Serum Bile Acid: an Alternative Liver Function Marker in the Obstructive Jaundice Patient

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ABSTRACT

Aim: to confirm the role of bile acid value as single marker for liver function test as compared to the conventional liver function tests on obstructive jaundice patients. Methods: before and after study on severe obstructive jaundice patients was performed from December 2007 until January 2009. The liver function markers were measured before, 7th day and 14th day after bile duct decompression (BDD). Open Cholecystostomy as BDD was used as a model to observe the markers changes. Samples were collected by trained medical professionals and Automated clinical chemistry analyzer (ACA) TRX 7010 was used to measure the markers value. All continuous data were presented as mean (SD) and the variables were compared and analyzed by t-test and multiple measurements test using SPSS v.16 with a p-value of < 0.05 considered to be statistically significant. Results: twenty one patients were included. All patients suffered bile acid accumulation and impairment of all conventional liver functions tests. After decompression, the average serum bile acid decreased significantly (p<0.05). Significant decrease after decompression happened to serum total bilirubin (p<0.05) and serum ALP (p<0.05). A trend towards improvement in coagulation function was evident by the shortening of PT and APTT. The albumin level increased slightly from 2.8 to 2.9 mg/dL while CHE activity was fixed at low level. A decrease
in average activity of transaminase enzyme (AST (p<0.05) and ALT) was also observed. **Conclusion:** the sBA level follow the pattern of changes of classic liver function markers. Serum bile acid could be considered to be used as alternative marker to evaluate liver function, which is simple and applicable.

**Key words:** bile acid, bilirubin, liver function.

**INTRODUCTION**

Since 1970, serum bile acids (sBA) has been recognized as the only index which is able to simultaneously assess the liver function such as liver cells integrities, excretion, synthesis, and metabolic activities.\(^1\) Bile acid (BA) is end product of cholesterol which was mostly metabolized in the liver cells and excreted to bile in bile duct as bile fluids and then enters the entro-hepatic circulation and then pooled in the liver.\(^1,2\) That role, however, has been abandoned for the last five decades due to the complexity of its assay method and less popular among physician in clinical work.\(^3\)

Sensitivity and specificity of sBA to assess liver function had been demonstrated by several studies in the last decade.\(^3-7\) Advance understanding of the cellular and molecular pathophysiology of sBA has been rapidly led to a better knowledge of hepatocyte injury, which became the point of liver function measurement.\(^6,8,9\)

Inaccurate understanding and the shortage of bile acid assay has made the role of sBA as a liver function test forgotten. Nowadays, modern assay equipment is already available and, therefore, bile acid assay is more feasible to be performed. We aimed to confirm the role of sBA compared to the conventional liver function tests on obstructive jaundice patients after BDD.

**METHODS**

A before-and-after study was done on obstructive jaundice patients, mostly due to peri-ampullar or Klatskin tumor with serum bilirubin above 10 mg/dL, who were admitted to Cipto Mangunkusumo Hospital from December 2007 to January 2009.

Patients with active Hepatitis A, B, or C, liver malignancy, severe liver impairment with massive ascites, had previously undergone decompression procedure or had prior implantation of an internal drainage device, and chronic liver failure were excluded. The study protocols were reviewed and approved by the Hospital Ethical Commission.

Bile duct decompression through an open cholecystostomy was used as a model to observe the marker changes. Routine laboratory investigation, sBA, level of bile acid in the bile fluid, direct and indirect bilirubin, alkaline phosphatase (ALP), gamma glutamyltransferase (γ-GT), albumin, cholinesterase (CHE), protrombine time (PT), activated partial thromboplastin time (aPTT), aspartate transaminase (AST) and alkaline transferase (ALT) were done before, 7 days, and 14 days after decompression procedure. Samples were collected by trained medical professionals and Automated clinical chemistry analyzer (ACA) TRX 7010 was used to measure the marker values.

All continuous data were presented as mean (SD) and the variables were compared and analyzed by t-test and multiple measurements test using SPSS v.16 with a p-value of <0.05 considered being statistically significant.

**RESULTS**

Along the study timeframe, 21 severe obstructive jaundice patients due to mostly Periampulary tumor acceptable to the protocol criteria were included. Baseline characteristics of patients included in the study are presented in Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Sex - female/male</td>
<td>7/14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 (12.7)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>- Peri-ampullar Malignancy</td>
<td>15</td>
</tr>
<tr>
<td>- Peri-ampullar Benign Tumor</td>
<td>6</td>
</tr>
<tr>
<td>Routine Laboratory Examination (before decompression)</td>
<td></td>
</tr>
<tr>
<td>- Hb (g/dL)</td>
<td>11.2</td>
</tr>
<tr>
<td>- Ht (%)</td>
<td>32.7</td>
</tr>
<tr>
<td>- WBC (1000/μL)</td>
<td>11.3</td>
</tr>
<tr>
<td>- Platelets (1000/μl)</td>
<td>260</td>
</tr>
<tr>
<td>- Ureum/Creatin (mg/dL)</td>
<td>35,50,9</td>
</tr>
<tr>
<td>- Blood Glucose (mg/dL)</td>
<td>104</td>
</tr>
</tbody>
</table>
All the patients underwent bile duct decompression procedure. sBA accumulation as well as impaired liver functions occurred in all patients.

