Acute Kidney Injury Following Ingestion of Raw Fish Gallbladder of Indian Crap (*Labeo Rohita*): Thirty Case Series During 1975–2018

Abstract

Introduction: Ayurveda describes using desiccated and well-processed gallbladder of Indian carp (*Labeorohita*) as a traditional remedy for some diseases. People consume it irrationally following the hearsay advice for all types of chronic diseases. **Methods:** Here we report 30 sporadic cases of acute kidney injury (AKI) following ingestion of raw gallbladder of Indian carp during 1975–2018 (44 years). **Results:** Most of the victims were males (83.3%) with an average age of 37.7 years. The mean onset of symptoms was 2 to 12 hours after ingestion. All patients presented as acute gastroenteritis and AKI. Among them, 22 (73.33%) needed urgent dialysis, and 18 (81.81%) of them recovered with four (18.18%) deaths. Eight patients (26.6%) were managed conservatively, of which seven (87.5%) recovered with one (12.5%) death. Septicemia, myocarditis, and acute respiratory distress syndrome were the causes of death. **Conclusions:** This longest four-decade case series highlights that indiscriminate ingestion of raw fish gallbladder by unqualified prescription results in toxic AKI with multiple organ dysfunction and death.

Keywords: *Acute kidney injury, gallbladder, hepatitis, Indian carp (Labeo rohita), MODS, toxic acute tubular necrosis*

Amod Chandra Mahakur, Himanshu Sekhar Mahapatra[1]

Department of Nephrology, Kalinga Hospital, Bhubaneswar, Odisha, [1]Department of Nephrology, ABVIMS, Dr. R.M.L. Hospital, New Delhi, India

Introduction

In tropical countries like India, poisons and toxins are important contributing factors in the etiology of acute kidney injury (AKI) besides infections such as malaria, leptospira, and gastroenteritis. Fishes have been used as delicious food that is rich in protein, vitamins, fatty acids, and minerals. The Indian carp (*Labeo rohita*) is the most superior of all fresh water fishes, and its gallbladder has been used as Ayurvedic and traditional medical remedies in improving the brightness of eyes, night blindness, bronchial asthma, rheumatism, chronic ill health, dyspepsia, and improvement of general health.[1] [Figure 1] Besides fish poisoning (ichthyotoxicosis), ingestion of some selected parts of fish such as gallbladder, ovary, testes, and liver for homicidal and suicidal purpose have been described as *fugu* in Japan and *fuguism* in the Philippines.[2] The common carp fishes (*Cyprinouscarpio*) such as Indian carp (*Labeo rohita*), grass carp (*Ctenopharyngodonidella*), and silver carp (*Hypophthalmichthysmolitrix*) have been reported from Assam, Manipur, Maharashtra, and Odisha. Here we report 30 sporadic patients who developed AKI following ingestion of raw gallbladder of Indian carp fish during 1975–2018 (44 years).

Materials and Methods

All admitted AKI patients following a definite history of ingestion of raw fish gallbladder of Indian carp were admitted to two medical colleges and one superspeciality hospital. Detailed history of the mode of ingestion of raw fish gallbladder, indication for which ingested, and details of prescriber/advisor (Ayurvedic physicians, well-wishers, family members, friends, or quacks) were obtained. The time lag between ingestion and onset of symptom, clinical features, and management details were recorded. Laboratory investigations, including kidney function tests, liver function test, complete blood count, and urine analysis, were done. Electrocardiogram and echocardiography were done whenever required. Kidney biopsy was done in selected patients with

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Address for correspondence: *Dr. Himanshu Sekhar Mahapatra, 307, Admn Block, ABVIMS, Dr. R.M.L. Hospital, New Delhi, India.*
E-mail: hsmnephro@gmail.com

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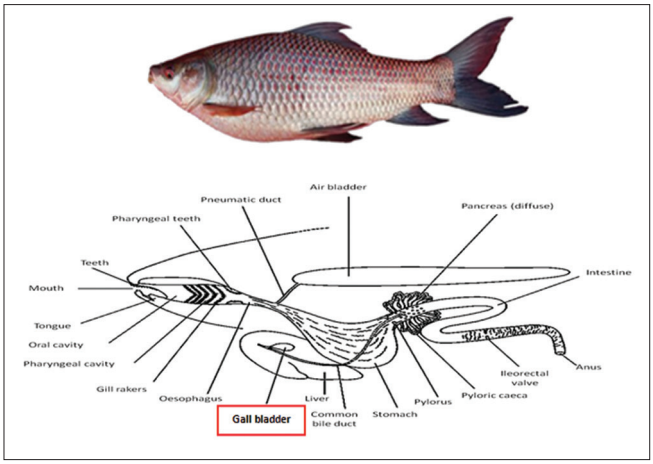

Figure 1: (a) Taxonomy of Indian carp (*Labeorohita*). Kingdom: Animalia, Phylum: Chordata, Class: Actinopterygii, Order: Cypriniformes, Family: Cyprinidae, Genus: *Labeo*, Species: *rohita*. (b) Digestive system of the fish (*Labeorohita*)

Franklin's modification of Vim–Silverman's needle with or without ultrasound guidance. Kidney tissue was obtained in 14 patients and liver tissue in six patients. Only light microscopic study of biopsy specimen was done.

