Clinical analysis of the treatment of pediatric hyperbilirubinemia with *Qing Jie Tui Huang Tang* (Clear, Resolve, and Abate the Yellow Decoction)

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Hyperbilirubinemia, a condition which presents as neonatal jaundice, is a commonly seen illness in newborns and infants [1]. If the jaundice continues for prolonged periods of time and if the bilirubin level is markedly elevated, it can lead to kernicterus and permanent brain damage. In very severe cases, it may even pose a risk to the child’s life.[2] Thus, it is important to treat and abate the jaundice quickly. The following report discusses the treatment of 40 cases of pediatric hyperbilirubinemia using our department’s *Qing Jie Tui Huang Tang* (Clear, Resolve, and Abate the Yellow Decoction).

Cohort Description

The patients were selected between October 1998 and September 1999. They were all less than 2 months old and had been diagnosed with hyperbilirubinemia. They were divided into two groups: the treatment group included 40 patients of which 25 were male and 15 were female (male : female ratio of 1.0 : 0.6). Twenty-five cases were between 6 and 28 days old, 12 cases were around 40 days, and 3 cases were around 45 days old. The average age was 21.3 days. All children had been born after a normal gestational period (*i.e.*, were mature). Birth weight of the infants was 3200g + 400g.[3] Out of the 40 patients, 9 cases suffered from unconjugated hyperbilirubinemia, 12 cases from breast milk jaundice, 9 cases from infections [viral or bacterial], 6 cases from cephalatomas, and 4 cases from lack-of-breast milk jaundice.[4] Twenty-five cases were under external supervision (*i.e.*, were outpatients); 15 cases had to be treated in the hospital.

The control group included 38 cases. Out of these 38 cases, 24 were male and 14 were female (male : female ratio of 1 : 0.58). Their age ranged from 5 to 28 days in 25 cases, around 40 days in 11 cases and around 45 days in 2 cases. The average age was 20.4 days. All children had been born after a normal gestational period. Their birth weight was 3100 + 350g. Out of the 38 cases, 11 suffered from unconjugated hyperbilirubinemia, 9 cases from breast milk jaundice, 11 cases from infections, 5 cases from cephalatomas, and 2 cases from lack-of-breast milk jaundice. Twenty cases were treated in the outpatient department; 18 cases had to be hospitalised and were treated in the inpatient department.

In both groups, haemolytic jaundice was ruled out.

The diagnostic criteria followed *Practical Pediatrics*. The serum haemoglobin level was at or above 220.6 : mol/L in all patients. In the treatment group, the highest level was 365.9 : mol/L and in the control group it was 396 : mol/L. Thus, the patients of both treatment and control groups conformed to the diagnosis of hyperbilirubinemia.

Treatment method

First of all, the various treatments for the different disease causes were stopped. Furthermore, breast feeding and the use of antibiotics was suspended. The treatment group received the Chinese medicinal formula *Qing Jie Tui Huang Tang* and the control group
received fluid replacement and light treatment as well as steroids and albumin transfusions.[5]

*Qing Jie Tui Huang Tang* consisted of the following medicinals: *Herba Artemesiae Capillaris* (*Yin Chen Hao*), 9g added later, *Herba Lysimachiae* (*Jin Qian Cao*), 9g, *Fructus Gardeniae Jasminoidis* (*Zhi Zi*), 3g, *Radix et Rhizoma Polygoni Cuspidati* (*Hu Zhang*), 5g, *Radix Scutellariae Baicalensis* (*Huang Qin*), 3g, *Radix Salviae Miltiorrhizae* (*Dan Shen*), 3g, *Semen Plantaginis* (*Che Qian Zi*), 8g, *Pericarpium Citri Reticulatae* (*Chen Pi*), 3g. The following modifications were made based on the infants’ conditions: for high fever, *Huang Qin* was increased to 5g. For pronounced dampness, 5g of *Rhizoma Alismatis* (*Ze Xie*) were added. If there presented a tendency towards cold dampness, *Huang Qin* and *Zhi Zi* were eliminated and dried *Rhizoma Zingiberis Officinalis* (*Gan Jiang*), 3g, and *Rhizoma Atractylodis Macrocephalae* (*Bai Zhu*), 5g, were added. For simultaneous blood stasis, 3g of *Herba Lycopi Lucidi* (*Ze Lan*) were added. The medicinals were prepared into 50-60mL water decoctions and one ji, divided into 3-4 portions, was administered to the child daily.

