 years.
- Recurrent abdominal discomfort over the past 3 months or more.
- Han Chinese ethnicity.

- 18-60 years of age.

Exclusion criteria

- Mental retardation or unable to give informed consent.
- Co-existing biliary disorders including recurrent pyogenic cholangitis, primary sclerosing cholangitis, IgG4 sclerosing cholangiopathy and HIV cholangiopathy.
- Other significant medical co-morbidities.

A screening log will be kept on the total number of ketamine users referred to our center and the number of participants who were enrolled into the study.

Assessment and subsequent evaluation

Informed consent was obtained from all participants. Baseline sociodemographic information was obtained. A standardized method was used to assess and quantify the degree of ketamine use, as well as the recreational use of other psychotropic drugs, which included cannabis, methylenedioxymethamphetamine (MDMA or commonly known as “ecstasy”), methamphetamine, heroin, cocaine, sedatives including midazolam, triazolam and zopiclone, cough mixtures and others) and alcohol intake. Recreational drug use was further supplemented by urine toxicology testing (Multidrug One Step Screen Test Panel, Abon Pharma, Hangzhou, China). Any subsequent abstinence to ketamine and other recreational drugs was recorded, with abstinence verified via the participant’s respective charitable service organization or substance abuse clinic. Subjects were then assessed for the upper gastrointestinal symptoms (including abdominal discomfort, bloating, reflux, nausea, easy satiety) following standard criteria using the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) score [23]. The Chinese

version of the standard questionnaire is depicted in Figure 1. The presence of urinary tract symptoms or requirement for regular Urology follow-up was also documented.

All recruited participants underwent clinical assessment and blood tests which included complete blood counts, liver and renal biochemistry. Patients with an elevated alkaline phosphatase (ALP) (upper limit 110 U/L for men, 93 U/L for women), or at the discretion of the clinician a biliary cause might possibly explain the patient's abdominal symptoms were referred for a magnetic resonance (MR) cholangiography of the biliary tract, using a 1.5 Tesla Philips Achieva MR imaging scanner (Philips Healthcare, Amsterdam, Netherlands). The MR imaging protocol consisted of coronal and axial T2-weighted sequences, T1-weighted in and opposed phase, 2-dimensional MR cholangiography sequences and 3-dimensional MR cholangiography sequences with maximum intensity projection reconstruction. MRC was not performed in patients with standard contraindications for MR imaging (including pacemaker or metal implant insertion).

Figure 1. Chinese version of the standardized questionnaire provided to patient in the assessment of upper gastrointestinal symptoms [23].

病人上消化道症狀嚴重程度評估量表（PAGI-SYM）

本問卷旨在瞭解你的腸胃道疾病相關症狀的嚴重程度。題目的答案沒有對錯之分。請儘量準確地回答每一個題目。

對於每一個症狀，請在最能準確描述你在過去六月內出現症狀嚴重程度的相應數字上劃圈。如果你並沒有體驗到任何症狀，請在0上劃圈。如果症狀非常輕微，請在1上劃圈。如果症狀為輕度，請在2上劃圈。如果症狀為中度，請在3上劃圈。如果症狀為重度，請在4上劃圈。如果症狀非常嚴重，請在5上劃圈。請務必回答每一個題目。

請評估在過去六月內出現的以下症狀的嚴重程度。

		無症狀	非常輕微	輕度	中度	重度	非常嚴重
1.	白天出現胃灼熱（出現於胸部或咽喉部的灼熱感疼痛）	0	1	2	3	4	5
2.	白天出現胃反流或逆流（胃內的流體或液體倒流到咽喉部）	0	1	2	3	4	5
3.	噁心（胃部不舒服，好似即將要嘔吐）	0	1	2	3	4	5
4.	上腹部（肚臍以上）疼痛	0	1	2	3	4	5
5.	胃脹	0	1	2	3	4	5
6.	食欲減退	0	1	2	3	4	5
7.	上腹部（肚臍以上）不舒服	0	1	2	3	4	5
8.	腹脹（好似你需要鬆開衣服）	0	1	2	3	4	5
9.	在躺下時出現胃灼熱（出現於胸部或咽喉部的灼熱感疼痛）	0	1	2	3	4	5
10.	在躺下時出現胃反流或逆流（胃內的流體或液體倒流到咽喉部）	0	1	2	3	4	5
11.	下腹部（肚臍以下）疼痛	0	1	2	3	4	5
12.	白天感覺到胸部不舒服	0	1	2	3	4	5
13.	嘴巴內出現苦，酸或發酵的味道	0	1	2	3	4	5
14.	下腹部（肚臍以下）不舒服	0	1	2	3	4	5
15.	夜晚（睡覺時）感覺到胸部不舒服	0	1	2	3	4	5
16.	幹嘔 （感到噁心想吐，但是吐不出來）	0	1	2	3	4	5
17.	胃部或腹部明顯變大	0	1	2	3	4	5
18.	嘔吐	0	1	2	3	4	5
19.	不能吃完正常的飯量	0	1	2	3	4	5
20.	飯後感覺極度的飽	0	1	2	3	4	5

