Tc-99m Sestamibi imaging: Can it be a useful substitute for hepatobiliary scintigraphy in infantile jaundice?

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For Peer Review

99mTc-BrIDA (a) and 99mTc-MIBI (b) imaging of a patient with proven biliary atresia. Note bowel visualization with 99mTc-MIBI.

174x345mm (300 x 300 DPI)
Tc-99m Sestamibi imaging: Can it be a useful substitute for hepatobiliary scintigraphy in infantile jaundice

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Running head: Tc-99m sestamibi in infantile jaundice.

Key Words:
Biliary atresia; Tc-99m BrIDA, Tc-99m MIBI, P-glycoprotein, Cholestasis syndrome
Summary:

Aim: Hepatobiliary scintigraphy is an integral part in the diagnostic work-up of the neonatal cholestasis syndrome. However, less than optimal specificity is its major disadvantage. Differentiation between biliary atresia and neonatal hepatitis is nearly impossible in some cases with poor hepatocellular function. Tc-99m sestamibi(MIBI) is a cationic lipophilic agent which is a substrate of P-glycoprotein. This glycoprotein is normally expressed in biliary canalicular surfaces of hepatocytes. This property provides a hepatic excretory mechanism which is different from bilirubin excretion. In this study we evaluated the value of Tc-99m MIBI in differential diagnosis of neonatal cholestasis.

Methods: 20 infants with a mean age of 2.41 months (range, 0.1-5 months) were included in the study. Ten infants turned out to have extrahepatic biliary atresia and the other 10, had neonatal hepatitis. Hepatobiliary (with Tc-99m BrIDA) and Tc-99m MIBI scintigraphy were performed for all the patients. Results: Tc-99m MIBI scintigraphy has shown bowel activity in all patients, including the patients with biliary atresia. Hepatobiliary scintigraphy revealed bowel activity only in 5 patients with neonatal hepatitis. Conclusion: Bowel visualization with Tc-99m MIBI may be seen in patients with biliary atresia and Tc-99m MIBI has limited value in differential diagnosis of neonatal cholestasis.
**Introduction**

Cholestasis is defined as direct bilirubin more than 15-12% of total serum bilirubin level and is definitely a non-physiological finding, which affects approximately 1 in 2500 neonates. The most common causes of neonatal cholestasis are hepatitis, biliary atresia, and choledochal cyst (1-3). Among these etiologies choledochal cyst can be definitely diagnosed by Ultrasonography (4). The other two causes of neonatal hepatitis should be differentiated from each other as soon as possible, since early surgical intervention in biliary atresia significantly improves patient outcome. Unfortunately referral of the patients to the therapeutic facilities is usually late in the course of the disease, which severely limits the therapeutic efficacy (3,5-8).

Liver biopsy, Ultrasonography, cholescintigraphy, Endoscopic Retrograde Cholangio-Pancreatography (ERCP), and duodenal aspiration are the common diagnostic approaches for neonatal cholestasis (9).

Hepatobiliary scintigraphy is an integral part in the diagnostic work-up of the neonatal cholestasis syndrome. Although the sensitivity of this kind of imaging is very high for detection of biliary atresia (83-100%), less than optimal specificity (75%-80% in most of the series) is its major disadvantage (9-14). Entrance of the radiotracer into the bowel excludes biliary atresia in cholescintigraphy, however poor hepatic function impedes proper biliary excretion and differentiation between neonatal hepatitis and biliary atresia become impossible in some cases (14,15).

It is shown that Phenobarbital, Ursodeoxycholic acid or Betamethasone administration can increase the specificity of hepatobiliary scintigraphy (14-
17). However, liver biopsy and intraoperative cholangiography are still required for a large number of patients to establish the correct diagnosis (18,19). Even hepatocyte extraction fraction didn’t improve the diagnostic accuracy of cholescintigraphy (20).

$^{99m}$Tc-MIBI is a myocardial perfusion agent with significant biliary excretion (21). It is a lipophilic cationic radiopharmaceutical which has been reported to be substrate of P-glycoprotein (P-gp). P-gp is normally present in the biliary canalicular surface of hepatocytes and excretion of $^{99m}$Tc-MIBI through the liver is mediated by this protein. (22,23)

As $^{99m}$Tc-MIBI is excreted from the liver with a completely different mechanism compared to IDA agents, we hypothesized that biliary excretion of this agent may be less affected by hepatic disease. We compared the ability of $^{99m}$Tc-MIBI with $^{99m}$Tc-BrIDA to differentiate biliary atresia from other causes of neonatal jaundice.

**Materials and Methods:**

20 consecutive infants with neonatal cholestasis who were admitted in the Pediatric Gastroenterology Unit of our institute from January 2006 to December 2007 were included in this study. A pediatric gastroenterologist examined the patients thoroughly, and any relevant clinical data were recorded. All the patients were examined with liver function tests (LFTs), and ultrasonography.

Each infant first received an intravenous injection of 1 mCi of $^{99m}$Tc-BrIDA. Dynamic images (60 seconds per frame) were acquired for 1 hour in supine position. Delayed images were also acquired especially when
intestinal activity was not clearly seen. Lateral images were also obtained (if needed) to differentiate intestine from genitourinary tract. Scintigraphy was repeated after 24 hours with 2 mCi of 99mTc-MIBI and the same protocol. Liver biopsy and Intraoperative cholangiography (IOC) were used for patients in whom no bowel activity on $^{99m}$Tc-BrIDA scan was detected. If bowel activity was seen, biliary atresia would be excluded. The final diagnosis was made by considering the results of clinical data and the findings of serologic and other etiologic investigations (including thyrosinemia, galactosemia, $\alpha_1$-antitrypsin deficiency, glycogen storage diseases, Cystic fibrosis, and TORCH and Hepatitis viruses’ infections).

