

Original Article

Observations on the curative effect of lactulose for postpartum constipation based on a large sample study

Yu Zhou¹, Xinghua Yang², Ling Fan³, Yuanfang Zhu⁴, Yurong Jiang⁵, Zhen Li⁶, Guoping Xiong⁷, Jingxin Shen⁸, Zhihong Su⁹, Ping Wu¹⁰, Danrui Wang¹¹, Xietong Wang¹

¹Department of Obstetrics, Shandong Province Hospital, Jinan 250014, Shandong, China; ²School of Public Health, Capital Medical University, Beijing 100069, China; ³Department of Obstetrics, Beijing Gynaecology and Obstetrics Hospital of Capital Medical University, Beijing 100069, China; ⁴Department of Obstetrics, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi, China; ⁵Department of Obstetrics, Maternal and Child Health Hospital of Hunan Province, Changsha 410008, Hunan, China; ⁶Department of Obstetrics, Xinqiao Hospital, Chongqing 400037, Sichuan, China; ⁷Department of Obstetrics, Wuhan Central Hospital, Wuhan 430014, Hubei, China; ⁸Department of Obstetrics, The Third Xiangya Hospital of Central-South University, Changsha 410013, Hunan, China; ⁹Department of Obstetrics, Lanzhou General Hospital of Chinese People's Liberation Army, Lanzhou 730050, Gansu, China; ¹⁰Department of Obstetrics, Chongqing Three Gorges Central Hospital, Chongqing 404000, China; ¹¹Department of Obstetrics, The Second Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang 830028, China

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Abstract: To evaluate the efficacy and safety of lactulose in the intervention treatment of postpartum women with constipation. **Methods:** The study adopted the multicenter clinical survey with a big sample which enrolled 4781 valid questionnaires from postpartum women in 18 different districts. All of them were treated with lactulose oral solution. Their constipation-related symptoms and routine examination on blood, urine and stool were monitored before and after lactulose intervention. The treatment duration lasted 2 weeks and all the patients were followed for 4 weeks. **Result:** Their stool consistency, daily defecation frequencies, defecating time and dyschezia were improved significantly after lactulose intervention, and the good therapeutic effect was remained at the off-medication session. Furthermore, abnormal rate of each index in blood, urine and stool examination showed a decreased trend. **Conclusion:** Lactulose offered good therapeutic benefit and could be developed as an effective intervention to postpartum women with constipation.

Keywords: Postpartum, constipation, lactulose

Introduction

Constipation is a common clinical disorder in gastrointestinal tract, which seriously affect the life quality of patients. As the special characteristics of physical and psychological for postpartum women, they had the higher prevalence of constipation than others. The prevalence of postpartum constipation was estimated to be up to 24% at three months postpartum period as reported by Bradley [1]. Its symptoms may include infrequent defecation, lumpy or hard and dry stools, sensation of incomplete evacuation, anorectal obstruction, or the use of manual manoeuvres [2]. The postpartum women with constipation often in the situations of abdominal distension/pain, headaches,

insomnia, emotional irritability and loss of appetite. In severe cases, hemorrhoids, prolapse and other postpartum complications might occur. Such physical discomforts seriously influenced the mother's postpartum recovery and galactopoiesis. If the postpartum constipation did not receive timely or proper treatment, there is a higher possibility to develop into chronic conditions, and even influenced the function of pelvic floor. As the major challenge for most of the postpartum women, postpartum constipation had received a lot of attentions.

A wide range of pharmacological agents have been used in the treatment of constipation for ordinary patients, but their usage for postpar-

tum women were limited by the needs of lactation. Although there were few interventions specially tailored for postpartum constipation, some of them for general constipation can also be used to postpartum period [3]. Among them, lifestyle modifications which include adequate fibre and water/fluids in the diet as well as proper levels of physical activity can help to relieve the symptoms of constipation [4]. Chinese herbal medicine was also reported as intervention in treating postpartum constipation [5]. Due to the special period for postpartum constipation patients, non-pharmacologic management is their first choice. Hence, simply, effective and noninvasive interventions with the least possible adverse effects to mother and her newborn baby are in a urgent need to be explored.