To consolidate efforts in the understanding of ketamine-related cholangiography, we combined our cohort of patients with MR cholangiography performed with a previous cohort supported by the Beat Drugs Fund (principal investigator: Dr. Siu-king Mak, BDF reference number: 150034). The MR cholangiography images were then analysed independently by two gastrointestinal radiologists with at least 8 years of experience in abdominal MR imaging. Both radiologists were blinded to the clinical and biochemical data of all study participants. MR cholangiographic findings were categorized anatomically, as the extrahepatic ductal system (common and hepatic bile ducts), the biliary confluence, the left and right intrahepatic ducts, the pancreatic duct, and the gallbladder. The presence of dilatation, strictures, beading and other cholangiographic abnormalities were reported. Extrahepatic ductal diameter was measured at midpoint, with dilatation defined as >7 mm in diameter [24]. Intrahepatic ductal dilatation was gauged using their corresponding extrahepatic ducts as reference. Any discordance in reporting was resolved by consensus reading prior to reaching a final decision.

At the discretion of the attending physician, additional investigations were performed to delineate the cause of abdominal discomfort, including urea breath testing for Helicobacter pylori infection, upper gastrointestinal endoscopy, and ultrasonography of the abdomen. Additional informed consent was obtained for upper gastrointestinal endoscopy and other standard-of-care invasive procedures. Any prior and subsequent hospital admission or visits to the emergency department for gastrointestinal and urinary symptoms were recorded.

Statistical analyses

Continuous variables were expressed as mean (standard deviation (SD)) or median (interquartile range (IQR)) as appropriate. The weighted kappa statistic was used to calculate inter-observer agreement [25]. Statistical comparisons were carried out using Student's t-test or Mann-Whitney U test for continuous variables and chi-squared test or Fisher's exact test for categorical variables. Variables with $p<0.10$ in univariate analysis were entered into a multivariate model which was performed using binary logistic regression. The predictions of biliary tract anomalies on MR cholangiography were examined by the construction of corresponding receiver operating characteristic (ROC) curves, followed by an assessment of accuracy via areas under the curves (AUCs). The Youden Index, defined as sensitivity plus specificity minus one, was used to define the optimal cut-off level for prediction. All data was analysed using SPSS 22.0 software (SPSS Inc, Chicago, IL). A two-tailed p-value <0.05 was considered as statistically significant.

Results

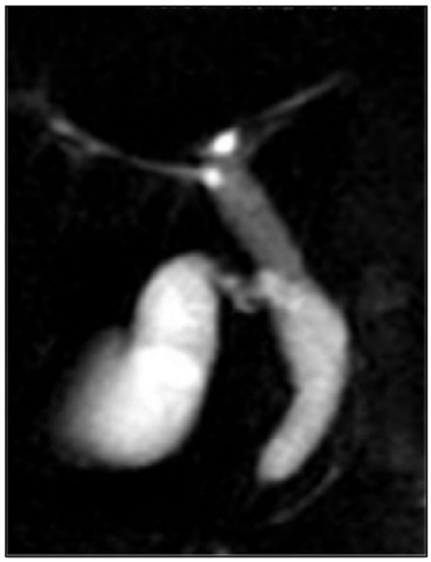
Our recruited cohort of 127 participants (mean age 29.6±5.4 years, 46.5% male), had been using ketamine for a mean duration of 10.6 (±3.9) years. Forty-three participants (33.9%) were using concomitant recreational drugs, of which 12 (27.9%) had use of 2 or more concomitant drugs. Such recreational drugs included cocaine (65.1%), metamphtamine (37.2%), MDMA (16.3%) and cannabis (11.6%)

All had active or prior abdominal discomfort after commencement of ketamine use. Ninety-two (72.4%) and 31 (30.7%) had prior emergency attendance for abdominal discomfort and prior inpatient admission for abdominal discomfort respectively. The mean PAGI-SYM score was 70.8 (±17.3) (Full score: 100). Five patients were found to have Helicobacter pylori infection which can explain the patient's abdominal discomfort. For the remaining 122 patients, ketamine use is likely a contributing factor to patients' symptoms.

