## Kampo Medicine - Current Research

# *Kampo (Japanese Traditional) Medicine and Gastrointestinal Symptoms in Pediatric Surgery*

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Summary
With the dramatic improvements in the prognosis of pediatric surgical diseases indefinite symptoms related to the digestive organs associated with prolonged survival are now also frequently observed. For these patients Kampo medicines then become a powerful choice. Frequently used prescriptions in the field of pediatric surgery for diseases of the digestive system *rikkunshito*, *daikenchuto*, *shokenchuto*, *inchinkoto*, *daiokanzoto*, *hangekobokuto*, *yokukansan*, *juzentaihoto* and *hainosankyuto* are outlined here. In order to meet the enthusiasm of pediatric surgeons, Kampo experts must cooperate in efforts to search for new indications.

[Introduction]
The progress in medicine has dramatically improved the prognosis of pediatric surgical diseases. Associated with this progress an increase in indefinite symptoms related to the digestive organs due to the prolonged survival has been observed. Yet, further improvements in postoperative long-term quality of life (QOL) and ADL (Activities of Daily Living) still need to be achieved. Under these circumstances the value of Kampo medicines has received attention for their action in adjusting the general condition of the patients. Moreover, during daily clinical pediatric surgical practice, even if surgery is not required, many patients are counseled regarding symptoms of the digestive organs and Kampo medicines are at that time a powerful choice. In this manuscript we will discuss first mainly pediatric surgical diseases of the digestive organs and later would like to outline the frequently used prescriptions in the field of pediatric digestive system diseases *rikkunshito* (Liu Jun Zi Tang), *daikenchuto* (Da Jian Zhong Tang), *shokenchuto* (Xiao Jian Zhong Tang), *inchinkoto* (Yin Chen Hao Tang), *daiokanzoto* (Da Huang Gan Cao Tang), *hangekobokuto* (Ban Xia Hou Po Tang), *yokukansan* (Yi Gan San), *juzentaihoto* (Shi Quan Da Bu Tang) and *hainosankyuto* (Pai Nong San Ji Tang) with reference to clinical trials.

[Overview of pediatric surgical diseases]
1) Gastroesophageal Reflux Disease (GERD)
Based on the anatomical characteristics a mild reflux from the stomach into the esophagus happens in all infants. It occurs in 50% of newborn under three months of age and 67% of the 4-month old, but resolves often spontaneously when the infants start to assume a sitting position. The gastroesophageal reflux in 10% of infants under 1 year of age is said to be associated with complications. The symptoms associated with gastroesophageal reflux are called Gastroesophageal Reflux Disease (GERD). A portion of these symptoms are due to hypoactivity of the sphincter of the lower esophagus. Persistent reflux causes inflammation of the lower esophagus. Due to the still immature faculty of speech of the infants, they cannot complain of heartburn and the condition may manifest as bad mood, frequent crying, decreased appetite, abdominal pain, throat pain, asthma, chronic cough, middle ear infection etc. This shows, that once these infant specific characteristics are understood, in cases of indefinite complaints of the upper abdomen or a variety of other symptoms, the possibility of GERD should also be suspected. Also, since experience has shown, that the use of Kampo medicines in infants is comparatively safe, their application is worth a try.
Actually, in addition to the clinically easy development of gastroesophageal reflux in infants, aerophagia, constipation, frequent crying, excessive feeding of milk and other factors may contribute to the condition. *Rikkunshito* is used as the drug of choice for infants with GERD, but when aerophagia is the main aggravating factor, *hangekobokuto* and similar prescriptions can be effective. Even if the drug of choice

is not effective, Kampo medicines may be advantageous if there is a next therapeutic choice.