The serum bilirubin level was measured in both groups prior to the beginning of treatment and after 3 and 7 days of treatment.

**Treatment results**

The treatment results were defined as follows:

- **Marked effect:** after 3 days of treatment, the bilirubin level had decreased by over 50% and the jaundice of the skin was markedly reduced. After 7 to 10 days, the condition had dispersed completely.

- **Some effect:** After 3 days of treatment, the bilirubin level had decreased between 10-50% and the jaundiced skin had improved. After 7 to 10 days, the condition was basically dispersed.

- **No effect:** After 3 days of treatment, the bilirubin level had decreased by less than 10% and the jaundiced skin did not show any clear improvements.

According to these treatment result criteria, the treatment group experienced the following results: 20 cases experienced marked effects, 18 cases experienced some effect, and 2 cases experienced no effect. Thus, the amelioration rate was 95%. In the control group, 22 cases experienced marked effect, 15 cases experienced some effect, and 1 case experienced no effect. Thus the amelioration rate was 97.6%. The change in the serum bilirubin level before and after 3 days of treatment is depicted in the diagram below.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After 3 days of treatment</th>
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</thead>
<tbody>
<tr>
<td>Treatment group (n=40)</td>
<td>279.30 &quot; 50.01</td>
<td>123.74 &quot; 59.20</td>
</tr>
<tr>
<td>Control group (n=38)</td>
<td>282.20 &quot; 52.12</td>
<td>125.03 &quot; 60.08</td>
</tr>
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</table>

Diagram 1: Serum bilirubin levels (mol/L) of both groups before and after 3 days of treatment

In the treatment group, after taking the herbs for 1 to 2 days, 8 children developed slight diarrhea. However, this resolved spontaneously after the herbs were stopped. It is also notable that in the treatment group, in 66.7% of the cases which suffered from the breast milk jaundice (8 out of 12 children), breast feeding was not stopped. However, the jaundice abatement results were similar to the other cases, in which breast feeding was stopped.
Discussion

Hyperbilirubinemia belongs to the Chinese medical disease category of fetal jaundice (tai huang). It is often caused by internal heat, damp heat steaming, and stasis and heat internally obstructing which leads to a loss of liver and gallbladder coursing and disinhibition. Thus, the gallbladder juice drains outside and transversely seeps into the flesh and skin. *Qing Jie Tui Huang Tang* is based on the classical formula *Yin Chen Hao Tang* (Artemesia Decoction). It is augmented by heat clearing and dampness disinhibiting as well as stasis transforming and toxin resolving medicinals. Within the formula, *Yin Chen Hao* and *Huang Qin* clear damp heat and disinhibit the liver and gallbladder. Furthermore, *Yin Chen Hao* promotes bile excretion and lowers serum bilirubin as well as inhibits staphylococci bacteria. Thus, it is the governing medicinal in this prescription. *Zhi Zi* clears and drains heat in the three burners, disinhibits the gallbladder, and promotes the secretion of bile, thus also lowering the serum bilirubin level. Furthermore, it has a broad-spectrum antibiotic effect. Therefore, it is an effective medicinal in the treatment of septicemia-induced jaundice. “In the treatment of dampness, it is wrong not to disinhibit urination.” According to this Chinese medical statement, the formula includes *Jin Qian Cao* and *Che Qian Zi* to clear heat, disinhibit dampness and abate jaundice; these medicinals expel damp heat through urination. *Jin Qian Cao* also promotes the excretion of bile. “All jaundice patients have copious damp heat; in prolonged disease, the channels and vessels must become obstructed and stagnated by static blood.” According to this statement, *Dan Shen* and *Hu Zhang* are added to the prescription so as to clear heat, quicken blood, transform stasis, and resolve toxins. This also follows the saying: “In the treatment of jaundice, blood must be quickened. If blood moves, jaundice will abate.” Furthermore, *Dan Shen* has a beneficial effect on the liver function and is able to shrink a swollen liver and spleen. *Chen Pi* regulates and frees the qi mechanism, rectifies the spleen, transforms dampness, and harmonizes the middle. If the qi mechanism is freed and outthrust, damp heat is eliminated spontaneously.

All the medicinal in combination clear heat and disinhibit dampness, transform stasis and resolve toxins, move qi and abate jaundice. After the children had taken this formula for 3 days, the jaundice was markedly lessened and the serum bilirubin levels were markedly improved. This confirms *Qing Jie Tui Huang Tang*’s effectiveness in the treatment of neonatal jaundice.