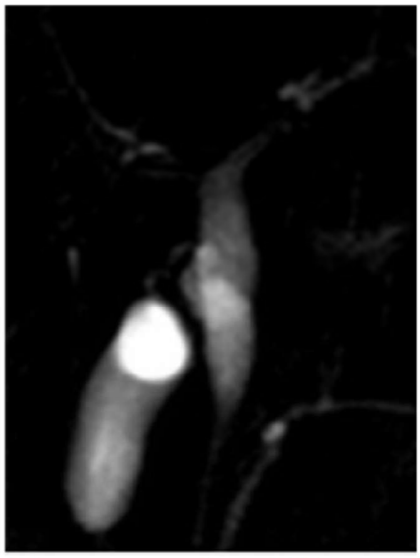
Fifty-two (40.9%) had magnetic resonance cholangiogram performed, of which 38

patients (73.7%) were found to have biliary anomalies on magnetic resonance cholangiogram. 26 patients (68.4%) had anomalies of the common bile duct, which included diffuse extrahepatic duct dilatation or fusiform extrahepatic dilatation with distal tapering (Figure 2). 20 patients (52.6%) had intrahepatic duct changes, which included ductal dilatation, ductal beading and strictures (Figure 2).

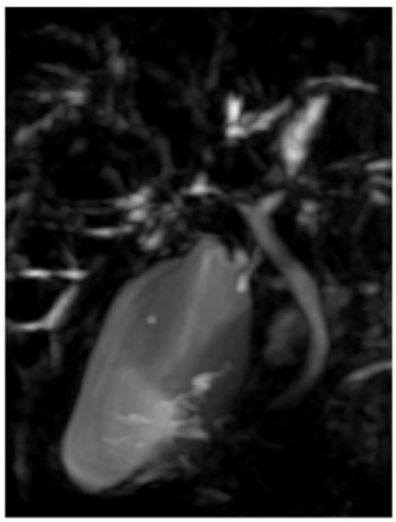
Figure 2. Examples of biliary tract anomalies on magnetic resonance cholangiogram in patients with recreational use of ketamine.



Diffuse extrahepatic duct dilatation



Fusiform extrahepatic duct dilatation with distal tapering

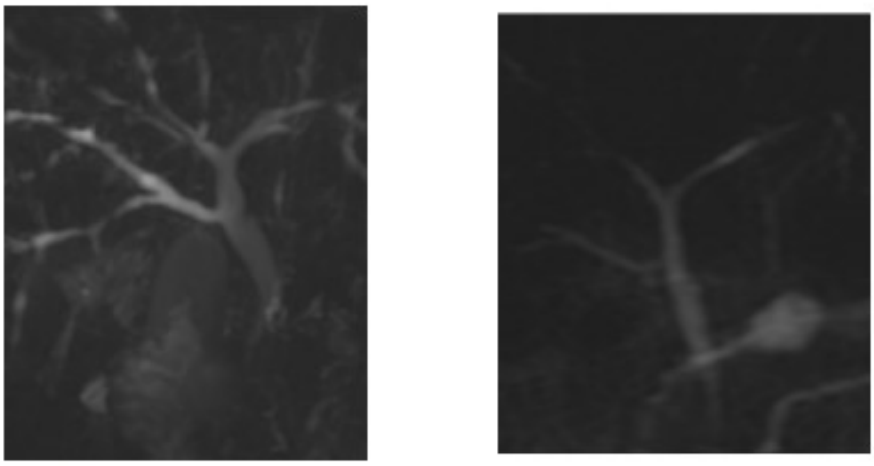


Intrahepatic duct dilatation or beading
Normal extrahepatic ducts

Thirty-four patients (26.8%) were subsequently confirmed abstinent from ketamine.

Abstinence was defined as no further exposure to ketamine for a minimum of 6 months, as mentioned by patients during clinical follow-up and verified by the patient's respective charitable service organization or substance abuse clinic when appropriate. All thirty-four patients had improvements in their abdominal discomfort at follow-up, with a statistically significant reduction in mean PAGI-SYM score from 69.7(±18.2) to 34.3(±13.3) ($p<0.001$). These included six patients with baseline magnetic resonance cholangiogram showing biliary anomalies and agreed for a reassessment scan. Resolution of biliary tract anomalies and improvement in liver biochemistry was noted in five patients. A MR cholangiogram example is depicted in Figure 3. Only one patient had persistent intrahepatic duct changes and liver biochemistry derangement, this patient is now being continuously followed up at our clinic.