2) Anal atresia (anorectal anomaly)

Anal atresia is properly called anorectal anomaly. This anomaly is caused by incomplete development of the urorectal septum separating the urogenital sinus and the anorectal region, persisting cloacal duct or deficient opening of the anal membrane. There is no sex difference in incidence rate. The condition is classified into a high level type above rectum and coecum, an intermediate level and a low level type. Frequently fistulas develop between the lower end of the rectum and urethra on one side and the perineum on the other side. Approximately 70% of anorectal anomalies are complicated by some other form of anomaly. Complication of anorectal anomaly with spinal anomalies, cardiac anomalies, esophageal atresia, renal malformation and the like are called VATER (or VACTER, VACTERL) association.

Presentations made on academic conferences regarding Kampo treatment following surgery for anorectal anomalies are mainly reports dealing with the use of Daikenchuto.

Management of bowel movements following surgery for anorectal anomalies, in particular maintenance of normal bowel movements and toilet training, is extremely important. Measures like enemas etc. are a great burden on the guardians and meet at higher age of the children with greater resistance. It is not an overstatement, that toilet training towards independent evacuation until a time when communal life like school starts, will affect the future of that particular child. Examination of the development of the rectal muscle group allows to assess, whether the constipation is mainly of organic origin, or whether training will likely lead to improvement. In cases of a high probability of improvement through training, Kampo medicines play an important role as supportive treatment promoting in particular independent evacuation.

3) Hypertrophic pyloric stenosis

Hypertrophic pyloric stenosis is a disease characterized by continuous vomiting in newborn and hypertrophy of the pyloric ring. Fiberscopic surgery has developed as curative surgery for hypertrophic pyloric stenosis and the number of cases is increasing, but there is still no agreement as to whether fiberscopic surgery is actually the optimal therapy for this condition. The continuous vomiting is considered to be due to the hypertrophic pyloric ring, but spasms of the pyloric muscles themselves are also a conceivable cause for the vomiting treated with atropine sulfate. If the treatment of this disease with atropine sulfate is done appropriately, most of the cases are cured[1]. Prior to oral administration 6 times/day, 0.01 mg/kg is administered intravenously and when the vomiting has stopped, the regimen is switched to 0.02 mg/kg per os 6 times/day. A gradual increase in the uptake of milk paralleled by a gradual reduction of the atropine sulfate dose led in 45 out of 52 patients (87%) to a cure without complications. The average duration of the hospitalization was 13 days. In those patients in whom the administration of atropine sulfate was not effective, r*ikkunshito* was reportedly effective[2]. There is a possibility that a combination therapy may lead to an earlier improvement.

4) Hirschsprung's disease

Hirschsprung's disease is a congenital functional obstructive disease of the intestines where the gangliocytes of the intestinal canal are lacking from the anal side extending towards the mouth, impairing the peristaltic movements of the intestinal canal. The range of the aganglionosis varies widely, but the prognosis worsens in proportion with the size of the aganglionic region. The condition is classified as follows.

(1) short segment aganglionosis: the aganglionic region is restricted to the sigmoid colon, 70-80%

(2) long segment aganglionosis: the aganglionic region extends past the descending colon towards the mouth, 20%

(3) total colon aganglionosis: the aganglionic region affects the entire colon, 1-2%
(4) extensive aganglionosis: the aganglionic region extends into the small intestines, 2%
(5) ultra-short segment aganglionosis: an aganglionic region is observed within the lower third of the anorectal canal, 4-5%.

Treatment consists of resection of the aganglionic region of the intestines. When the region affected by the aganglionosis is limited, the condition often runs a favorable course. However, in conditions like (3) and (4) marked by extensive areas of aganglionosis postsurgical diarrhea or colonitis may easily develop and progress into septicemia and shock. Further, due to a reduction is the absorption intravenous nutrition is required over a prolonged period. The general condition and parameters including the nutritional state, electrolytes, urinary volume etc. must therefore be carefully observed.

