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Mirabilite and Lactulose Improves Postoperative Gastrointestinal Mobility among elderly patients undergoing abdominal surgery

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Wenyan PAN [1#]; Shining CAI[1#]; Jos M. LATOUR[2]; Ming ZHONG[3]; Minzhi LV[4]; Jingjing LI[1]; Xiaomin ZHANG[5]; Yuxia ZHANG[1*]

1. Department of Nursing, Zhongshan Hospital, Fudan University, Shanghai, 200032, China

2. School of Nursing and Midwifery, Faculty of Health and Human Sciences, University of Plymouth, Plymouth, UK

3. Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, 200032, China

4. Department of Biostatistics, Zhongshan Hospital, Fudan University, Shanghai, China

5. Faculty of Nursing, Fudan University, Shanghai, China

#Equal contribution: Wenyan Pan and Shining Cai should be considered joint first author.

*To whom correspondence should be addressed: Yuxia Zhang Tel: 86-21-64041990, Email: zhang.yuxia@zs-hospital.sh.cn

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Conflict of interest

No conflict of interest has been declared by the authors.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ABSTRACT

Aims: To evaluate the feasibility and efficacy of Mirabilite combined with Lactulose in older patients after abdominal surgery.

Design: It is a retrospective observational cohort study with a pre and post intervention group.

Methods: Medical records were retrospectively reviewed of postoperative Intensive Care patients with postoperative gastrointestinal tract dysfunction (aged >60 years) in the Surgical Intensive Care Unit from January 2017 - December 2018.

Results: One hundred and sixty-seven post-surgical Intensive Care patients with postoperative gastrointestinal tract dysfunction were analysed; 74 patients received Mirabilite + Lactulose treatment and 93 patients received Lactulose treatment. The recovery rate of bowel sounds was better in the Mirabilite+Lactulose group (62.16%) compared with the Lactulose group (37.63%) after three-day treatment (p=0.002) and the Relative Risk (RR) was 1.65 (95% CI, 1.20, 2.27). Moreover, 70.27% patients in the Mirabilite+Lactulose group finally had flatus or defecation compared with 46.24% patients in Lactulose group (p=0.003) and the RR was 1.52(1.17, 1.98). The abdominal girth and Inter Abdominal Pressure in Mirabilite+Lactulose group showed significantly greater decrease over a 3-day period compared with Lactulose group (4.86 vs. 3.46 cm, p=0.027; 4.80 vs. 3.11 mmHg, p=0.002, respectively). The pain score had greater decrease from the baseline in Mirabilite+Lactulose group than in Lactulose group (2.40 vs. 1.11; p<0.01). Patients in the Mirabilite+Lactulose group had shorter hospital stay than the Lactulose group (12.5 SD 3.51) versus 13.9 (SD 5.14), p=0.05).

Conclusions: This study demonstrated that external use of Mirabilite combined with Lactulose can be considered as an easy intervention to improve postoperative gastrointestinal mobility in

older intensive care patients who suffer from postoperative gastrointestinal tract dysfunction after surgery.

Impact: Our results provide a great option to alleviate the sufferings of postoperative patients. The externally use Mirabilite is a painless and safe interventions that is easy to implement by ICU nurses.

Key words: Mirabilite, intensive care, nursing, postoperative gastrointestinal mobility, intra-abdominal surgery

INTRODUCTION

Postoperative Gastrointestinal Tract Dysfunction (PGID) is one of the most common and bothersome symptoms in patients after intra-abdominal surgery, especially for the older patients[1, 2]. Bowel frequency of older patients is more susceptible to be influenced by several factors, including alterations in dietary habits, type of anaesthesia, immobility and psychological morbidity after surgery[3]. PGID is associated with increased patient suffering, morbidity, cost of care and length of hospital stay[4, 5]. Despite the potential hazard and persistent discomfort, PGID has been largely ignored[6]. The clinical signs of PGID including abdominal distension, lack of bowel sounds and delayed passage of faeces and/or flatus. The pathogenesis of PGID is multifactorial which is still lack of effective measurements. The inhibition of luminal contents clearance and edema of intestinal wall significantly contributes to the elevation of intra-abdominal pressure (IAP) and further to distension[7]. The growing girth resulted from distension may cause incisional pain or even anastomotic leakage, which should be vigilant during the early days after intra-abdominal surgery. Lactulose is commonly used for intestinal dysfunction in postoperative patients in the Surgical Intensive Care Unit (SICU). Mirabilite, also named Natrii sulfas or Glauber's salt, is a hydrous sodium sulphate mineral with the chemical formula $Na_2SO_4 \cdot 10H_2O$. Mirabilite is a traditional medicine to promote intestinal peristalsis and attenuate tissue edema in Asian countries.

