Review
Pregledni članak

ISSN 1848-817X
Coden: MEJAD6 53 (2023) 1

High-volume post-obstructive choleresis (biliary hyperproduction) with acute kidney injury after choledochotomy, gallstones extraction, and T-tube drainage, successfully treated with octreotide –Report of a case

Poslijeopstrukcijska žučna hiperprodukcija (kolereza) s akutnom ozljedom bubrega nakon koledokotomije, odstranjenja kamenaca i T-drenaže, uspješno liječena oktreotidom - Prikaz slučaja

Luka Blagus, Jakov Mihanović, Emilio Dijan, Petra Grbić Pavlović, Iva Pavić, Ivo Ćoza, Ivan Bačić*

Summary

Only several cases of postprocedural choleresis (biliary hyperproduction) were reported, and guidance on management is scarce, although an application of octreotide was anecdotally described.

We herein present a rare post-obstructive choleresis complicated with acute kidney injury due to dehydration, successfully treated with an off-label application of octreotide. A 58-year-old female, following cholecystectomy and choledochotomy with numerous stones extraction, developed excessive bile loss via a T-tube complicated with acute kidney injury. Despite aggressive fluid replacement, the patient continued to deteriorate, prompting a trial of subcutaneous octreotide 0.1 mg three times per day over five days. Therapy yielded a rapid decline in bile production with improved diuresis and normalizing kidney function. The patient was discharged with a ligated T-tube, which we removed a month later. The follow-up was unremarkable, with normalized laboratory findings and symptom-free.

Early use of octreotide could help resolve complicated biliary hyperproduction; however, further research is required to determine the risks and benefits of such an approach.

Key words: biliary excretion; choledocholithiasis; acute kidney injury; octreotide; off-label use

Sažetak

U literaturi je opisano samo nekoliko slučajeva poslijeopstrukcijske kolereze (hiperprodukcije žuči), smjernice o liječenju ne postoje, a primjena oktreotida se spominje anegdotalno.

Ovdje predstavljamo rijetku poslijeoperacijsku kolerezu kompliciranu akutnom ozljedom bubrega zbog dehidracije, što je uspješno liječeno primjenom oktreotida izvan odobrene indikacije.

U 58-godišnje bolesnice nakon kolecistektomije, koledokotomije i vađenja brojnih kamenaca, došlo je do prekomjernog gubitka žuči preko T-drena, što se kompliciralo akutnom ozljedom bubrega. Unatoč agresivnoj nadoknadi tekućine, stanje bolesnice se nastavilo pogoršavati, stoga smo se odlučili na supkutanu primjenu oktreotida 0,1 mg, tri puta dnevno tijekom pet dana. Liječenje je dovelo do brzog smanjenja produkcije žuči, poboljšanja diureze i normalizacije bubrežne funkcije. Bolesnica je otpuštena s podvezanim T-drenom koji smo odstranili mjesec dana kasnije. Kontrolni pregled je bio uredan, laboratorijski nalazi normalizirani, a bolesnica bez simptoma.

*__General hospital Zadar, Department of surgery, Zadar, Croatia__ (Luka Blagus,MD; Assist.prof. Jakov Mihanović PhD, MD; Emilio Dijan, MD; Ivo Ćoza, MD; Associat. Prof. Ivan Bačić, PhD, MD); __University of Zadar, Department of health studies, Zadar, Croatia__ (Assist.prof. Jakov Mihanović PhD,MD, Associat. Prof. Ivan Bačić, PhD, MD); __General hospital Zadar, Department of nephrology, Zadar, Croatia__ (Petra Grbić Pavlović, MD); __General hospital Zadar, Department of radiology, Zadar,Croatia__ (Iva Pavić, MD);

Corresponding address /*Adresa za dopisivanje:*Jakov Mihanović PhD, General hospital Zadar, Department of surgery, B. Peričića 5, 23 000 Zadar, Croatia +385 23 505 310 E-mail: jmihanovi@unizd.hr

Received/*Primljeno* 2022-11-17; Revised/*Ispravljeno* 2022-12-27; Accepted/*Prihvaćeno* 2023-01-22

Rana primjena oktreotida mogla bi pomoći u rješavanju kompliciranе žučne hiperprodukcije, međutim potrebna su daljnja istraživanja kako bi se utvrdili rizici i dobrobiti takvog pristupa.