In particular in cases of extensive resections destruction of the intestinal bacterial flora through the use of antibiotics is undesirable. However, because infants are easily susceptible to infections, the use of antibiotics is often necessary. For common cold or upper respiratory infections the early use of Kampo medicine can avoid the administration of antibiotics and is thus extremely important. The authors often use *shoseiryuto* or *kakkonto* for sick children. *Maoto* was mostly unsuitable following surgery of the gastrointestinal tract, because the condition is predominantly one of "spleen deficiency". Usually administration of *kenchuto* resembling formulas tends to result in a lower susceptibility to common colds. Although it is difficult to provide evidence to substantiate this claim, Kampo medicine played definitely an important role in the improvement of the individual conditions.

5) Hirschsprung's disease related diseases

Chronic and continuous intestinal obstruction caused by deficient or absent of normal peristaltic movements of the intestinal tract are refractory diseases. These include Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome (MMIHS), Chronic Idiopathic Intestinal Pseudo-Obstruction (CIIP) and hypoganglionosis.

In these diseases the regions affected by the lesions are often very large and the distribution of gangliocytes throughout the intestinal tract is not uniform. Prolonged central venous hyperalimentation is required and bowel movement management extremely difficult, rendering the long-term prognosis poor. Causes of death include infection of the central venous catheter and a transition towards bacterial translocation from enteritis can lead to sepsis. Recently, transplantation of the small intestine has also been attempted, but the choice of donors difficult because of the strong rejection. Occasionally relevant case reports describe that *daikenchuto* was markedly effective for MMIHS or CIIP[3-5]. This is highly significant. When the author administered Shokenchuto to patients with CIIP in his care, septicemia and enteritis due to repeated central venous hyperalimentation infections already led to the loss of absorption from the intestinal tract and therefore, so that the formula did not show any effects at all. Through the early introduction of Kampo medicine, provided bowel movement management is possible, the vicious cycle of enteral infections or intestinal dysfunction can be broken and there is a sufficient probability of improvement in the long-term prognosis. Further investigations in this field are desirable.

6) Perianal abscess

Perianal abscesses are relatively common in outpatients during infancy and the incidence is higher in boys. This suggests an immunological immaturity restricted to the anorectal region that is characteristic of infancy[6]. Most cases heal spontaneously, but there may be repeated recurrences and treatment periods often extend over long periods. Ambulatory treatment for pain and care of the wound etc. pose a great burden on the sick child and its family. In the past incision of the abscess and administration of antibiotics constituted the mainstream therapy, but the number of reports on the value of using Juzentaihoto have increased[7-10]. It is not an exaggeration to state, that it has already been

established as a therapeutic drug for the treatment of perianal abscess. Juzentaihoto is compounded of ginseng, cassia bark, *Cnidium rhizome*, *Rehmanniae* Radix, hoelen, *Atractylodes rhizome*, *Astragali* Radix, angelica root, peony and *Glycyrrhiza glabra*. Examination of the composition reveals, that this formula is a combination of *shimotsuto* and *shikunshito* with the addition of cassia bark and *Astragali* Radix. In addition of supplementing Qi and Blood it conceivably also has exterior supplementing effects. In particular *Astragali* Radix is said to have diuretic and swelling dispersing, internal expulsion and detoxifying actions, which would explain the effectiveness of Juzentaihoto for perianal abscesses.

Recently published reports describe *hainosankyuto* as being effective during the acute phase of perianal abscesses. Also, while no clinical studies have been published yet, there have been related reports on academic conferences. *Hainosankyuto* is comprised of *Zizyphi fructus*, orange pease, peony, platycodon, *Glycyrrhiza glabra* and ginger. Asada Sohaku too mentioned that the effect of this formula is "due to the combination of orange pease and platycodon". By combining *hainosan* and *hainoto* the pus discharging action is amplified.

Regarding the combination of orange pease and peony the "Synopsis of the Golden Chamber" (Jin Kui Yao Lue) also stipulates in the section for Kijitushakuyakuto: "for abdominal pain after delivery, when a person cannot lie down because of vexation and fullness, *kijitushakuyakuto* will control this … and at the same time controls abscesses". This shows, that it acts to dispel some kind of swellings by relieving muscle tension. During the acute phase of perianal abscesses tumors are formed from pus, so that discharge of this pus leads to healing. That is why administration of Hainosankyuto during the acute phase has adequate effects. Further investigations in this field are desirable.