Lactulose is a semi-synthetic disaccharide and can be used in the adjustment of circadian rhythm for colon. As an osmotic laxative, it is a non-absorbable, non-metabolic agent and harmless to breastfeeding babies. Meanwhile, it also acted as Prebiotic to improve the micro-environment of mother's gastrointestinal tract. It has been approved by Food and Drug Administration (FDA) for the treatment of constipation and widely used in the treatment of constipation for elderly [6], pregnant women [7], children [8] and so on.

In this study, we conducted a research on the efficacy and safety of lactulose for the treatment on the postpartum constipation on a large sample. Lactulose was applied as the basic treatment to the participants coming from 18 provinces in China. Their daily defecation frequencies, stool consistency, defecating time and dyschezia were monitored to evaluate the changes of constipation-related symptoms before and after treatment. We resorted to this large multicenter study to elucidate the effectiveness of lactulose for postpartum constipation, and make guidance on the clinical usage for doctors.

Materials and methods

Participants

4806 participants were recruited from the obstetrics clinics after cesarean section at different hospitals in 18 different provinces between October 2011 and April 2012. They had no postpartum complication, the average

age and weight were 27.65 ± 4.75 years old and 68.21 ± 10.42 kg, respectively. The study protocol was approved by the Ethics Committee of each hospital which has been incorporated into this study. All the patients signed informed consent document before participation.

Interventions

The lactulose oral solution (purity level in 0.667 g/mL) was obtained from Hanmi Pharm, Co., Ltd. Participants received 2 or 3 administrations with an initial total dose of 22 mL lactulose per day. The following dose was adjusted according to the changes of their defecation frequencies, stool consistency, defecating time and other constipation symptoms. The maintenance total dose was ranged in 11-14 mL per day and divided into 1 or 2 administration(s). The treatment duration was 2 weeks and all the patients were followed for 4 weeks.

Assessment

The self-administered questionnaires were completed and collected. The questionnaire includes the items of defecation frequencies, stool consistency, defecating time, defecation difficulty and any other symptoms. Meanwhile, adverse events together with the blood, urine and stool routine testing were monitored. After a 4-week follow-up after the lactulose interventions, a total of 4781 valid questionnaires were collected. All the data were recorded into Epidata and processed by SPSS software. The rank sum test was used to analyze the ranked data. The comparisons were made at a two-sided α level of 0.05 unless noted otherwise.

Results

Stool consistency

Stool consistency was recorded by Bristol Stool Scale [9], ranging from 1 (separate hard lumps, like nuts) to 7 (watery, no solid pieces). Typed 1-2 indicate constipation, with 3 and 4 being the ideal stools (especially the latter), as they are easy to defecate while not containing any excess liquid, and 5, 6 and 7 tending towards diarrhoea [10]. The proportion variations of stools in typed 1-2 and 3-4 were shown in **Figure 1**. Compared with the distribution of different stool consistency before lactulose interventions, there was an apparent decline in typed 1-2 and increase in typed 3-4 at each

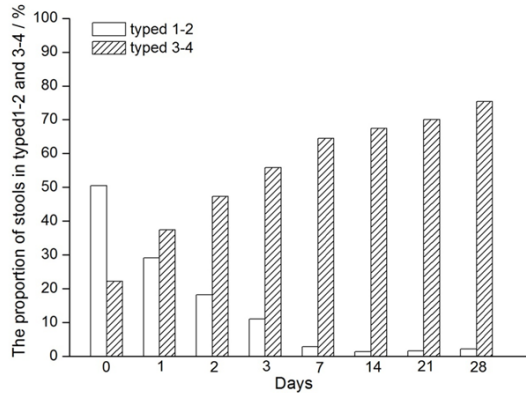


Figure 1. The proportion of stool consistency before and after lactulose interventions.

observing time, the differences were statistical significance ($P < 0.01$). A steady proportion of different stool consistency was reached at the 7th day after interventions, and the good therapeutic effect on constipation was remained at the off-medication session.