Figure 3. An example of biliary tract anomalies resolution in a 37 year old male participant who quitted ketamine. After 12 months, extrahepatic ductal diameter decreased from 12 mm to 5 mm. Intrahepatic beading had also been resolved.

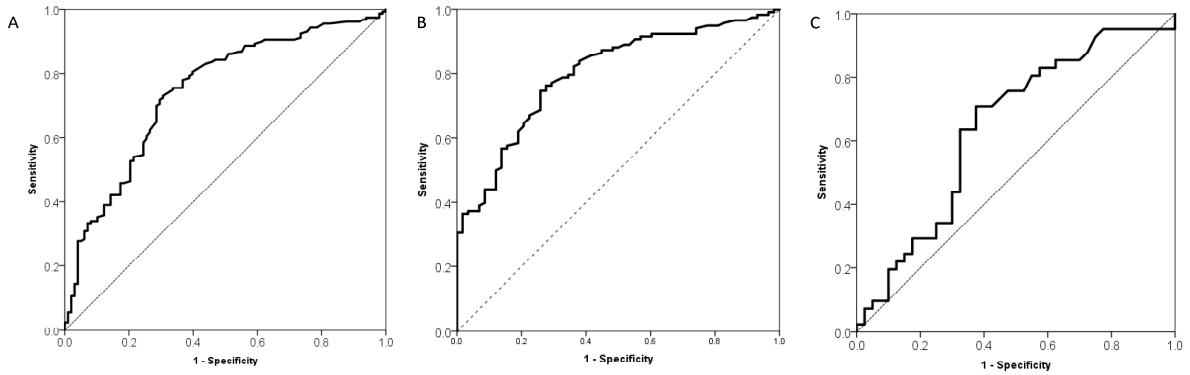


One patient (56 year old male) developed decompensated cirrhosis, with a bilirubin level of 114 umol/L and a Model of End-stage Liver Disease score of 17 on presentation. He had no other concomitant chronic liver disease, but had been recreationally using ketamine solely for 21 years. MR cholangiogram showed diffuse intrahepatic ductal strictures and a diffusely dilated extrahepatic duct of 8 mm. He was diagnosed with

secondary biliary cirrhosis and was referred for liver transplantation, but developed sudden cardiac arrest due to pneumonia prior to completion of transplant workup.

As mentioned above, we combined our cohort with MR cholangiography with a previous cohort supported by the Beat Drugs Fund (BDF reference number: 150034) for further analysis. Multivariate analysis of the combined cohort (n=257) found the lack of concomitant recreational drugs (odds ratio 1.99, 95% confidence interval (CI) 1.11-3.58, p=0.021), and history of emergency attendance for urinary symptoms (odds ratio 1.95, 95% CI 1.03-3.70) were independently associated with biliary tract anomalies. Duration of ketamine exposure had no association with biliary pathologies (p>0.05). Serum ALP was able to predict biliary tract anomalies, achieving an AUC of 0.800 in participants with sole ketamine use and an AUC of 0.745 in the overall patient cohort (Figure 4). In both the overall study cohort and in participants solely using ketamine, based on the Youden index, the optimal cut-off serum ALP level to predict biliary tract anomalies was ≥113 U/L.

Figure 4. Receiver operating characteristic curves of serum ALP in predicting biliary tract anomalies in (A) all participants; (B) participants solely using ketamine; and (C) participants using concomitant recreational drugs in addition to ketamine.



		Area under curve	Standard error	p value	95% confidence interval
A	All participants (n=257)	0.745	0.032	<0.001	0.683-0.807
B	Solely ketamine users (n=176)	0.800	0.034	<0.001	0.733-0.866
C	Ketamine users with concomitant recreational drugs (n=81)	0.642	0.063	0.028	0.519-0.765

ALP, alkaline phosphatase
Assessment of accuracy performed via areas under the curves of constructed receiver operating characteristic curves.

Discussion

With a mean age of 29.6 years and a mean ketamine exposure duration of 10.6 years, our study cohort was representative of real-world recreational drug user situation in our region [26]. Our present study characterized the severity of abdominal discomfort in recreational ketamine users and demonstrated an improvement in symptomatology after abstinence. In addition, our present study characterized the MR imaging patterns among a large population of recreational ketamine users and its association with different clinical profiles.