[Explanation of the individual formulas]

1) *Rikkunshito*

For loss of appetite, early feeling of fullness during meals, gastric discomfort, stomach-upset and similar digestive symptoms found not only in adults, but also in infants. When in case of infants the food intake continues to be low because of these symptoms, they may impair growth, making it necessary to achieve improvements earlier than in adults.

The concept expressed by the general term Functional Dyspepsia (FD), which is characterized by continuing epigastric digestive symptoms in adults, even if organic diseases have been ruled out, has been proposed and here too *rikkunshito* has received attention as one therapeutic choice. *Rikkunshito* increases the discharging capacity of the stomach and improves the adaptive relaxation of the stomach. This conceivably results in improvement of the so-called early satiety during meals. The L-arginine content of this formula, providing the substrate for the nitric oxide (NO) involved in causing an appropriate adaptive relaxation of the stomach, is probably related to this action[11].

In the period following pediatric digestive organ surgery electrogastrography reportedly verified the effectiveness of *rikkunshito* for epigastric indefinite symptoms in the absence of organic diseases. Following administration of Rikkunshito (0.2 g/kg/day (tid)) for an average of 10 months improvement of the irregularities in gastric myoelectric activity were observed[12]. For the pathologic condition a combination therapy with the H2 blocker famotidine (0.8 mg/kg/day (bid)) and Rikkunshito (0.2 g/kg/day (tid)) was used and after disappearance of the clinical symptoms improvements of the irregularities in gastric myoelectric activity were observed. This suggests, that a combination therapy using famotidine and Rikkunshito possibly contributes to improvements in gastric myoelectric activities and the coordination of the latter[13]. Also, according to recent reports based on improvements in symptoms and esophageal pH monitoring, a decrease in the duration of esophageal acid exposure and acid clearance time have been observed in pediatric patients with GERD. This

suggests, that treatment of GERD with Rikkunshito alone too seems to be possibly under certain circumstances[14]. Moreover, some reports describe that this formula improved the delay in gastric emptying time in GERD after cardioplasty in children with severe psychosomatic disorders[15].

In the field of pediatric surgery there is frequent counseling for pediatric patients presenting with upper gastrointestinal symptoms, but in whom surgery of the digestive organs is not indicated. In these cases too *rikkunshito* represents an important therapeutic choice. Then again, *rikkunshito* probably promotes appetite by increasing the secretion of active ghrelin16). Thus, it is also effective for loss appetite, even if there are no obvious upper gastrointestinal symptoms.

From the long-term perspective, after administering *rikkunshito* some effects like improved appetite, alleviation of stomach upset and epigastric bloating, improvement of growth impairment and fatigue are often observed. Prognosis can be assumed to be favorable, when *rikkunshito* is continued for several months, in case effects have been observed at this point of time. It is further important to instruct the patients to use single doses, if symptoms should recur.

2) *Daikenchuto*

*Daikenchuto*, first mentioned in the "Synopsis of the Golden Chamber" (Jin Kui Yao Lue), is a formula compounded of 2 parts of *Zanthoxylum piperitum*, 5 parts of *Zingiber siccatum* and 3 parts of ginseng with added malt extract. The source text states: "severe cold pain in chest and heart, vomiting and inability to eat or drink, chilling within the abdomen, rising of Qi from the abdomen to the hypochondrium, it emerges from the skin and flows up- and downwards to the head and feet; thus *daikenchuto* cures people suffering from pain that cannot be approached or touched." Thus this formula is considered to be beneficial for conditions abdominal pain and vomiting due to chilling and where abnormal peristaltic movements of the intestines are observed in the abdominal region.

