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Severe jaundice with life-threatening liver failure after Kratom use: Reversed by plasma exchange

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ABSTRACT

Kratom is an herbal supplement which is used for its stimulating properties and pain reduction due to interaction with opioid receptors. Kratom overdose may cause fatality. A 56-year-old man was admitted to the emergency department with severe jaundice and liver failure. His total bilirubin reached at 70.6 mg/dL, but extensive workup did not show any liver mass. Family informed that the patient was taking Kratom. Plasma exchange was suggested as an unconventional therapy and consent from the patient was obtained because this procedure has never been performed to treat Kratom toxicity before. After four procedures, his total bilirubin was reduced to 23.9 mg/dL and his clinical condition improved significantly. Finally on day 5 he was discharged at stable condition with a total bilirubin value of 21.3 mg/dL. There is no antidote for Kratom, and treatment is supportive. To our knowledge this is the first report of reversing Kratom poisoning using plasma exchange.

1. Introduction

Kratom, a tropical evergreen tree *(Mitragyna speciosa)* native to Southeast Asia, is gaining popularity in the U.S as an herbal supplement for its stimulating properties and analgesic effect. An estimated 2.1 million US residents used kratom in 2020, as a "legal high" for pain, treating opioid withdrawal, and other conditions. Severe toxicity and death have been reported from Kratom use. More than 90 deaths have been caused by Kratom between July 2016 and December 2017 according to CDC [1,2]. Kratom abuse is an emerging public health emergency. Post et al. reported that from 2011 through 2017, 1807 kratom exposures were reported to United States Poison Control Centers mostly in adults over 20 years of age (88.9%) and males (70.8%). Almost two-thirds (65.0%) of these exposures occurred during 2016–2017 and most exposures were intentional (74.3%). After Kratom use, 51.9% of subjects had adverse effects [3]. In one study based on investigating 27 Kratom related deaths, the authors reported that the concentration of active ingredient mitragynine ranged from 8.7 to 1800 ng/mL [4]. Active ingredients of Kratom are indole-based alkaloids with no similarity with opiates but bind with mu-opiate receptor resulting its pharmacological effects. Unfortunately, urine drug screen is negative in a suspected Kratom overdose patient. Tobarran et al. reported case of a 31-year-old male with history substance use, presented to the emergency department after loss of consciousness for 6 h after smoking Kratom. He suffered from rhabdomyolysis, acute renal and hepatic injury, and electrolyte disturbances. No ethanol was detected, and urine drug screen was negative [5].

Kratom overdosed patients present with various symptoms including hypertension, tachycardia, agitation, dry mouth, hallucinations, cognitive and behavioral impairment, cardiotoxicity, renal failure, cholestasis, seizures, respiratory depression, and less commonly rhabdomyolysis. Both coma, and sudden cardiac death from cardiac arrest after use of Kratom has been reported [6]. Kratom in a rare case may cause severe liver injury resulting in the need for liver transplantation [7]. Schimmel and Dart reviewed Kratom induced liver injury pattern, which is variable, most required hospitalization but no death [8].

2. Case Report

The 56-year-old patient with a past medical history of hypertension, hypothyroidism, known nephrolithiasis, and biliary stricture causing hepatic dysfunction presented to the emergency department of our hospital for his acute liver injury and jaundice. Patient was also admitted prior to this admission with extensive workup for similar issue including endoscopic retrograde cholangiopancreatography (ERCP) revealing a single 3 cm biliary stricture which was stented at that at time. He showed elevated bilirubin, creatinine of 3.4 mg/dL, acute

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anemia along with concerns for acute liver/kidney failure as well as in vivo hemolysis. His initial alkaline phosphatase was also elevated significantly to 1023 U/L. His other liver enzymes were also moderately elevated, but toxicology report was negative. At that point family member informed that the patient was abusing Kratom for some time and this time her also abused Kratom before presenting to the hospital.

He was started on bicarbonate drip due to acidosis from non-oliguric renal failure. Other biochemical test results were not remarkable. His urine drug screen and serum alcohol screen were negative. Unfortunately, bilirubin continued to rise with the highest value of 70.6 mg/dL. Hepatology, nephrology, hematology, nutrition, and cardiology services were consulted during this time. Subsequent extensive workup remained negative. Patient was evaluated for liver transplant. During patient's stay numerous imaging exams were performed (ultrasounds, CTs, MRI, ERCP) which showed numerous small subcentimeter T2 hyperintense lesions throughout both lobes of the liver, likely cysts, or benign hamartomas, and mildly enlarged liver. However, no mass was observed. A biopsy of patient's liver showed chronic cholestatic process and mild portal fibrosis (stage 1/4). PET scan showed no discrete hypermetabolic mass or metastatic disease.

Patient was initially started on a steroid taper and some clinical improvement was observed. When patient was evaluated for liver transplant, plasma exchange was also considered due to very high bilirubin of 70.6 mg/dL, and the patient consented to that experimental procedure as plasma exchange was never documented to our knowledge to treat life-threatening Kratom overdose. A temporary hemodialysis catheter was placed by an interventional radiologist for plasma exchange. Patient received a total of four plasma exchanges (we use 100% fresh frozen plasma for exchange). Photo of plasma exchange waste bag is shown in Fig. 1. Bilirubin values started to decline with initiation of plasma exchange and after 4th procedure value was reduced to 23.9 mg/dL (Table 1). Finally, patient was discharged in a stable condition the following day.