Results

Thirty patients were admitted to hospitals with AKI following definite history of ingestion of raw fish gallbladder of Indian carp. Associated comorbidities for which it was taken, number of ingestions of raw fish gallbladder, reason or diseases for which ingested, duration with the onset of symptom after ingestion, clinical features, and management details were recorded are highlighted in Table 1. All the individual cases details such as year, place, prescriber, number of fish consumed, liver toxicity, number of dialysis, and clinical outcome have been described**.** All 30 patients had taken one gallbladder each, except three patients who took two at a time. One patient gave the history of taking fish gallbladder at regular intervals of months and years on three to four occasions for improving health and vitality. The severity of the disease was dose related. The patient who took at the regular interval had AKI with less severity with normal urine output. The demography details, symptomatology, and investigations are detailed in Table 2**.** The symptoms appeared 2 to 12 hours after the ingestion of gallbladder. The gastrointestinal symptoms such as nausea, severe vomiting, abdominal cramps or pain, and loose motion were prominent in all (100%) of cases. Hepatic involvement was noted in 10 (33.3%) patients. Six patients had hypertension in addition to vomiting, diarrhea, and hypovolemia. The first organ affected was the gastrointestinal tract. Oliguria and anuria with jaundice were observed after 24 to 72 hours. Skin rashes appeared after the first week. Urine examination revealed hematuria, proteinuria along with red blood cells (RBCs), hyaline, granular, and hemoglobin casts. The mean levels of hemoglobin, urea, creatinine, sodium, potassium, bilirubin, and liver enzymes are shown in Table 2**.** Six patients had hyponatremia (113–126 mmol/L). Five patients had hyperkalemia (6.5–8.6 mmol/L). Kidney tissue obtained in 14 patients showed glomerulitis in three patients and acute tubular necrosis in all 14 cases. Distal tubular degeneration with hemoglobin casts was seen in two cases. There was interstitial edema with inflammatory cell infiltration in six cases. Liver biopsy tissue was obtained in six out of 10 cases with hepatic involvement. All of them showed features of acute toxic hepatic necrosis. Twenty-two of them required hemodialysis support, and the other eight patients were managed conservatively. There were six patients with multiorgan dysfunction with renal, hepatic, gastrointestinal, and cardiac involvement. They had a fulminating clinical course with catastrophic consequences. Two patients developed intravascular hemolysis with hemoglobinuria, and one of the two had glucose-6-phosphate dehydrogenase (G6PD) deficiency. Two of them had myocarditis, and one of the two expired. Thus, out of 30 patients, 25 cases (83.3%) recovered and five (16.7%) died due to septicemia, and myocarditis. Early and intensive hemodialysis resulted in a better prognosis.

Discussion

The fish gallbladder ingestion-associated toxic AKI case series consists of 30 patients admitted in three different tertiary hospitals of Odisha. There have been many case reports of AKI and acute hepatic toxicities after ingestion of Indian carp (*Labeorohita*), grass carp (*Ctenopharyngodonidella*), silver carp (*Hypophthalmichthysmolitrix*), and carps (*Cyprinous carpio*) seen all across the country.[3] The severity of the disease is dose dependent. The volume of bile ingested depends on the size of the gallbladder and the fish. The larger the size of the ingested fish and gallbladder, the higher is the risk of intoxication.[3]

Fish bile, like mammalian bile, contains a similar composition of bile salts, cholesterols, phospholipids, bile pigments, organic anions, glycoproteins, and inorganic ions.[4] The bile of *rohu* and *mrigal* contains mainly taurine derivatives of lithocholic acid. In *Cyprinids* (carp fishes), bile alcohol sulfate is the principal bile salt.[5] The main toxin of fish gallbladder poisoning in carp fishes is believed to be water-soluble sodium cyprinol sulfate.[6] Besides the kidney, it can also damage the heart, liver, and gastrointestinal tract leading to multiple organ dysfunction.[7] The toxin in the fish gallbladder can directly damage the mucous membrane of the gastrointestinal tract. It also produces toxic hepatitis and toxic myocarditis.[6] In the present report, we noticed AKI and gastrointestinal tract involvement in all cases. Ten patients had hepatic involvement, and three had myocarditis. Vomiting and diarrhea resulting in hypovolemia may be a contributing factor in the pathogenesis of AKI. The toxin, sodium cyprinol sulfate,