Ključne riječi: bilijarna sekrecija; koledokolitijaza; akutna ozljeda bubrega; oktreotid; primjena izvan odobrene indikacije

Med Jad 2023;53(1):41-46

Introduction

Choledocholithiasis with biliary obstruction is usually managed with endoscopic retrograde cholangiopancreatography (ERCP). In the case when ERCP is unsuccessful or unavailable, surgical intervention is indicated. Laparoscopic or open approaches are legitimate options, depending on local expertise. After common bile duct (CBD) exploration, stone extraction, and intraoperative cholangiography, the choledochotomy incision should be closed by direct suturing (primary closure) or suturing over T-tube, which is considered to be a safer option. The latter scenario using a T-tube has the disadvantage of significant external bile output in cases when natural drainage of bile into the duodenum is impaired by retained CBD stones or edema caused by surgical manipulation of Vater's papilla.

The mean volume of bile secretion is around 600 mLper day. Opposite to cholestasis, the convenient but seldomly used term *choleresis* depicts the above-average increase of flow of bile from the liver. Excessive biliary output after external drainage of an obstructed biliary system is a rare entity with scarce literature coverage. External biliary drainage can be permanent as in palliative procedures, such as after percutaneous biliary drainage for inoperable periampullary cancers, or temporarily, to bridge the acute phase of obstructive jaundice, resectable malignancy, and most commonly after CBD exploration and T-tube drainage.

Since there are few reports on complications of choleresis and its treatment, in the following section, we present a patient who became dehydrated with acute kidney injury (AKI) and metabolic derangement due to excessive bile loss. The patient was successfully treated with aggressive fluid replacement and off-label application of octreotide.

Case report

The patient was a 58-year-old female with a history of arterial hypertension and smoking. She was on regular beta-blocker bisoprolol 2.5 mg daily and reported an allergy to penicillin. She was employed, and her physical and abdominal examinations were unremarkable. On a routine annual check-up, her liver enzymes were found elevated: alanine transaminase (ALT) was 178 IU/L (range 10-33); aspartate transaminase (AST) was 119 IU/L (range 10-32); gamma-glutamyltransferase (GGT) was 736 IU/L (range 10-40); with normal bilirubin level (0.88 mg/dL, range 0.18-1.17) and undisturbed synthetic liver function tests: albumin 5.9 g/dL (range 5.4-6.5); total protein level 7.4 g/dL (range 6.6-8.3.), international normalized ratio (INR) 0.87, and activated partial thromboplastin time (aPTT) 32 seconds. The abdominal ultrasound (US) exam revealed multiple gallbladder and common bile duct (CBD) stones with significant dilatation of extrahepatic and intrahepatic biliary duct dilation. Surprisingly, the patient never had any symptoms related to gallstones. Since CBD stones were large in diameter (>20 mm) and numerous, gastroenterologists ruled out endoscopic retrograde cholangiopancreatography (ERCP) extraction, so we decided on open surgical intervention. In general intubation anesthesia through the right subcostal incision, we approached the gallbladder appearing chronically inflamed (thickened wall with localized adhesions) and dilated saccular CBD with numerous palpable stones in both gallbladder and CBD. The infundibular part of the gallbladder was firmly attached to the duodenum requiring sharp dissection with deserosation repaired with seromuscular sutures. After performing choledochotomy, most of the CBD stones were extracted through the incision. The larger stones were clamp-crushed and removed in pieces, with detritus being washed down to the duodenum. We confirmed CBD clearance with intraoperative cholangiography (Figure 1). Due to intraoperative manipulation of the Vater's papilla, we anticipated edema, which could impair normal bile flow, so we decided to place a T-tube inside the CBD through a choledochotomy incision. After achieving hemostasis, we placed a silicone drain in the gallbladder fossa and closed the abdominal wall in layers. The patient was allowed to drink early after the surgery, and the usual daily volume of intravenous fluids was administered (2500 mL/24 h). The postoperative course was complicated with copious biliary secretion via T-tube: 7300 mL of bile over the first 24 h. On the second postoperative day, biliary production was reduced to 4600 mL/24 h; alas, the patient started vomiting, aggravating dehydration,