[1] Nearly all newborns develop a serum bilirubin above 2mg/dL (note that 1mg/dL = 17.2: mol/mL of bilirubin). According to *Current Pediatric Diagnosis and Treatment*:

“Anthropologically speaking hyperbilirubinemia is likely to confer some biologic advantage if it occurs so often. Bilirubin is a potent antioxidant and peroxyl scavenger which may help the newborn, who is deficient in most antioxidant substances, such as vitamin E, catalase, and superoxide dismutase, to avoid oxygen toxicity in the days after birth.” (48)

Neonatal jaundice is not always pathologic. It is classified as physiologic if the following criteria apply: a) clinical jaundice appears after 24 hours of age, b) total bilirubin rises by less than 5mg/dL (86: mol/mL) per day, c) peak bilirubin occurs at 3-5 days of age with total bilirubin of no more than 15mg/dL (258: mol/mL) and 4) clinical jaundice is resolved by one week in term infants and by 2 weeks in pre-term infants.

There are several different causes for neonatal jaundice. However, all causes affect one of the steps in the bilirubin metabolism. When red blood cells are broken down, heme (of hemoglobin) is metabolised to iron, carbon monoxide (which is exhaled) and biliverdin. Biliverdin is further metabolised to bilirubin. Bilirubin is then bound to albumin and carried into the liver cells. There, it is conjugated (glucuronyl transferase acts as the enzyme and attaches two glucuronide molecules). The conjugated bilirubin is excreted through the bile into the intestine. In the presence of normal gut flora, the conjugated bilirubin is further metabolised to stercobilins and excreted in the stool. In the absence of gut flora or with slow intestinal motility, the conjugated bilirubin remains in the intestinal lumen too long. A mucosal enzyme can then cleave off the glucuronide molecules and convert the conjugated bilirubin back into unconjugated bilirubin. This is then reabsorbed into the blood and circulated back to the liver (enterohepatic circulation of bilirubin).
Clinical jaundice appears at a bilirubin level of 5mg/dL (86: mol/mL). It first appears on the head and progresses down the chest and abdomen as the bilirubin level increases. If the jaundice can be noted on the distal extremities, the level is likely to be at 15mg/dL (258: mol/mL). Generally, infants who develop jaundice on the first day of life or who appear excessively jaundiced require further evaluation.

[2] Kernicterus can also be called bilirubin encephalopathy. It is named for the yellow staining of the subthalamic nuclei (kerns) seen at autopsy. Clinically, early bilirubin encephalopathy consists of lethargy, hypotonia, and poor sucking, progressing to hypertonia, opisthotonos, and a high-pitched cry. Long-term sequelae include cerebral palsy, sensorineural deafness, limitation of upward gaze, and dental dysplasia. Whether or not bilirubin causes more subtle neurologic abnormalities remains debatable. The exact mechanism by which bilirubin is toxic to cells is not clear. It seems that “free” (unconjugated) bilirubin can enter neurons and damage them. It is also notable that bilirubin encephalopathy is very rare with current neonatal management and dangerous bilirubin levels present more often in Asian or Mediterranean babies (see endnote 4 below).

[3] For term infants without hemolysis, the risk of kernicterus is very small. Premature infants are at increased risk because of a compromised blood-brain barrier and lower albumin levels. One common method of determining if the bilirubin level is too high is to define the critical bilirubin level (in milligrams per decilitre) to be 1% of the birth weight in grams (i.e., 12mg/dL for a 1200g infant).

[4] There are two main causes for unconjugated hyperbilirubinemia: increased bilirubin production and decreased rate of conjugation. The latter is rare as only the congenital disease Crigler-Najjar syndrome type I and type II lead to a lack of the conjugating glucuronyl transferase enzyme and therefore to a lack of conjugation in the hepatocytes. (Another congenital disease, Gilbert’s syndrome, is under investigation of possibly also being linked to neonatal jaundice.)