One interesting aspect of this case is extremely high bilirubin of 70.6 mg/dL. Botejue et al. described liver injury in two patients after using Kratom but total bilirubin was 1.3 mg/dL in the first patient and 39.5 mg/dL in the second patient. Although the 1st patient responded to supportive therapy and eventually discharged from the hospital, the 2nd patient was transferred to a liver transplant center for appropriate management [9]. To our knowledge 70.6 mg/dL total bilirubin is the most elevated bilirubin value after Kratom use.

3. Discussion

Kratom overdose may be life-threatening. Unfortunately, urine drug screen is negative and detection of active ingredient of Kratom in urine using liquid chromatography-tandem mass spectrometry is not available even in major academic medical centers. Only few reference laboratories offer such testing.

The treatment of Kratom overdose is mostly conservative as in most cases symptoms resolve after supportive therapy although severe overdose may not respond to supportive therapy causing fatality. Sublingual buprenorphine-naloxone (Suboxone) is reported as a promising treatment for detoxification and maintenance replacement therapy for kratom-dependent users but not for reversing Kratom overdose [10].

The patient was using Kratom on a regular basis almost one year for pain relief. He has several conditions including known nephrolithiasis, and biliary stricture causing hepatic dysfunction. Therefore, Kratom may be a contributing factor to his liver failure but not the only cause. To our knowledge this is the first report of reversing Kratom overdose and preventing fatality using plasma exchange. Plasma exchange can remove small molecules like bilirubin effectively as well as big molecules such as antibodies. We demonstrated that severe hyperbilirubinemia in this patient was corrected by plasma exchange. The patient survived and was eventually discharged in a stable condition from the hospital.

Fig. 1. Photo of plasma exchange waste bag.

Table 1
High bilirubin in a patient corrected after therapeutic plasma exchange.

Day	Total bilirubin	Comments
Day 1, admission	70.6 mg/dL	Evaluated as a candidate for liver transplant.
Day 2	58.6 mg/dL	Bilirubin decreased significantly after 1st plasma exchange.
Day 3	42.3 mg/dL	Bilirubin further decreased after 2nd plasma exchange.
Day 4	35.6 mg/dL	Further reduction of bilirubin after 3rd plasma exchange.
Day 5	23.9 mg/dL	Bilirubin after 4th and final plasma exchange.
Day 5	21.3 mg/dL	Patient discharged in a stable condition.

4. Limitation of this study

We do not have capacity to analyze Kratom and its metabolites in serum. Therefore, reversing life-threatening overdose after plasma exchange was an indirect observation that such procedure may be useful in reversing Kratom overdose. Active ingredients of Kratom; mitragynine (molecular weight 398.5) and 7-hydroxy mitragynine (molecular weight 414.5) are small molecules. Therefore, we only hypothesize that plasma exchange may have removed these compounds along with bilirubin. Moreover, Kratom used by the patient may be contaminated with other adulterants that may have contributed to liver damage. Unfortunately, we do not have capability of analyzing Kratom in our laboratory.

5. Conclusions

Currently, there is no antidote for Kratom overdose and therapy is only supportive. We report for the first time that life-threatening Kratom overdose can be reversed by plasma exchange.

CRediT authorship contribution statement

Dasgupta Amitava: Writing – original draft. **Ye Zhan:** Formal analysis, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing.

References

[1] Gorelick DA. Kratom: Substance of abuse or therapeutic plant? Psychiatr Clin North Am 2022;45:415–30.
[2] Kuehn B. Kratom related deaths. JAMA 2019;321:1966.
[3] Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposures reported to United States poison control centers: 2011-2017. Clin Toxicol (Philos) 2019;57:847–54.
[4] Schmitt J, Bingham K, Knight LD. Kratom-associated fatalities in Northern Nevada-What mitragynine level is fatal? Am J Forensic Med Pathol 2021;42:341–9.
[5] Pressure necrosis requiring fasciotomy after Kratom overdose. J Addict Med 2022;16:252–3.
[6] Sangani V, Sunnoqrot N, Gargis K, Ranabhotu A, et al. Unusual presentation of Kratom overdose with rhabdomyolysis, transient hearing loss, and heart failure. J Invest Med High Impact Case Rep 2021;9. 23247096211005069.

[7] Dorman C, Wong M, Khan A. Cholestatic hepatitis from prolonged Kratom use: a case report. Hepatology 2015;61:1086.
[8] Schimmel J, Dart RC. Kratom (Mitragyna Speciosa) liver injury: a comprehensive review. Drugs 2020;80:263–83.
[9] Botejue M, Walia G, Shahin O, Sharma J, Zackria R. Kratom-induced liver injury: a case series and clinical implications. Cureus 2021;13:e14679.
[10] Bin Abdullah MFIL. Kratom dependence and treatment options: a comprehensive review of the literature. Curr Drug Targets 2020;21:1566–79.