

Effect of the Herbal Medicine Dai-Kenchu-To on Gastrointestinal Motility in Patients with Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome (MMIHS) and Chronic Idiopathic Intestinal Pseudo-Obstruction (CIIP): Report of Two Cases

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(Received July 16, 2008; Accepted February 25, 2009)

Dai-kenchu-to (DKT), a traditional Japanese herbal medicine (Kampo medicine), composed of zanthoxylum fruit, ginseng root, dried ginger rhizome and malt sugar, is clinically effective for postoperative ileus and chronic constipation. MMIHS and CIIP are severe motility disorder associated with high morbidity. The aim of this study was to evaluate the effect of DKT on functional intestinal obstruction.

DKT was clinically effective for gastrointestinal motility in a case with MMIHS, but not effective in one with CIIP. MMIHS and CIIP are speculated to have different pathogenesis regarding gastrointestinal pseudo-obstruction based upon the effect of this drug.

Key words: Dai-kenchu-to, herbal medicine, gastrointestinal motility, megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), chronic idiopathic intestinal pseudo-obstruction (CIIP)

INTRODUCTION

Dai-kenchu-to (DKT), a traditional Japanese herbal medicine (Kampo medicine), composed of 20% zanthoxylum fruit, 30% ginseng root, 50% dried ginger rhizome and malt sugar, is clinically effective for postoperative ileus, chronic constipation and irritable bowel syndrome (IBS) [1]. Megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMIHS) and chronic idiopathic intestinal pseudo-obstruction (CIIP) are Hirschsprung's disease that severe motility disorder associated with high morbidity [2]. MMIHS, a visceral myopathy causing intestinal obstruction in the newborn, is a generally fatal condition, with death being secondary either to sepsis or to malnutrition if long-term intravenous nutrition is not provided [3]. CIIP is a rare feature but it is well characterized and should be treated as a primary visceral myopathy related to the striated and smooth muscle degenerative process [4]. We describe our experience with two cases with MMIHS and CIIP in whom of DKT was used for poor gastrointestinal motility. We compared clinical findings before and after using DKT in the both cases, and the aim of this report was to evaluate the effect of DKT on functional gastrointestinal obstruction.

CASE REPORT

Case 1: A 22-year-old female, the longest survival of MMIHS patient who required for home parenteral nutrition (HPN) has high out-put (2-5 liter/day) intestinal juice from upper jejunostomy. She was born at 36 weeks' gestation and her birth weight was 4050 g.

She had a hugely distended abdomen, and a plain radiography showed a mass of soft tissue (full bladder by urine) displacing the stomach and the diaphragm (Fig. 1a, b). The bladder was easily catheterized with recovery of 1200 ml of urine, resulting in decreased abdominal distention. She showed pneumoperitoneum on the second day of life and emergency laparotomy was performed. A thin-walled stomach with a sealed perforation and dilated proximal jejunum were found. Partial gastrectomy and tube jejunostomy were performed and the normo-ganglionosis of the biopsied specimen, which made us diagnose of this syndrome. Repeated operations, including Martin's side-to-side anastomosis failed to build a functional intestinal tract. Martin's side-to-side anastomosis of the jejunum and the descending colon was done to increase absorptive capacity. Although it was not functioning, we performed small bowel resection and right colostomy due to increase retention time to improve absorption (Table 1, Fig. 2). She has to live with an eventual stoma at the upper jejunum and parenteral fluid and nutritional replacement has been necessary. Cyclic TPN with home parenteral nutrition (HPN) and 43 times of CV catheterizations maintained her life but resulted in major vein occlusions, which made access through traditional way so difficult that percutaneous transhepatic IVC catheterizations have been utilized for 8 years (Fig. 3). It is difficult to give a fully nutrition by enteral feeding, but she has been able to eat and taste every foods as same as ordinary people. When she was 21 years olds, she felt appetite loss and her condition were changed, if tried to eat foods, easy to vomit. Her