Increased bilirubin production, on the other hand, is a more frequent cause and can result from a haemolytic or non-haemolytic increased rate of red blood cell destruction. Haemolytic increased red cell destruction includes red blood cell incompatibilities, abnormal red blood cells (shapes or enzymes) and bacterial or viral sepsis. Red blood cell incompatibilities mainly refer to ABO incompatibilities (antibodies directed against the major blood group antigens) and Rh incompatibilities (antibodies directed against the minor red cell antigens). The antigen-antibody complex on the red blood cell marks it for destruction. Haemolysis of red cells is also increased if RBCs present with abnormal cell shapes (i.e., spherocytosis, elliptocytosis, etc.; destruction occurs because of decreased red blood cell deformability) or if the cell contains an abnormal enzyme (i.e., G6PD deficiency; a deficiency of G6PD, a cell membrane enzyme, leads to hemoglobin precipitation with changes in the cellular membrane and subsequent haemolysis; G6PD deficiency is a sex-linked (male) congenital disease which most commonly presents people of Mediterranean or Asian descent). Non-haemolytic increased red cell destruction is the result of enclosed haemorrhages, such as cephalatomas, intercranial haemorrhage, or extensive bruising in the skin. The break down of the red blood cells leads to increased bilirubin. Furthermore, polycythemia, a condition in which the red blood cell mass is increased, leads to jaundice because of the increased numbers of red cells which reach senescence and are metabolised.

Causes of prolonged hyperbilirubinemia include Crigler-Najjar syndrome, haemolytic diseases (see above), bowel obstruction, congenital hypothyroidism, galactosemia, and breast feeding problems. Bowel obstruction and congenital hypothyroidism lead to jaundice because the decreased intestinal motility causes the conjugated bilirubin to be unconjugated by a mucosal enzyme and then re-enters the enterohepatic circulation (see above under endnote 1).

Galactosemia is a congenital disease which presents with a lack of the enzyme that catalyses the second step of galactose to glucose. As a result of this metabolic defect, galactose and its metabolites accumulate in the liver and obstruct the normal bilirubin conjugation and circulation. Jaundice secondary to galactosemia presents with mixed hyperbilirubinemia (conjugated and unconjugated bilirubin) and is accompanied by hepatosplenomegaly and hypoglycemia. Breast feeding problems leading to jaundice include the following: breast milk jaundice and lack-of-breast milk jaundice. Breast milk jaundice is believed to be caused by an inhibitor to conjugation in the breast milk of some mothers. The hyperbilirubinemia peaks at 10-15 days of age and declines slowly by 3-12 weeks of age. If nursing is interrupted for 24-48 hours, the bilirubin level falls precipitously and will not rebound to the same level when nursing is resumed.

The second type of breast feeding jaundice, namely lack-of-breast milk jaundice, is due to a decreased enteral intake (little milk intake) and an increased enterohepatic circulation. Because of decreased intake, the bowel motility declines and causes the unconjugation of bilirubin by the mucousal enzyme. This in turn increases the enterohepatic circulation. This may be a sign of failure to
establish an adequate milk supply. If indeed an inadequate intake is present, the infant should receive supplementation with formula and the mother should be instructed to nurse more frequently and to pump her breasts frequently to increase milk production. It is helpful to seek the advice of a lactation specialist.

[5] The authors here refer to treatments which not all are considered standard in the West. The treatment with steroids, for example, is most likely employed in hemolysis due to incompatibility and viral hemolysis (where the immune system has to be down-regulated). This is not standard of care in the West. The albumin transfusions, also not standard of care in the West, increase the binding of unconjugated bilirubin and its transport to the liver for conjugation; this treatment does not help much if the problem lies in the conjugation of the bilirubin (glucuronyl transferase deficiency). However, this treatment does seem to be appropriate in increased unconjugated bilirubin levels due to haemolytic or non-hemolytic breakdown of red blood cells or in cases of unconjugation because of slow gut motility; in both cases, there is an abundance of unconjugated bilirubin in the blood that needs to be bound and transported back to the liver conjugation. Albumin transfusion also seem to help prevent the damaging effect of the bilirubin, as it is unconjugated bilirubin that seem to be neuro-toxic. Phototherapy and fluids are also standards of care in the West. The unconjugated bilirubin in the skin is converted by light of the correct wavelength to a water-soluble bilirubin product which can be excreted in the bile without conjugation. Furthermore, a treatment option employed in the West in very severe cases of Rh incompatibility hemolysis is the invasive and relatively dangerous exchange transfusion. The risk of mortality is greatest in the smallest, most immature, and otherwise unstable infants; however, sudden death during the procedure can occur in any infant.

*The primary source for the commentaries was Current Pediatric Diagnosis and Treatment, 13th ed., William W. Hay et. al., eds., Appleton & Lange, Stamford, CT, 1997, p. 48-52.