Defecation frequencies and defecating time

Participants were asked to record the time of each bowel movement occurred and the number of weekly bowel movement. The time taken to defecate was shortened by the use of lactulose, the mean defecation time was 12.5886 min for every bowel movement before interventions, and that for the first 3 days after taking lactulose were 9.7909, 8.4023 and 7.3660 min, respectively. The defecating time tended to be stable at about 5 min after 7 days, and kept at this time 2 weeks after the lactulose withdraw. The mean frequency of defecation was not changed a lot after lactulose interventions (6.5863 times/week vs 7.1253 times/week).

Defecation difficulty

The extent of defecation difficulty was categorized into five grades [11]: Grade I, normal defecation; Grade II, straining during a bowel movement; Grade III, obvious defecation difficulty and hard or lumpy stools; Grade IV, sensation of incomplete evacuation and anorectal obstruction/blockade; Grade V, resort to manual maneuvers to facilitate defecations. Defecation condition before and after lactulose treatment were shown in **Table 1**, symptoms in Grade II to V were regarded as defecation difficulty. Compared with the defecation condition

before treatment, the proportion of participants without difficulty in bowel movements was improved significantly (31.7% vs 85.9%-91.8%) in both the initial days and two weeks after lactulose administrations. There were significant differences in the proportions of different defecation difficulty grading ($P < 0.01$).

Abdominal pain and bloating

The participants were asked to report abdominal pain and bloating after consuming lactose, from no symptoms to severe pain/bloating (by using a scale: no symptoms, mild, moderate or severe). The proportion of participants without discomfortable gastrointestinal symptoms has increased gradually at each observing time (**Table 2**). Statistic by rank sum test showed that there were obvious differences ($P < 0.01$) before and after treatment from the aspect of the improvement in abdominal pain/bloating.

Routine examination of blood, urine and stool

The evaluation parameters included blood, urine, and stool routine examinations [red blood cells (RBC) count, white blood cells (WBC) count and hemoglobin (Hb), thrombocyte in blood; WBC, RBC, ketone body, glucose and protein in urine; WBC, RBC and occult blood in stool]. According to Chi-square test (shown in **Table 3**), abnormal rate of each index in urine and stool routine examinations showed a downward trend and established significant difference ($P < 0.01$ or $P < 0.05$). For blood examinations, no distinct changes occurred in abnormal rate of RBC and Hb, while that of WBC and thrombocyte have reduced significantly ($P < 0.01$).

Discussion

There was a higher possibility for women to experience constipation during the postpartum period. This discomfort brought concerns and stresses to the new mothers, and actually interfered with their postpartum recovery. The occurrence of postpartum constipation had a close relationship with the unique characteristic of pelvic floor and physiological features during pregnancy. Generally, the serious problems are caused by the following reasons: the compression to rectum by fetus was disappeared after delivery, the reactivity of enterocolic was increased and the wastes were easy to be stayed in intestine; the injuries brought by the

Lactulose for the postpartum constipation

Table 1. The analysis of defecation difficulty before and after lactulose treatment, *n* (%)