Pharmacologically this formula is said to have peristalsis adjusting actions and increases blood flow in the intestinal tract. It has been clarified, that this action is mediated by the calcitonin gene related peptide (CGRP). Daikenchuto promotes the release of CGRP by peripheral nerves, induces RAMP1, initiates generation of large amounts of CGRP1 receptors and thereby increases the blood flow in the intestinal tract[17]. In the field of adult surgery it is frequently used for postsurgical intestinal movement disorders (ileus), where it shortens the time until the first postoperative flatus and thus reportedly contributes to a shortening of the hospital stay[18]. The improvement of postsurgical ileus induced by this formula is presumably due to an improvement in peristaltic movements of the intestinal tract, which in turn is brought about but the increased blood flow in the intestines. This formula has been reported to be useful in pediatrics for the treatment of postsurgical adhesive intestinal obstruction or early postsurgical recovery from dysperistalsis[19,20]. This applies in particular for the use as a conservative treatment for postsurgical ileus infusion of the formula through an ileus tube[19,20]. Additionally, it has also been reported to improve constipation or evacuation disorders following surgery for anorectal anomalies in infants[20-24] as well as chronic constipation[20,24].

For Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome (MMIHS), a functional anomaly of the intestinal tract or Chronic Idiopathic Intestinal Pseudo-Obstruction (CIIP) the available western medical therapies are currently limited.

Postsurgical constipation is frequent in infants, where chilling of the intestinal tract is one of the causes for dysperistalsis, so that *daikenchuto* is the drug of first choice. This does not contradict the Kampo medical concepts pertaining to d*aikenchuto*. Moreover, the formula is indicated in healthy infants too, when chilling adversely affects intestinal movements. However, in case it should be ineffective, other Kampo formulas need to be considered.

The dose of 6 packages of *daikenchuto* extract per day for adults is rather large, but this dose serves only as a

rough estimate and can be increased or decreased as appropriate. Since *daikenchuto* is a warming formula, it should be dissolved in hot water and then allowed to cool before ingesting, but if ingestion is difficult, commercially available jelly, wafers or a little honey can also be added.

Administered for the treatment of ileus 1 package of *daikenchuto* is dissolved in 50 ml of hot water, allowed to cool and then infused through an ileus tube. After application of an appropriate amount and clamping the ileus tube for 30 to 60 minutes the contents is released. Similarly dissolved material can also be applied in form of enemas. The above described treatment is administered as required once to three times a day.

*Zanthoxylum piperitum, Zingiber siccatum* do provide a sort of warming stimulus. Since *Zanthoxylum piperitum* "disperses cold dampness, but people with lung and stomach heat avert it" *daikenchuto* may not be suited in cases of heat in the intestinal tract. In terms of Kampo medical concepts infants are considered to have a purely yang body, they tend to be hotter than adults and therefore *daikenchuto* is rarely indicated in healthy infants. Accordingly, it happens that while *daikenchuto* had been effective during postsurgical recovery, the infants suddenly cannot tolerate it any longer. In this case it can be necessary to temporarily discontinue the administration or switch to a different formula. It must not be forgotten, that the condition of the body constantly changes.

3) *Daiokanzoto*

In the "Synopsis of the Golden Chamber" it says: "for people who immediately vomit on eating, *daiokanzoto* controls the condition". It is used for a condition, where people vomit immediately after meals due to poor flow in the intestines. Also, the entry pertaining to Daiokanzoto in Asada Sohaku's text "Butsugo Yakushitsu Hokan" reads: "when there is no desire for the so-called 'southern fume' of this formula, you must first open the 'northern lights', meaning that the stomach content closed up in the stomach must be guided as stool to prevent it from upsurging and to stop the vomiting." Thus, like opening a small window on the north to let in a southern breeze in order to guide the obstruction in the stomach towards the excrements will prevent the vomiting caused by upsurging. Regarding this usage the formula has a wide range of application as a Kampo medicine.