All patients received Phenobarbital before the study (5 mg/kg in divided doses for 5 days).

Parents signed an informed, written consent to participate in the study which was approved by the local ethical committee.

**Results:**

20 infants (11 male, 9 female) with a mean age of 2.41 months (range, 0.1-5 months) were included in the study. Ten infants turned out to have extrahepatic biliary atresia and the other 10, had neonatal hepatitis (cystic fibrosis in 3, galactosemia in 2, CMV infection in 2, $\alpha_1$-antitrypsin deficiency in 2, and toxoplaasmosis in 1). The initial $^{99m}$Tc-BrIDA scan showed biliary excretion in 5 patients with neonatal hepatitis, while all patients showed bowel activity on $^{99m}$Tc-MIBI scan (Fig. 1).

**Discussion:**

Many radiological and laboratory test can aid in the correct diagnosis of biliary atresia. Ultrasonography is an easily accessible, affordable, and
noninvasive test for initial investigation of conjugated hyperbilirubinemia and is very sensitive in the detection of choledochal cysts. Some studies have indicated that the "triangular cord" sign on ultrasonography is specific for extrahepatic biliary atresia (24). Some studies have suggested duodenal intubation and aspiration for the presence of bile to establish the patency of the bilioenteric pathway. However, these procedures are invasive and time consuming and do not significantly increase the accuracy of diagnosis (25). Biopsy or IOC is still recommended for a large number of patients (18,19). Hepatobiliary scintigraphy is an integral part in the diagnostic work-up of the neonatal cholestasis syndrome and has been used for couple of years. However hepatobiliary scintigraphy has a suboptimal specificity for detection of biliary atresia, which limits its usefulness (9-14). Our study also confirmed this issue (specificity of 50%). Several approaches including premedication with Phenobarbital, betamethasone, and Ursodeoxycholic acid, were reported to increased the specificity of hepatobiliary scintigraphy (14-17). Majd et al. reported an increase in specificity from 68% to 94% by Phenobarbital premedication (14). However, not all studies agree with this finding, even Charneanrad et al. reported the accuracy of scintigraphy to be 73% after phenobarbital premedication and 100% with no premedication (16). Gupta et al. have shown a significant fall in the number of false-positive findings, from 36% to 18%, by addition of betamethasone (2.2 mg/kg/d for 7 d) to phenobarbital before scintigraphy (15). By using Ursodeoxycholic acid Poddar et al. have found a significant increase in specificity from 54.3% to 88.6% in diagnosing biliary atresia (17).
Hepatocyte extraction fraction measurements was also recommended without any significant improvement in specificity (20).

Although these additional procedures have improved the overall accuracy of hepatobiliary scintigraphy, the specificity for the diagnosis of extrahepatic biliary atresia in cases with a nondraining scintigraphic pattern is very low (about 54% in Poddar et al. study) (17). Biopsy and IOC, are essential in such cases to confirm the diagnosis, both of which are invasive and impose a significant risk for infants (18,19).

In the hope of decreasing unnecessary liver biopsy or IOC, we evaluated usefulness of $^{99m}$Tc-MIBI for diagnosis of biliary atresia. $^{99m}$Tc-MIBI is a cationic lipophilic myocardial perfusion agent with a high biliary excretion (21). It is well known that $^{99m}$Tc-MIBI is a substrate for P-glycoprotein, which is normally expressed in biliary canalicular surfaces of hepatocytes and is responsible for the excretion of cationic metabolites from the liver. This mechanism is completely different from bilirubin excretory mechanism (22,23).

Interestingly, all patients in our study showed small intestinal activity (most likely jejunum) regardless of the etiology of the cholestasis, including 10 patients with biliary atresia. As far as we know, there is only one unpublished study on this subject (26). In this preliminary study, the authors have shown that $^{99m}$Tc-MIBI can be excreted into the bowel even when $^{99m}$Tc-BrIDA scintigraphy is negative for it, and suggested an alternative route of hepatic excretion for $^{99m}$Tc-MIBI. However, the authors didn’t have the final diagnosis of their patients.
Normal distribution of P-gp in human tissues is liver, pancreas, kidney, colon, and jejunum. Colon and jejunum both have high levels of P-glycoprotein on the apical surfaces of superficial columnar epithelial cells (27-29). This property is the main reason of multidrug resistance in the tumors originated from these tissues by excretion of the chemotherapeutic drugs out of the tumor cells. This also can explain small intestinal visualization (most likely jejunum) in $^{99m}$Tc-MIBI scan of patients with biliary atresia.

**Conclusion:**

We concluded that $^{99m}$Tc-MIBI has limited utility in differential diagnosis of the neonatal cholestasis. This curious finding can be due to secretion of this agent into the bowel through P-gp, which is normally expressed in jejunum and colon.

**Acknowledgment**

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Figure Legend:

Fig. 1 $^{99m}$Tc-BrIDA (a) and $^{99m}$Tc-MIBI (b) imaging of a patient with proven biliary atresia. Note bowel visualization with $^{99m}$Tc-MIBI