Table 1: Total AKI Patients after *Labeo rohita* fish gall bladder ingestion from 1975 to 2018. (*n*=30)

Case No.	Age	Sex	Year	Place	Prescriber	Comorbid	*No. of Fish Gallbladder	Kidney Biopsy	No. of Dialysis	Liver Toxicity	Improved/ Death
PS	50	M	1975	Bam	Ayurvedic D	DM	1	No	0	No	Improved
BP	15	M	1982	Bam	Grandfather	HTN	1	Yes	1	Yes	Improved
TP	16	M	1982	Bam	Grandfather	Rheumatism	3	No	0	Yes	Death
CP	50	M	1987	Bam	Neighbor	Myxedema	1	Yes	5	No	Improved
N	24	F	1987	Bam	Neighbor	RHD	1	No	2	Yes	Improved
ST	38	M	1988	Bam	Friend	Rheumatism	1	No	0	No	Improved
BT	42	M	1984	Bam	Quack	Dyspepsia	1	Yes	4	No	Improved
L	35	M	1986	Bam	Friend	Dyspepsia	1	No	3	No	Improved
RD	31	F	1989	Bam	Quack	Dyspepsia	1	Yes	0	Yes	Improved
AP	42	M	2013	BSR	Quack	Rheumatism	1	No	5	Yes	Improved
PD	50	M	2004	BSR	Quack	Asthma	4	No	6	No	Death
HS	40	M	2003	BSR	Neighbor	Bronchial asthma	1	No	2	No	Improved
PP	25	M	2003	BSR	Quack	HTN	1	Yes	2	Yes	Improved
AKS	44	F	2017	BSR	Friend	HTN	1	No	0	No	Improved
RT	56	M	2017	BSR	Quack	HTN	1	No	0	No	Improved
BP	40	M	1996	CTC	Quack	Bronchial asthma	1	Yes	0	No	Improved
MB	50	M	1991	CTC	Friend	Night Blindness	1	Yes	1	No	Improved
RB	35	M	1991	CTC	relative	Tuberculosis	2	No	2	Yes	Death
R	46	M	1996	CTC	Neighbor	DM	1	Yes	1	No	Improved
TK	25	M	1996	CTC	Quack	Dyspepsia	1	No	1	No	Improved
MM	39	M	1991	CTC	Quack	Bronchial asthma	1	Yes	3	No	Improved
RKJ	24	M	1995	CTC	Ayurvedic Doctor	HTN	1	Yes	1	No	Improved
RB	36	M	1992	CTC	Ayurvedic Doctor	Bronchial asthma	1	No	3	Yes	Improved
BS	52	M	1992	CTC	Friend	Bronchial asthma	3	Yes	5	No	Death
PD	38	M	1992	CTC	Friend	HTN	1	Yes	0	Yes	Improved
AM	30	M	1992	CTC	Quack	Night Blindness	1	No	1	No	Improved
RD	48	F	1998	BSR	Quack	Dyspepsia	1	No	3	No	Improved
S	38	F	1999	BSR	Relative	Rheumatism	2	Yes	5	Yes	Death
S	28	M	1986	Bam	Quack	Bronchial asthma	1	No	1	No	Improved
R	38	M	2018	BSR	Quack	Rheumatism	1	Yes	3	No	Improved

Age:37.5 years on an average;Sex:Male – 25 years;Place:M. K. C. G. Medical College, Berhampur (Bam) – 10, SCB Medical college Cuttack (CTC)– 11, Kalinga Hospital,Bhubaneshwar (BSR) – 9;Prescriber:Ayurvedic doctor(D) – 3, grandfather – 2, neighbor – 4, friend – 6, quack – 13, relative –2;Comorbidity: diabetes mellitus (DM)– 2, hypertension (HTN) – 6, night blindness – 2, myxedema – 1, rheumatic heart disease (RHD), Mitral stenosis(MS), Mitral Regurgitation (MR), Pulmonary Hypertension(PH)– 1, pulmonary tuberculosis – 1, bronchial asthma – 7, rheumatism – 5, chronic dyspepsia –5;No. of fish gallbladder: 1.4 on an average;Liver toxicity: 10;Kidney Biopsy:14;Improved:25;Death: 5;On Dialysis:22; and No. of Dialysis: 2 on an average. *Twenty-five out of 30 took one each at a time, two out of 30 took two each at a time, two out of 30 took three each at a time, one out of 30 took four each at a time. Death was more common in those who took more than one