Abdominal symptoms are present in one-third of frequent ketamine users [11], and is the second-most common symptom of presentation (21%) among ketamine users in the emergency department [12]. The PAGI-SYM score for abdominal symptoms has been validated to be accurate and representative, and is currently the scoring system of choice for clinical trials [27, 28]. PAGI-SYM has also been demonstrated to be a marker of quality of life and disability [29]. Our present study demonstrated that ketamine users have a high degree of abdominal discomfort as reflected by the high PAGI-SYM score, which also is supported by the high proportion of ketamine users seeking emergency attendance for the symptoms (72.4%). The vast improvement in PAGI-SYM score in patients with confirmed ketamine abstinence can be an important social health message that symptoms can be resolved once patients quit ketamine.

More than 70% of ketamine drug users had biliary tract anomalies, which can be further categorized distinctively as extrahepatic and intrahepatic involvement. Extrahepatic changes were common, seen in 68.4% of affected individuals, and were in the form of diffuse or fusiform dilatation, consistent with findings from published case series [19, 30-32]. No extrahepatic strictures were noted, which is a marked difference from the radiological presentation of primary sclerosing cholangitis [33]. Intrahepatic ductal changes, previously only described in a case report [16], was present in >50% of affected participants. The lack of concomitant recreational drug use was an important risk factor for biliary tract anomalies (odds ratio 1.99, 95% CI 1.11-3.58, p=0.021). Recreational poly-drug users are usually less dependent on ketamine when compared to other recreational drugs [34]. Thus, the lack of concomitant drug use might be a surrogate indicator for increased ketamine intake and exposure, leading to an increased risk of

biliary complications. The duration of ketamine exposure, in our present study, showed no relationship to biliary tract anomalies. This might be related to the unreliability of self-reporting from recreational drug users [35]. Hence, screening of ketamine users for biliary anomalies can be concentrated among individuals without concomitant drug use, or with a prior history of emergency attendances for urinary symptoms (odds ratio 1.95, 95% CI 1.03-3.70), which may indicate underlying concomitant ketamine-related uropathy. Serum ALP can also be an easily-available screening test for underlying ketamine-related cholangiopathy, as illustrated by its AUC of 0.800 especially in sole ketamine users.

The long-term clinical outcome of different ketamine-related cholangiopathic patterns is still unknown. Referencing to primary sclerosing cholangitis, distinct cholangiographic patterns might hold a prognostic value [36], and future longitudinal studies on this aspect will be required. It is important to note our study cohort comprised of a patient who developed decompensated cirrhosis. This patient not only had a longstanding exposure to ketamine, but was also much older (56 years). Secondary biliary cirrhosis in ketamine users has been reported previously [37], and is an additional ominous complication of continued ketamine use. At the same time, biliary tract damage was reversible after ketamine abstinence with biochemical and radiological improvement (Figure 3). The potential reversibility of ketamine-related biliary damage after abstinence is an important public health message in the combat against substance abuse, especially when withdrawal symptoms associated with ketamine cessation are milder when compared to other recreational drugs [1, 38].

Our study had several limitations. We did not recruit the targeted 150 subjects, due to the declining rate of ketamine use in Hong Kong during the latter part of this study. We hence combined our cohort with that of Beat Drugs Fund 150034, so as to achieve an adequate statistical power in exploring risk factors and predictors of ketamine-related cholangiopathy. At the same time, our study had important strengths. Through the collaboration with different charitable service organizations, we overcame the high default rates seen in studies involving drug users [20], and successfully recruited consecutive participants directly from the community, ensuring our study results would reflect the real-world scenario of substance abuse in Asia.

Conclusion

Both severe degrees of abdominal discomfort and distinctive MR cholangiographic patterns were noted in recreational ketamine users with prolonged ketamine exposure. Risk factors for ketamine-related cholangiopathy include sole usage of ketamine and concomitant urinary symptoms, while serum ALP has a predictive value for biliary tract anomalies. While ketamine-related cholangiopathy and ketamine-related abdominal discomfort are potentially reversible after abstinence, secondary biliary cirrhosis might develop after prolonged exposure. The present study findings enhance our understanding of ketamine's toxicities to the gastrointestinal tract, strengthen the clinical benefits of abstinence, and may aid the public health efforts against the global epidemic of recreational ketamine use.

Dissemination

1. Seto WK, Mak SK, Chiu K et al. Cholangiopathic patterns detected by magnetic resonance cholangiography in recreational users of ketamine: a prospective study (abstract). Presented in Digestive Disease Week, USA 2017.

2. Seto WK, Mak SK, Chiu K et al. Magnetic resonance cholangiogram patterns and clinical profiles of ketamine-related cholangiopathy in drug users. J Hepatol 2018 69: 121-128.

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