Seven and fourteen days after decompression, the average of sBA decreased as much as 59% after 7 days and 87% after 14 days (before: 96.4 (53.8) μmol/L, day 7: 39.9 (39.5) μmol/L, day 14: 13 (12.6) μmol/L; p<0.05). Meanwhile, bile acid in the bile fluid also increases as much as 30% after 7 days and 53% after 14 days (before: 987 (182) μmol/L, day 7: 1400 (182) μmol/L, day 14: 2087 (2076) μmol/L; p<0.05).

Serum total bilirubin (before: 20.0 (9) mg/dL, day 7: 13.3 (5) mg/dL, day 14: 6.2 (4.1) mg/dL; p<0.05) and serum ALP (before: 908 (873) IU/L, day 7: 453 (460) IU/L, day 14: 298 (198) IU/L; p<0.05) also decreased significantly after decompression. After decompression procedure, γ-GT decreased as much as 48% after 7 days and 59% after 14 days (before: 431 (421) IU/L, day 7: 222 (153) IU/L, day 14: 177 (96.6) IU/L; p<0.05).

The average of albumin level increased 3% from 2.8 (0.4) mg/dL to 2.9 (0.7) mg/dL while CHE activity was fixed at low level after decompression, and only 3 patients reached the normal level.

PT (before: 19.5 seconds, day 7: 14.3 seconds, day 14: 14.7 seconds) and aPTT (before: 57.5 seconds, day 7: 38.7 seconds, day 14: 42.1 seconds) were shortened after decompression.

After decompression procedure, activity of AST (before: 111.8 IU/L, day 7: 110.2 IU/L, day 14: 72.6 IU/L; p<0.05) and ALT (66.7 IU/L, day 7: 72.8 IU/L, day 14: 54.3 IU/L) decreased. Changes in the results of laboratory measurements are summarized in Table 2.

**DISCUSSION**

The liver function and volume are two important issues to be assessed preoperatively in order to evaluate the liver condition, especially in living donor transplantation. There is no diagnostic test that can exactly confirm the liver function, even liver biopsy. The sBA value have already been suggested as a simultaneous marker by Annoni and as a diagnostic test for hepatobiliary diseases by Heaton and Sardi. Due to the shortage of assay for sBA in the past, and negative physician opinion, the sBA value was abandoned for many years.

Alterations in sBA metabolism is usually the reflection of liver dysfunction. The increasing value suggests that uptake, secretion process, or porto-veno systemic shunt has been impaired. The fasting serum bile acid level in non cholestatic human is less then 6 -10 μmol/L. Sardi et al in 1987 reported the normal fasting value of sBA was 3.4 ±1.9 μmol/L.

In this study the average amount of sBA pre decompression was 94.6 μmol/L and the increment was caused by obstruction which regurgitate or redistribute the BA after conjugation process in the hepatocyte back to the liver sinusoids and the to the periphery circulation (due to tight junction rupture). Bile acids are the end products of cholesterol breakdown which takes place in the hepatocytes. It starts with the uptake of cholesterol at the liver sinusoid and then follows the classic or alternative pathways in the hepatocyte to be changed into primary bile acids as secretion product. Since bile acid metabolism mostly occurs in hepatocytes, there will be an accumulation of

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**Table 2. Changes of liver markers before, after 7 and 14 days**

<table>
<thead>
<tr>
<th>Markers (normal range)</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>Serum bile acid (6-10μmol/L)*</td>
<td>96.4 (53.9)</td>
</tr>
<tr>
<td>Bile acid in bile fluid*</td>
<td>987 (1229)</td>
</tr>
<tr>
<td>Bilirubin (&lt;1 mg/dL)*</td>
<td>20.08 (9)</td>
</tr>
<tr>
<td>ALP (&lt;270 IU/L)*</td>
<td>908 (873)</td>
</tr>
<tr>
<td>γ-GT (5-61 IU/L)*</td>
<td>431 (432)</td>
</tr>
<tr>
<td>ALB (3.4-5.0 g/dL)</td>
<td>2.8 (0.4)</td>
</tr>
<tr>
<td>CHE (5200-12900 IU/L)</td>
<td>3604 (1381)</td>
</tr>
<tr>
<td>PT (12-14 seconds)</td>
<td>19.5 (1.4)</td>
</tr>
<tr>
<td>aPTT (25.6-35.2 seconds)</td>
<td>57.5 (58.5)</td>
</tr>
<tr>
<td>AST (&lt;38 IU/L)*</td>
<td>111.8 (60.6)</td>
</tr>
<tr>
<td>ALT (&lt;41 IU/L)</td>
<td>66.7 (60)</td>
</tr>
</tbody>
</table>

* p<0.05
bile acid if there is impairment in hepatocyte uptake, synthetic or secretion function.\textsuperscript{1,14,17}

One important criterion to justify a marker as qualitative and quantitative liver markers is that the marker must be formed outside the liver and passes through the liver totally without being retained in the liver.\textsuperscript{2,18} Bile acid fulfills that criterion. Thus, such measurement is highly possible to be used to assess the endogenous clearance test.