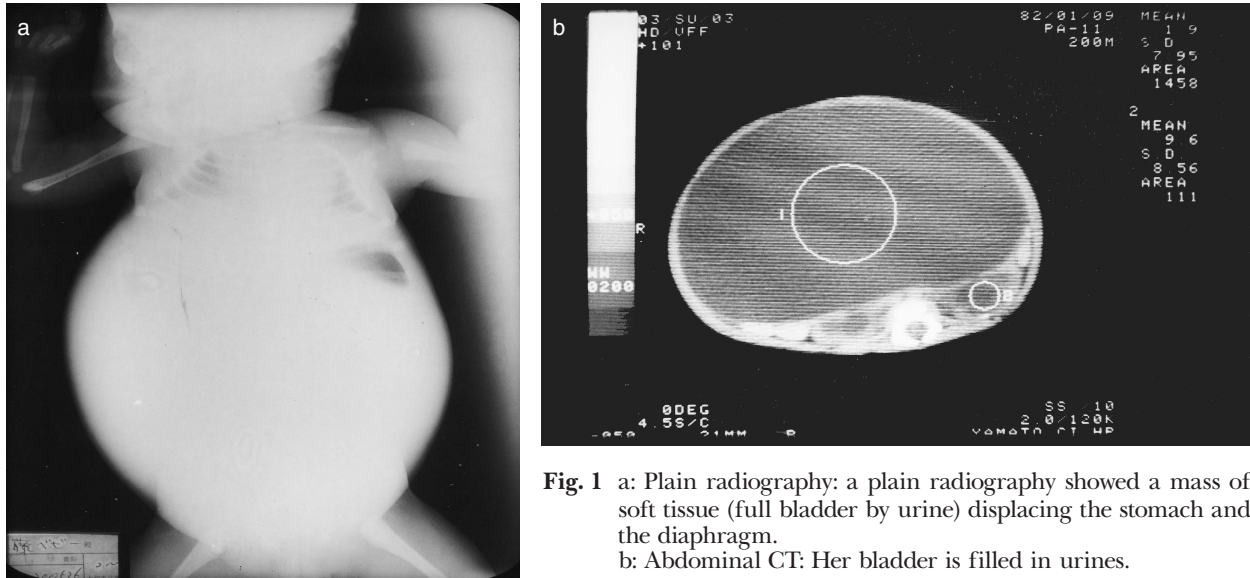


Table 1 Surgical procedures

| No. | Procedures | Age | Rationale |
|-----|---|------------|---|
| 1 | Partial gastrectomy Tube jujunostomy | 2nd day | Gastric perforation Ileus |
| 2 | Tube ileostomy | 1 mo | Irrigation of meconium |
| 3 | Marin's side-to-side jujunocolostomy | 1 yr 2 mo | Increase absorptive capacity |
| 4 | Diverting jujunostomy | 1 yr 3 mo | Leaking anastomosis |
| 5 | Closure of diverting jujunostomy | 1 yr 4 mo | |
| 6 | Small-bowel resection Right colostomy | 2 yr 3 mo | Increase retention time to improve absorption |
| 7 | Tube jejunostomy | 4 yr 2 mo | Recurrent ileus |
| 8 | Closure of jujunostomy Jejunocolostomy | 13 yr 4 mo | Easier stoma management Increase retention time to improve absorption |

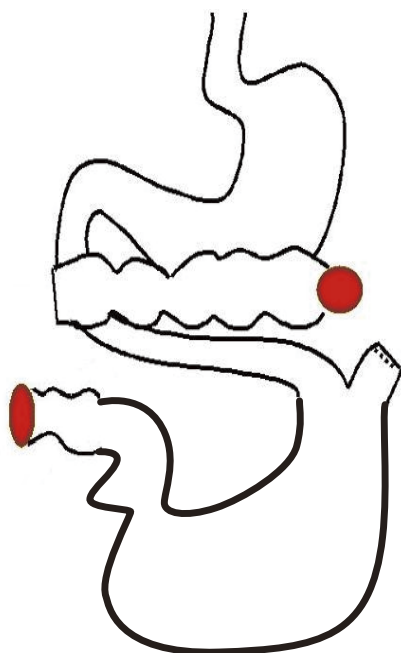


Fig. 2 8th surgical procedure (13yr 4mo): We performed small bowel resection and right colostomy due to increase retention time to improve absorption



Fig. 3 Percutaneous transhepatic IVC catheterization: Major vein occlusions, which made access through traditional way so difficult that percutaneous transhepatic IVC catheterizations have been utilized.



Fig. 4 Abdominal finding: She showed pneumoperitoneum on first day of life and her abdomen was so distended.