Extent of defecation difficulty	0 day	2 days	3 days	7 days	14 days	21 days	28 days
No difficulty							
Grade I	1516 (31.7%)	3131 (65.5%)	3583 (74.9%)	4301 (90.0%)	4391 (91.8%)	4105 (85.9%)	4282 (89.6%)
With difficulty (Grade II to V)							
Grade II	1138 (2.38%)	683 (14.3%)	664 (13.9%)	190 (4.0%)	135 (2.8%)	180 (3.8%)	163 (3.4%)
Grade III	577 (12.1%)	382 (8.0%)	153 (3.2%)	92 (1.9%)	15 (0.3%)	16 (0.3%)	9 (0.2%)
Grade IV	539 (11.3%)	123 (2.6%)	73 (1.5%)	9 (0.2%)	0 (0.0%)	3 (0.1%)	10 (0.2%)
Grade V	133 (2.8%)	17 (0.4%)	9 (0.2%)	1 (0.0%)	1 (0.0%)	3 (0.1%)	2 (0.0%)
Total	3903 (81.7%)	4336 (90.7%)	4482 (93.8%)	4593 (96.1%)	4542 (95.0%)	4307 (90.1%)	4466 (93.4%)
System-missing	878 (18.3%)	445 (9.3%)	299 (6.2%)	188 (3.9%)	239 (5.0%)	474 (9.9%)	315 (6.6%)
Z		-26.053	-40.413	-54.048	-57.641	-55.062	-56.362
P		0.000	0.000	0.000	0.000	0.000	0.000

Table 2. Percentage variations of subjects without discomfortable symptoms (%)

	0 day	2 days	3 days	7 days	14 days	21 days	28 days
Without abdominal pain	52.4	77.1	82.5	89.8	92.5	88.4	91.4
Without abdominal bloating	44.3	66.0	75.5	90.2	92.1	87.7	91.3

Table 3. Comparison of the abnormal rate in routine examinations

	Before	After	χ^2	P
Blood routine examinations				
Hb	2.5	2.3	1.681	0.195
RBC	3.1	2.7	0.917	0.338
WBC	9.1	5.0	24.678	0.000
Thrombocyte	3.6	1.6	17.754	0.000
Urine routine examinations				
WBC	28.8	14.4	107.911	0.000
RBC	27.1	15.0	107.911	0.000
Protein	11.5	3.7	112.050	0.000
Ketone body	6.1	1.3	97.199	0.000
Glucose	2.5	0.8	24.421	0.000
Stool routine examinations				
WBC	1.3	0.3	30.515	0.000
RBC	1.2	0.4	14.467	0.000
Occult blood	0.7	0.2	6.183	0.013

surgery or trauma to the cesarean parturient have inhibited the intestine peristalsis and absorption; the reduced contractility of abdominal muscle and pelvic floor muscle; lower physical activity and unreasonable dietary pattern, all those factors have contributed to the postpartum constipation [12].

For women in gestation, constipation was one of the most common afflictions. It might accompany with those pregnant women in their whole pregnancy, or even continued to the postpartum period. Recently, prolonged straining to

pass stool is suggestive of pelvic floor dysfunction [13]. Pregnancy and natural or cesarean delivery was regarded as the main factors of pelvic floor dysfunction. On one hand, constipation was one of the symptoms for postpartum woman with pelvic floor dysfunction. On the other hand, long-term straining during bowel movements generated injury to pelvic floor nerve. This vicious circle further aggravated inconsistencies between constipation and pelvic floor dysfunction [14].

Higher concentrations should be paid to postpartum constipation for the potential permanent impairment without improper interventions. As the representative of osmotic laxatives, lactulose is not absorbed in the intestine and can be broken down by human enzymes, and thus stays in the digestive bolus and does not appear in breast milk, mothers' normal lactation as well as blood sugar level was not disturbed. Due to the higher-severity and no threat to infants it presented, lactulose was a proper treatment for constipation during pregnancy and postpartum period. In this study, a survey with multicenter and large-sample was conducted to evaluate the efficacy and safety of lactulose. The results showed that the stool consistency, defecation frequencies, defecating time and dyschezia grading were improved significantly after intervention. After 1 week of lactulose administration, more than 60% of the participants were stabilized at the normal stool

consistency, and the defecating time was shortened from 10 min to 5 min, and nearly 90% of the participants without defecation difficulty in 2 weeks after complete cessation. The lactulose intervention was given in consecutive 2 weeks, the doses used was adjusted according to patients' response from the initial 22 mL to 12-19 mL. The full course of appropriate lactulose guaranteed the good curative effect and avoided the recurrences of constipation at the same time. The improved defecation condition was still kept after lactulose withdrawal. For routine laboratory examination, the abnormal rate of each index has dropped significantly.