In obstructive jaundice, as also shown in this study, the serum bile acid level will increase, while its level in the biliary duct decreases through absorption, regurgitation and urinary excretion. These phenomena were proven in this study by the high value of sBA and low value of fluid BA before decompression and these values inversed after BBD (Table 2). Bile duct decompression releases the high pressure and inhibits the activation of hepatocyte apoptosis cascade which impact the recovery of the hepatocyte count and functions.

In this study bile fluid BA increases after bile duct decompression. This indicates that the BA uptake and conjugation process at the level of hepatocyte have already been improved. The decrease of sBA was followed significantly by the liver secretion markers such as bilirubin, phosphate alkaline and γ-GT due to the same pathways as mentioned above (Figure 1).

Serum bile acids (sBA) values decrease along with the improvement of secretion function as confirmed by the decrease bilirubin, alkaline phosphate and GGT value although all those three markers were not specific due to hepatocyte dysfunction (Figure 1). This might be caused by the BDD which released the intra bile duct high pressure. Release of the accumulating pressure then promotes the BA metabolism on hepatocyte side. The second impact of BA break down is that the BA accumulation was inhibited which decreases the hepatocyte apoptosis and necrosis.\textsuperscript{8}

Pattern of changes in markers of liver synthesis, however, was not quite parallel with changes in sBA value. This may be due to the shortness of decompression compared to the half life of albumin and CHE synthesis. Extra liver factors might also influence both markers (Figure 2). According to the half life of albumin and CHE synthesis process, the serum BA metabolism process was more rationale and representative as synthesis marker in short period.

The PT and APTT values which represent synthesis function were not improved significantly after the bile duct decompression. These might be interpreted that the impairment itself was not in severe state or due to the high reserve liver function.

The prolongation of PT and APTT in obstruction jaundice patients was impacted by fat mal absorption, which induced vitamin K deficiency, and not due to liver factor itself. This study confirms that the sBA changes are followed by improvement of extrinsic haemostatic factor (Figure 3).

In this study the destruction of hepatocyte was attenuated after bile duct decompression. It was confirmed by the decreasing of AST and ALT values, which also meant as a clue of better functional hepatocyte to metabolize BA. (Figure 4).

Despite the increasing knowledge of the importance of sBA, the test on bile salts is unfamiliar in most hospital laboratories. Even
though there are technical problems, and shortage of assay in the past made the count of bile acid abandoned, but these are not beyond the ingenuity of chemical pathologists. Nowadays in the era of high performance liquid chromatography (HPLC) and enzymatic assay by automated clinical chemistry analyzer (ACA) those problems have been solved.

Our data confirmed that the functional hepatocyte mass was improved after the bile duct decompression, which was proven by decreasing sBA accumulation and increasing bile fluid BA (Table 2).

The reluctance to measure bile acids lies not in the laboratory but in the hands of the physicians. Most of them seem to think that they do not need to measure bile acid concentrations to diagnose or manage their patients adequately. Even though it is not an absolute approach to diagnose any important or common; our data suggested that sBA is actually very useful in assessing liver function.

Altered bilirubin metabolism is clinically obvious but it has no devastating effects, except in the neonatal period, whereas altered bile salt metabolism accounts for the major complications of cholestasis, including mal-absorption of fat and vitamin K and probably pruritus. Moreover, a raised serum bile salt concentration, especially after a meal, is a much more sensitive indicator of liver cell dysfunction than is a raised bilirubin concentration.

sBA is probably as sensitive as any liver function test and has been technically possible for half a century. The main reason why serum bile acids were not measured routinely may be due to emotional rather than intellectual. Bilirubin is visible, often dramatically; whereas bile salts (being colorless) are unseen. Another reason in the past is technical. The sBA assay is more difficult than that of bilirubin, and especially the old method requires extraction of the serum, which is more time-consuming. Nevertheless, simplified novel methods are becoming available, including enzymatic kits and rocket method, and even techniques which do not require extraction of serum.

The pattern of decrease in liver function markers as found in this study is similar to those found in animal study, and in a study by Franco et.al which examined the sBA concentration as liver function test in workers who occupationally exposed to organic solvents. The rapid decrement pattern occurred in the first week after the decompression, is due to reversible hepatocyte dysfunction. There fore, after the obstruction has been released, the hepatocyte will be normally functioning again. The slow decreased pattern needs new hepatocyte to replace the damaged hepatocyte from apoptosis to reach the adequate normal capacity. This finding has suggested that the repair of hepatocyte function is significantly followed to the inhibition of bile acid accumulation through biliary duct decompression.

CONCLUSION

Serum bile acid levels follow the pattern of changes of classic liver function markers. Serum bile acid could be considered being used as alternative marker to evaluate liver function, which is simple and applicable.

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