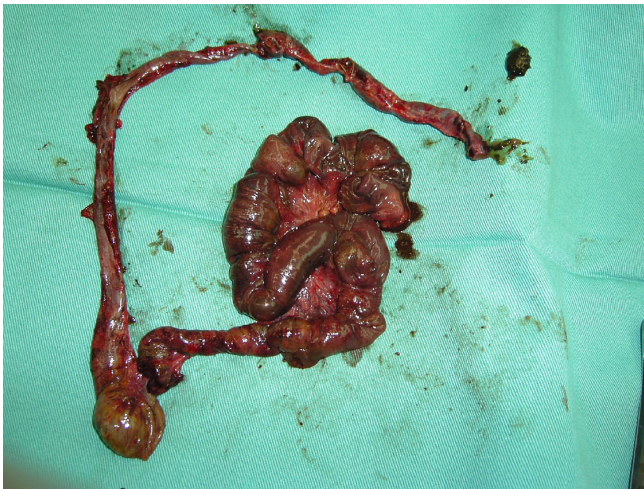


Fig. 5 Surgical specimen: Total colon and small intestine were fell into necrotizing enterocolitis, consequently most intestine include colon were resected and made a stoma at the upper jejunum length 60cm.

upper GI series was showed a plenty of fluid stasis in stomach. She was firstly given erythromycin (EM, 1500 mg/day, DIV), but her symptoms did not change. Then, we chose to give her DKT (15 g/day). Next day, nausea disappeared, and subsequent good appetite was restored. She said us “DKT is the most effective medicine in her life”.

Case 2: A 6-month-old girl, CIIP patient was born at 39 weeks' gestation and her birth weight was 3272 g. She showed pneumoperitoneum on first day of life and emergency laparotomy was performed (Fig. 4). Total colon and small intestine were fell into necrotizing enterocolitis, consequently most intestine include colon were resected and made a stoma at the upper jejunum length 60 cm (Fig. 5). Surgical specimen showed necrotizing enterocolitis with gram-negative rod bacterial infection through the intestinal wall and

there are observed normal size and number ganglion cells in both small intestine and colon (Fig. 6a, b).

Abdominal distension and bile vomiting were seen in spite of plenty of green discharge from jejunostomy. Therefore, she has functional ileus and her diagnosis was made CIIP. We started to give prokinetic treatment, and she was firstly given DKT (0.3 g/kg/day), but her condition did not change, then given erythromycin (25 mg/kg/day), symptoms resolved immediately. Her upper GI series was proved to improve a stasis of barium contrast in the dilatated intestine in spite of output from jejunostomy for 26 days. But after administration of erythromycin, barium contrasts were easy to move-out from intestine (Fig. 7). It is showed her clinical course in the table (Table 2). Discharge from jejunostomy was seen on 8th days of operation, oral diet was started on 3 weeks after jejunostomy, but

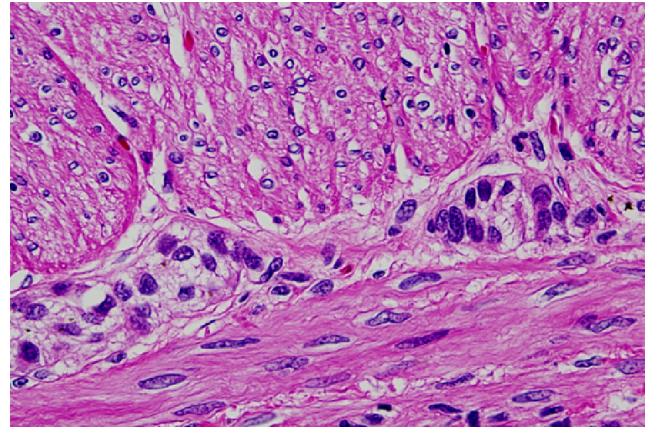
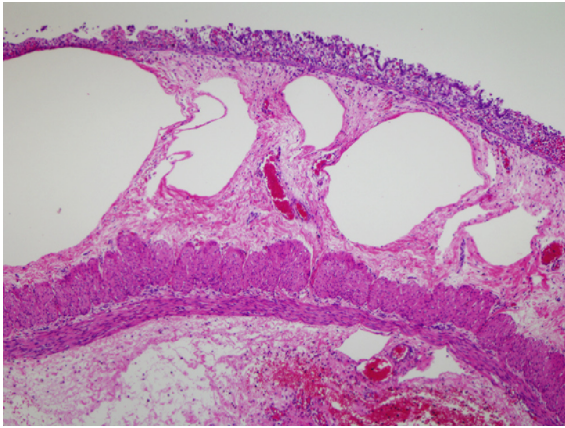


Fig. 6 Pathological findings
 a: Surgical specimen showed necrotizing enterocolitis.

b: There are observed normal size and number ganglion cells in both small intestine and colon.