Pharmacologically the sennoside content of the rhubarb is broken down by intestinal bacteria and after reduction metabolized into potent laxative rheinanthrones stimulating the colonic submucosal neural plexi in the intestinal wall to promote the movements of the smooth muscles. Subsequently the colonic mucosal epithelial cells inhibit the phosphodiesterase activity and thereby inhibit the absorption of water, salts, glucose, xylose etc.[25-26]. The transport capacity of the small intestine is not affected, so that the amount of feces and its water content increase dose independently and thereby promote bowel movements. Compared to an application of rhubarb alone increased tenesmus at the onset of the laxative action can be significantly inhibited when using *daiokanzoto*[26,27]. Moreover, renal function is also improved and without affecting urinary pH a marked increase in urinary output and electrolyte (Na, Cl) excretion has been observed. The tanine content of rhubarb increases renal blood flow and the glomerular filtration rate, leading to an improvement in renal function[26-28].

There are only few reports on the use of *daiokanzoto* for infants, but it has been reported useful for severe constipation in school children[29] and reportedly be effective in 56% of patients with constipation following treatment for Hirschsprung's disease[30]. As stated above, in cases of constipation in infants after surgery or diseases *daikenchuto* is the drug of first choice. This happens often when in healthy infants changes in dietary habits led to a febrile syndrome of the viscera, i.e., separation of clear and turbid elements in the colon is not processing smoothly. In this case this rhubarb containing formula should be taken into consideration. Concretely, it is considered useful when patients complain of accumulation of scatomas in the colon,

constipation due to hardened feces, abdominal pain due to the accumulation of feces or vomiting or else decreased appetite. Moreover, even if *daikenchuto* is useful, occasionally combination with *daiokanzoto* allows the treatment form so eloquently described as "when there is no desire for the so-called southern fume of this formula, you must first open the northern lights".

4) *Inchinkoto*

*Inchinkoto* has first been mentioned in the "Treatise on cold-induced diseases" (Shang Han Lun) and "Synopsis of the Golden Chamber" and is compounded of three crude drugs, namely of 3 parts of *Artemisiae capillaris flos*, 1 part of rhubarb and 4 parts of gardenia. Pharmacologically, the gardenia constituents iridoid glucoside geniposides and the intestinal metabolite Genipin have a non-bile acid dependent cholagogic action, activate a bilirubin transporter (multidrug resistance-associated protein: Mrp2), while the *Artemisiae capillaris flos* constituent dimethylesculetin reportedly has a relaxing action for the sphincter of Oddi[31,32]. Also, in rat models of hepatic fibrosis the concentration of liver hydroxyproline, serum hyaluronic acid increase, the expression and activation in hepatic extracellular matrix (type III procollagen mRNA) increases while the proliferation of activated Kupffer cells is inhibited, thereby allegedly inhibiting the development of hepatic fibrosis[33].

Cases of clinically effective treatment of patients with delayed postsurgical biliary atresia, recurrent icterus, liver function failure with Inchinkoto have been reported[34-37]. Following administration of Tsumura's Inchinkoto extract for a period of 2 to 4 years after surgery for the treatment of pediatric postsurgical biliary atresia, improvements in serum GOT, GPT, γ-GTP and hyaluronic acid levels were observed. While similar improvements of serum GOT and GPT over time were observed in non-treated patients too, the serum γ-GTP and hyaluronic acid levels did not improve over time. This confirmed liver protective and anti-liver fibrotic effects of Inchinkoto[35].

Also, adult cases of delayed onset hyperbilirubinemia following liver transplantation with small-for-size grafts also suggest the possibility, that Inchinkoto will lead to improvements. In the field of pediatric surgery too the number of liver transplants for the treatment of biliary atresia is increasing and applicability of this formula in infants seems conceivable.

Conclusions

Kampo therapy too is about to develop into an established therapeutic choice in the field of pediatric surgery. This can also be interpreted as a manifestation of the enthusiasm with which pediatric surgeons use those choices, as long as they lead to improvements in their patients. Kampo expert physicians should cooperate in order to investigate new indications and thus respond to the aforementioned enthusiasm. Since individual differences are particularly marked in infants, the therapy for each individual patient must be considered separately. If that is done, still greater developments are expected to be accomplished for Kampo therapy in the field of pediatric surgery.

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