produces direct toxic damage to the lysosome and targets the kidney, liver, heart, and gastrointestinal tract, resulting in multiorgan dysfunction.[7] The cyanide and histamine inhibit cytochrome oxidase, thereby blocking the cellular energy metabolism causing necrosis of tubular epithelial cells in the proximal tubule.[8] Xuan BHN *et al*.[7] reported 11 patients with multiple organ dysfunction after ingestion of raw gallbladder of grass carp in south China. Other reports are from Japan,[9] Taiwan,[10] Formosa,[11] Korea, Vietnam,[8] Maryland, Pennsylvania, USA,[12] and India. Multiple organ dysfunction following ingestion of raw fish gallbladder of Indian carp has also been reported from Assam,[13] Maharashtra,[3] Bihar,[14] and Odisha.[15,16] Other sporadic case reports have also been published in the recent literature.[17,18] Recently, a large case series has been published with the similar presentations of AKI with consumption of raw gallbladder of Indian carp fish.[19] The species of fishes belonging to the order Cypriniformes common carp (*Cyprinouscarpio*), grass carp (*Ctenopharyngodonidella*), Indian carp (*Labeorohita*), and silver carp (*Hypophthalmichthysmolitrix*) have been associated with hepatorenal syndrome.[14] The bile components responsible for this syndrome have not been characterized fully. The bile in the gallbladder of Cyprinid fishes (carp fishes) contains principal bile salt, the sodium cyprinol sulfate that is responsible for toxicity.

Table 2: Initial presentation and Laboratory Characteristics of all Toxic Acute Kidney Injury Patients after ingestion of fish (*Labeo rohita*) Gallbladder (*n*=30)

Parameter	(Mean±SD or Percentage)
Symptoms after intake	
Interval of symptoms (in hours)	9.5±5.41
Acute gastroenteritis	30 (100%)
Urine output (mL/day)	384.33±173.58
Oliguria	20 (66.6%)
Anuria	9 (30%)
Edema	4 (13.3%)
Fluid overload with LVF	3 (10%)
Tachycardia	5 (16.6%)
Bradycardia	2 (6.6%)
Skin rashes	7 (23.3%)
Hepatomegaly	10 (33.3%)
Investigations	
Hemoglobin (g/dL)	12.9±2.21
Pack cell volume (mg/dL)	35.7±7.46
Serum bilirubin (mg/dL)	6.01±1.54
SGOT (mg/dL)	85.4±94.2
SGPT (mg/dL)	83.03±96.26
Urea (mg/dL)	155±48.1
Creatinine (mg/dL)	8.03±4.04
Sodium (mg/dL)	129.3±7.79
Potassium (mg/dL)	4.28±0.58

All cases data in categorical/nominal variables are shown as per percentage and continuous data as mean±standard deviation (*SD*). LVF=left ventricular failure, SGOT=aspartate aminotransferase, SGPT=alanine aminotransferase

It was reported that the toxic effect of 5α-cyprinol sulfate on kidney function was more harmful than that of 5α-bile-induced hepatitis and renal failure. Xuan BHN *et al*. and Hwang DF *et al*.[5] have described the light microscopy, which showed hydropic bubbles and fatty degeneration of damaged epithelial cells in the proximal tubule.[7,20] Furthermore, in all said studies, histopathology of kidney and liver tissue specimen demonstrated acute tubular necrosis of the proximal tubule and hepatic necrosis in the liver. Electron microscopy examination showed vacuolar degeneration of mitochondria in the tubular epithelial cell, swelling of tubular endothelial cells, partial fusion of foot processes of glomeruli, deformation, and narrowing of Bowman's capsule. We performed only light microscopy in all 14 patients, which showed toxic glomerulitis in three cases, acute tubular necrosis in all, and RBC cast in three cases. Two cases had intravascular hemolysis and hemoglobinuria where distal tubular degeneration with hemoglobin casts was seen; one of them had G6PD deficiency. There was interstitial edema with inflammatory cell infiltration in the interstitial with mononuclear and polymorphonuclear cells in six patients. Six out of 10 patients with hepatic involvement, where liver biopsy was available, showed evidence of acute toxic hepatic necrosis of liver tissue as in the previous reports of toxic hepatitis.

Conclusion

This largest and longest four-decade case series highlights that indiscriminate ingestion of raw fish gallbladder by unqualified prescription results in AKI with multiple organ dysfunction and death. This very uncommon cause of AKI is a lesson to physicians and nephrologists to keep in mind for the future while probing the etiology of AKI. Public health workers need to educate the rural mass where such practices are seen and to prevent them from such poisoning.

Declaration of patient consent

Patients' consent was taken.

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Conflicts of interest

There are no conflicts of interest.

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