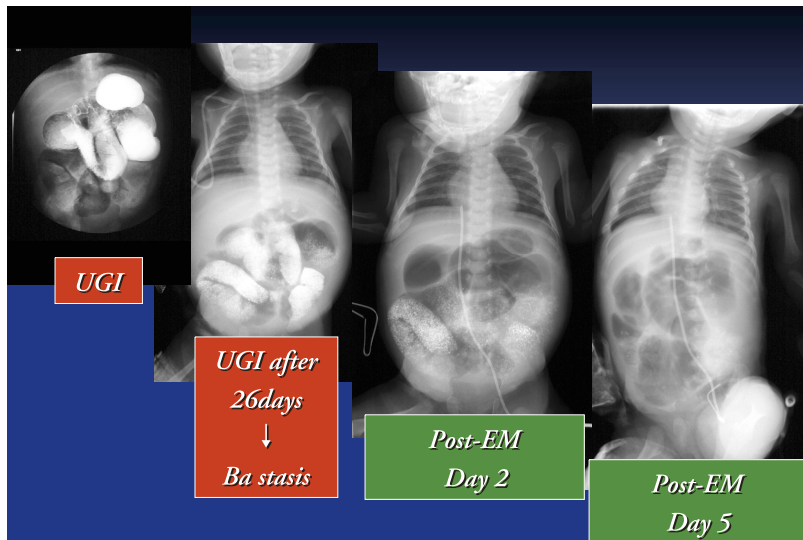
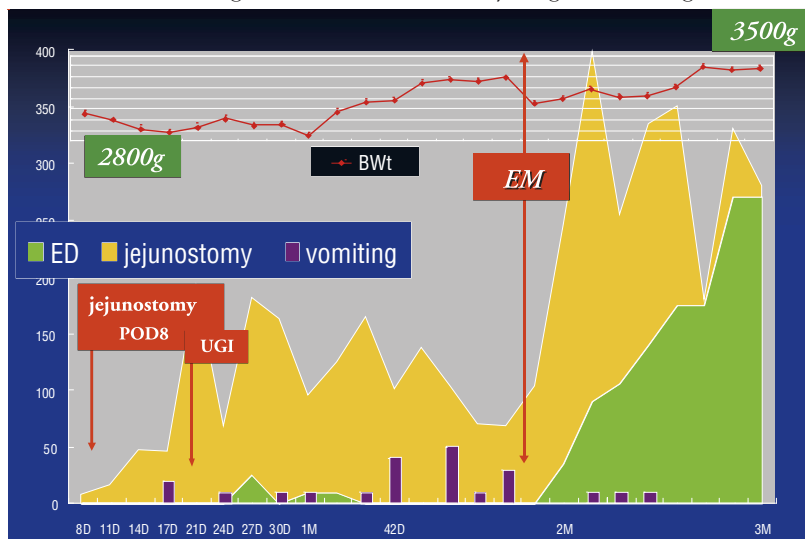


Fig. 7 Barium clearance after EM: Her upper GI series was proved to improve a stasis of barium contrast in the dilatated intestine in spite of output from jejunostomy for 26 days. But after administration of erythromycin, barium contrasts were easy to move-out from intestine.

Table 2 Clinical course of pre/post EM: After administration of erythromycin, amount of discharge from jejunostomy were more increased, and frequency of vomiting were decreased. Oral feeding was also increased. Body weight was also gained after EM.



easy to vomit green bile, and we gave up her oral diet. But after administration of erythromycin, amount of discharge from jejunostomy were more increased, and frequency of vomiting were decreased. Oral feeding was also increased. Body weight was also gained after EM.