and leading to hypotension (95/60 mmHg) and prerenal AKI. Her blood urea nitrogen (BUN) peaked at 97.17 mg/dL, serum creatinine at 6.3 mg/dL, and potassium at 4.9 mmol/L, despite aggressive intravenous volume replacement. At that moment, we consulted a nephrologist and gastroenterologist who agreed on a trial of subcutaneous octreotide (Sandostatin® Novartis, Basel, Switzerland) 0.1 mg three times per day over the next five days. Initiation of the therapy yielded a rapid decline in bile production, dropping from 4600 to 1100 ml per day. From the third to the fifth postoperative day, the daily average of 1100 mL was further reduced to 600 mL on the sixth postoperative day, with improved diuresis and normalizing kidney function tests, plateauing at 1100 mL of bile per day till the end of the treatment (Figure 2). Although we found a report on the beneficial effect of ketorolac, we decided to avoid nonsteroidal anti-inflammatory drugs (NSAID) to avoid potential nephrotoxicity.[1,2] The patient's laparotomy wound healed well, and we removed the stitches. On the ninth postoperative day, we performed secondary cholangiography through a T-tube, demonstrating the passage of bile into the duodenum without signs of residual stones or contrast leakage (Figure 3). The patient was dismissed with a ligated T-tube, and we removed it a month later through overnight admittance. The follow-up visit was unremarkable, with normalized laboratory findings and symptoms free. We obtained written informed consent from the patient for this study.

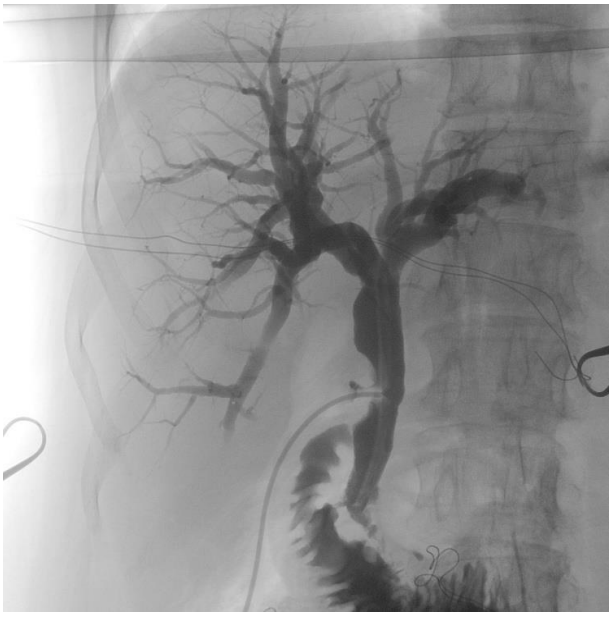

Figure 1 Intraoperative cholangiography showing dilated intrahepatic biliary tree and cleared common bile duct

Slika 1. Intraoperativna kolangiografija koja prikazuje proširenо intrahepatično bilijarno stablo i pročišćeni zajednički žučni kanal

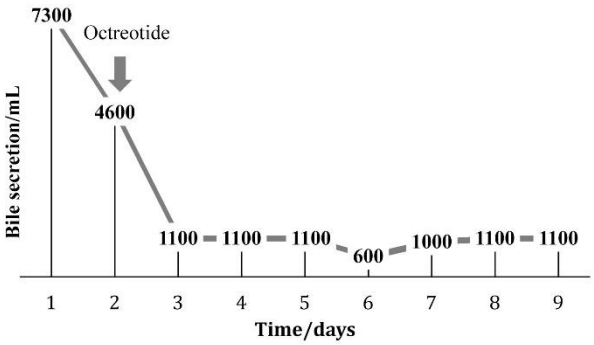

Figure 2 Graph showing daily biliary drainage. The arrow indicates when the octreotide treatment was started