Nowadays, there were little research conducted on a large sample [12], a prospective and multicenter as well as large-scale trial was desperately needed. The samples in this study came from 18 different districts and the diet compositions as well as postpartum diet customs were varied between different districts. As the diet had a close relationship with the occurrence of constipation, the large sample in this study provided wider presentation, which suggested the study was effective and extensive. But, it was limited by the lack of control study, and the questionnaire employed as the style of follow-up with the unavoidable defects of subjectivism, one-sidedness and incompleteness. In future research, double-blind controlled studies and further long-term follow up are needed. In conclusion, through this study, it should be noted that postpartum constipation could be reduced or avoided absolutely by timely and effective interventions. Under the circumstance of no serious complications occurred, most of the patients employed self-medication, rather than resort to doctors for individual guidelines, which might cause long-term health risks. More attentions should be paid to the postpartum women with constipation. Prevention is the first and it is better than treatment, lactulose could be used as a proper and safe intervention, which contributed to the formations of regular defecate habits as well as their postpartum recovery.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xietong Wang, Department of Obstetrics, Shandong Province Hospital, Jinan 250014, Shandong, China. Tel:

+86053187938911; Fax: +86053187904002;
E-mail: xietongwang18@126.com

References

- [1] Bradley CS, Kennedy CM, Turcea AM, Rao SS and Nygaard IE. Constipation in pregnancy: prevalence, symptoms, and risk factors. *Obstet Gynecol* 2007; 110: 1351-1357.
- [2] Higgins PD and Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004; 99: 750-759.
- [3] Turawa EB, Rohwer AC and Musekiwa A. Interventions for treating postpartum constipation. *Cochrane Database Syst Rev* 2014; 9: CD010273.
- [4] Derbyshire E, Davies J, Costarelli V and Dettmar P. Diet, physical inactivity and the prevalence of constipation throughout and after pregnancy. *Matern Child Nutr* 2006; 2: 127-134.
- [5] Cheng CW, Bian ZX and Wu TX. Systematic review of Chinese herbal medicine for functional constipation. *World J Gastroenterol* 2009; 15: 4886.
- [6] Sanders J. Lactulose syrup assessed in a double-blind study of elderly constipated patients. *J Am Geriatr Soc* 1978; 26: 236-239.
- [7] Signorelli P, Croce P and Dede A. A clinical study of the use of a combination of glucomannan with lactulose in the constipation of pregnancy. *Minerva Ginecol* 1996; 48: 577-582.
- [8] Dupont C. PEG versus lactulose in childhood constipation. *J Pediatr Gastroenterol Nutr* 2004; 39: S553.
- [9] Lewis S and Heaton K. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997; 32: 920-924.
- [10] Vandenplas Y and De Hert S. Randomised clinical trial: the synbiotic food supplement Probiotical vs. placebo for acute gastroenteritis in children. *Aliment Pharmacol Ther* 2011; 34: 862-867.
- [11] Thompson WG, Longstreth G, Drossman D, Heaton K, Irvine E and Müller-Lissner S. Functional bowel disorders and functional abdominal pain. *Gut* 1999; 45: II43-II47.
- [12] Müller M and Jaquenoud E. Treatment of constipation in pregnant women. A multicenter study in a gynecological practice. *Schweiz Med Wochenschr* 1995; 125: 1689-1693.
- [13] Cullen G and O'Donoghue D. Constipation and pregnancy. *Best Pract Res Clin Gastroenterol* 2007; 21: 807-818.
- [14] Soligo M, Salvatore S, Emmanuel AV, De Ponti E, Zoccatelli M, Cortese M and Milani R. Patterns of constipation in urogynecology: clinical importance and pathophysiologic insights. *Am J Obstet Gynecol* 2006; 195: 50-55.