DISCUSSION

CIIP and MMIHS are characterized by the failure of the intestinal tract to propel its contents appropriately. This leads to signs and symptoms of bowel obstruction and, in the absence of an associated systemic disorder or the administration of drug known to result in bowel dysmotility, are termed CIIP or MMHIS [5]. MMIHS is congenital disorder characterized by hypoperistalsis with microcolon, malrotation and non-obstructive urinary bladder filled plenty urine [3]. So the diagnosis of MMIHS at birth is not so difficult for that peculiar morphologic appearance. The other side, CIIP occur more often as secondary to diseases in adult but most commonly a primary abnormality in children. Analysis of published studies has shown that most patients of CIIP develop symptoms in the first year of life, often in the neonatal period. 44 CIIP series of Heneyke *et al.* show 24 children (55%) developed obstructive symptoms during the 1st month of life: 18 (75%) were sick at birth. A further 8 (18%) developed symptoms during the first year and 10 (23%) before the third year of life. So 73% of CIIP patients develop symptoms in the 1st year of life [6]. CIIP is one of the diseases that gastrointestinal motility disorder without lumen obstructed lesion. There are variety kinds of names for CIIP resemble disorder; chronic idiopathic intestinal pseudo-obstruction syndrome (CIIPS), chronic intestinal pseudo-obstruction (CIP), pseudo-Hirschsprung's disease, gastrointestinal dysmotility (GID) [7]. MMIHS is also considered to be the most severe form of CIIP in which onset is antenatal period [8].

Chinese treatises from nearly 2 thousands years ago describe herbal formulations and symptoms for treatises formulation. Japanese practitioners develop a system framework of Kampo treatment in the 17 or 18 centuries. Today, Japanese Kampo medicines are distinct from traditional Chinese medicines [9]. DKT is one of the most popular Kampo medicines in Japan. There are many pharmacological researches concerning DKT and using it widely in Japan [1]. DKT has several functions to intestine that regulations of motility mediated by many neurotransmitters or receptors on smooth muscles, increasing blood flow in mesenteric artery and anti-inflammatory effects inhibited by COX-2 so that DKT is clinically useful for treatment of abdominal distention, adheisional ileus, postoperative intestinal paralysis, pediatric constipation and irritable bowel syndrome. [10] There is a few reports regarding the clinical experience with DKT for MMIHS and CIIP in only Japan. Yamazaki *et al.* showed DKT is effective for MMIHS (1 year old girl), but not CIIP (12 years old boy) as same result for us [11]. Kakita *et al.* showed their 3 months old MMIHS case improve intestinal motility for using DKT [12].

The other side, erythromycin is also using to regulate intestinal motility. Itoh *et al.*, while studying the effects of erythromycin in dogs, noted that the drug

stimulated strong gastric antral contractions similar to those induced by motilin [13]. Frederick *et al.*, motilin is to play a role in contractile activity that occur in the fasting state, known as the migrating motor complex (MMC) [14]. Fasting gastrointestinal motility in humans is characterized by regular cyclic activity of the MMC, which may be used as an objective indicator of intestinal motility [15]. Motilin appears to be involved in stimulating or recruiting the gastrointestinal contractions during phase III of MMC.

Pathology of MMIHS and CIIP are still unknown. MMIHS patients have normal ganglion cells in the gastro intestine on histologic examination, so the hypothesis for MMIHS have induced disturbance in myocellular contractile fiber synthesis, imbalance between gut peptides, intestinal myopathy, neuroaxonal dystrophy, and defective autonomic inhibitory neuroeffector activity [16]. The mechanisms of enteric neuromuscular dysfunction of CIIP can be classified into three major entities; neuropathies, mesenchymopathies, and myopathies, depending on the predominant involvement of enteric neurons, interstitial cell of Cajal (pacemaker activity in gastrointestinal tract), or smooth muscle cells [17]. Although against each of these mechanisms of MMIHS and CIIP may be responsible for DKT, combined roles of DKT may also coexist in the same patient. We have just clinical experienced data only and there is no pharmacological, manometric and electrophysiological research report about using gastrointestinal tissues with MMIHS and CIIP combine with DKT so it is difficult to say why DKT is effective for MMIHS but not CIIP in our cases. Because intestinal dysmotility of MMIHS and CIIP are difficult to manage and have a high mortality rate, intestinal transplantation is currently the only therapeutic option that would allow these patients to survive. But we can show possibility of new therapeutic approaches to MMIHS and CIIP by Japanese herbal medicine DKT. We need further combined clinical and histological studies in order to elucidate the pathology of MMIHS and CIIP.

CONCLUSION

DKT was clinically effective for gastrointestinal motility in MMIHS, but not effective in CIIP in our cases. MMIHS and CIIP have a different mechanism regarding gastrointestinal pseudo-obstruction.

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