Slika 2. Grafikon koji prikazuje dnevnu bilijarnu drenažu. Strelica pokazuje kada je započeto liječenje oktreotidom

Figure 3 Secondary cholangiography showing a toned biliary tree with passage of contrast into the duodenum

Slika 3. Sekundarna kolangiografija koja prikazuje tonirano bilijarno stablo s prolazom kontrasta u duodenum

Discussion

The bile secretion depends on the production of canalicular (primary) bile by hepatocytes and the modification of bile by secretory and absorptive processes in the bile duct by cholangiocytes. Whereas

hepatocytes have mainly constant production, hormones and nerves significantly affect the cholangiocytes, mainly altering the concentration of bile acids. Also, the anatomical integrity of bile ducts is necessary for bile secretion to function appropriately. Bile mainly consists of water with dissolved electrolytes in higher (Na^+, K^+, Ca^{2+}, HCO_3^-) or lower (Cl^-) concentrations than respective plasmatic concentrations. Bile is rich in bile acids and lipids such as cholesterol and phospholipids. It also contains peptides, proteins, fat-soluble vitamins, and thyroid and steroid hormones.

As mentioned, the biliary output is regulated by several hormones, some increasing (secretin, VIP - vasoactive intestinal peptide, and bombesin) or decreasing secretion (gastrin and somatostatin).[3] Octreotide, the analog of natural somatostatin, suppresses other hormones and neuropeptides, reducing gastrointestinal secretions (including bile secretion). Therefore, it is commonly used as a drug to treat diarrhea associated with metastatic carcinoid tumors and VIP-secreting tumors but shows potential for other indications.

The presented case illustrates the successful treatment of high-volume post-obstructive choleresis and AKI with octreotide in the patient after choledochotomy, biliary stones extraction, and T-tube drainage. Several papers underline overlooked bile cast nephropathy as a potential cause of renal injury in patients with hyperbilirubinemia, which we excluded in our patient.[4,5]

Literature on managing the persistent choleresis from the biliary drain is scarce, although octreotide is reportedly helpful (2). PubMed search for "high-volume biliary excretion" or "percutaneous biliary drainage" combined with "octreotide" or "acute kidney injury" retrieves 21 results, where only three of them are related to our case. Taber and colleagues published a retrospective analysis of 120 patients with external biliary drainage, where seven patients had choleresis.[6] The other two relevant studies are single case reports - both presented patients with dehydration and AKI due to high external biliary drainage, and one showed the beneficial effects of octreotide application.[2,7] The other 18 articles were excluded because they were not describing excessive bile secretion or octreotide use.

Back in 1982, Taber reported outcomes in seven patients with malignant obstructive jaundice managed by external biliary drainage, with an above-average biliary output exceeding 2 liters per day. Two patients developed severe hypotension and required aggressive fluid administration. This report focused on describing rare complications of choleresis.[6]

Jayarajah et al. described high output biliary drainage (3-4 liters per day) complicated by pre-renal AKI in a patient with malignant biliary obstruction. Her palliative metal stent for hilar cholangiocarcinoma was obstructed, and an attempt to pass the blocked stent failed. Therefore, external biliary drainage remained, but it showed excessive biliary output leading to oliguric AKI and metabolic acidosis. The authors emphasize the importance of early recognition of the high output biliary loss and prompt fluid replacement, although they were not focused on the specific treatment of choleresis. Theirpatient showed spontaneous resolution of choleresis with supportive measures, although the moment when the amount of bile secretion began to decrease is unclear.[7]

Tiruneh et al. described the favorable effect of octreotide on choleresis, and its use was reasonable based on its physiological potential to inhibit bile secretion mediated by secretin.[2] The patient presented with high output biliary loss (3-4 liters a day) after the percutaneous biliary drainage for malignant obstruction of the distal common bile duct. Due to continuous high biliary drain output, the patient suffered dehydration, hypotension, and AKI, remaining dependent on intravenous fluids despite various treatment attempts over the next seven days. Soon after the unconventional subcutaneous octreotide trial was initiated (0.1 mg three times a day), a notable decline in daily biliary drainage occurred. The patient had been discharged on intramuscular long-acting depot octreotide but presented again with dehydration and AKI. At that point, a trial of ketorolac was attempted but resulted in less significant improvement in bile drain output than octreotide. Unfortunately, the report does not say how long the long-acting depot octreotide was administered, and the adherence to such protocol needs to be revised.

The reports mentioned above described the palliative management of patients with inoperable malignancies. Our case study shows unusual complications of a common benign pathology (gallstones) after a common surgical procedure, having far more significance to general surgeons and gastroenterologists dealing with it daily.

After the sudden deterioration of our patient's condition, we decided to administer octreotide much earlier (second *vs*. seventh postoperative day). Similarly, a noticeable decline in bile secretion was observed and soon normalized (on the third vs. the tenth postoperative day) with gradually improving kidney function. The effect of the octreotide on biliary secretion was well documented in both cases, and we showed much faster resolution of the

choleresis and consequential complications. It is reasonable to assume that in both patients, the bile secretion would spontaneously resolve with supportive care after some time. However, the question is whether supportive measures may be sufficient and timely. According to the available literature, no deaths due to choleresis have been described, only severe complications, but the condition might be underreported. As the previous cases show, high output biliary drain can be challenging and have various consequences, from only above-average biliary secretion to hypotension, severe dehydration, and prerenal AKI. We could not prove a causal effect between octreotide administration and decreased bile secretion with the insufficient number of patients treated. However, the observed trend of reduction in biliary production linked to the timing of octreotide application is hard to disregard. The mere fluid management was insufficient in our case. The search for more efficient medical treatment yielded an off-label octreotide trial which helped our patient without adverse effects. Despite encouraging reports, optimal treatment, identifying risk factors, and exact mechanisms for choleresis remain uncertain. Therefore, we propose further studies on octreotide use in patients with high-output biliary drainage, even before the onset of dehydration, oliguria, and AKI.

Conclusion

The presented case illustrates successful octreotide treatment of choleresis (biliary hyperproduction) complicated with AKI due to dehydration. Persistent and refractory high output from external biliary drainage is rare; however, the risk of dehydration and AKI should not be overlooked. Intravenous fluid replacement is standard therapy, but more specific treatment should be considered in selected cases. Early use of octreotide could shorten hospital stays and prevent further complications of increased biliary secretion and consequent dehydration. Further research is required to determine treatment benefits and potential risks.

References

1. Lee A, Cooper MG, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. Cochrane Database Syst Rev 2007; 2007(2): CD002765.
2. Tiruneh F, Awan A, Musa A, Chen D. Successful Trial of Octreotide and Ketorolac for the Management of Increased Biliary Drain Output: A Case Report. Cureus 2017; 9: e1421.
3. Nyberg B. Bile secretion in man. The effects of somatostatin, vasoactive intestinal peptide and secretin. Acta Chir Scand Suppl 1990; 557:1-40.
4. El Chediak A, Janom K, Koubar SH. Bile cast nephropathy: when the kidneys turn yellow. Ren Replace Ther 2020; 6:15.
5. Somagutta MR, Jain MS, Pormento MKL et al. Bile Cast Nephropathy: A Comprehensive Review. Cureus 2022 ;14:e23606.
6. Taber DS, Stroehlein JR, Zornoza J. Work in progress: hypotension and high-volume biliary excretion following external percutaneous transhepatic biliary drainage. Radiology 1982; 145:639-40.
7. Jayarajah U, Basnayake O, Wijerathne PK, Sivaganesh S. Acute kidney injury due to high-output external biliary drainage in a patient with malignant obstructive jaundice: a case report. J Med Case Rep 2019; 13:251.