Background

Numerous pharmacological strategies have been used in the treatment of PGID, such as cholecystokinin, metoclopramide and vasopressin[8]. However, the use of drugs to stimulate the bowel in the postoperative period has been disappointing[8]. Additionally, traditional strategies

to treat PGID, such as the use of nasogastric tube drainage, prokinetic drugs and the avoidance of early fluid and/or food intake, are apparently not beneficial[5]. Some studies have stated that abdominal massage can effectively alleviate abdominal distension and constipation[9]. However, massage is not a suitable intervention for surgical patients undergoing abdominal surgeries as it may influence initial wound healing. Traditional Chinese Medicines (TCMs) becomes a popular treatment for improving gastrointestinal mobility in the Chinese population. Growing evidences have shown that some TCMs could obtain satisfactory results in controlling IAP[10]. A systematic review of 15 studies looking at the effect of TCM identified three studies specifically testing Mirabilite[10]. These studies demonstrated that applying Mirabilite could obtain satisfactory results in controlling IAP of critically ill patients and significantly improve prognosis[10]. It is reported that external use of Mirabilite can create a hypertonic solution that can inhibit moisture absorption and promote intestinal peristalsis in rats[11]. Despite the promising effect of Mirabilite documented in these few studies, the reports of external use of Mirabilite in older patients remains limited. Based on the previous studies and the mechanism of Mirabilite, our study aims to explore the effectiveness of Mirabilite on the PGID of older patients after intra-abdominal.

THE STUDY

Research question

If Mirabilite combined with Lactulose could better alleviate PGID than Lactulose only?

Aims

The aim of this study was to evaluate the effectiveness of external use of Mirabilite combined with Lactulose to improve gastrointestinal mobility in older ICU patients after intra-abdominal surgery.

Design

It is a retrospective observational cohort study with a pre and post intervention group. The study adhered to the quality of standard of performing studies[12] and has been reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies [13].

Setting

The study was conducted in the SICU of a tertiary teaching hospital. The 28-bedded SICU has annually around 2,450 admissions of postoperative patients.

Participants

We retrospectively reviewed the medical and nursing records of all older patients (age >60 years) who received Mirabilite or/and Lactulose for PGID after intra-abdominal surgery from January 2017 - December 2018 at the SICU of our hospital. The exclusion criteria were acute peritonitis, intestinal obstruction, Acute Physiology and Chronic Health Evaluation II (APACHE II) score > 30 or undergoing mechanical ventilation. Since February 2018, our SICU department cooperated with Traditional Chinese Medicine department to apply a new protocol to patients with PGID. Therefore, we divided patients into two groups: 1) Patients receiving Lactulose only from January 2017 - January 2018 (L group, N=93); and 2) Patients receiving M+L from February 2018 - December 2018 (M+L group, N=74).

Data collection

Primary outcomes

The primary outcomes were defined as the recovery of gastrointestinal mobility after three-day treatments, which was measured by the bowel sounds and the time of first defecation or flatus postoperatively. Bowel sounds were defined as the number of bowel sounds in one minute by listening to the abdomen with a stethoscope, which were counted by nurses every day in the morning. Since all patients were immobile, defecation was cared for by nurses and flatus was reported by asking the patients.

Secondary outcomes

Secondary outcomes including the abdominal girth, IAP and pain level after three-day treatments and the length of hospital stay. Measurement and record of these outcomes were completed by well-trained nurses. The girth was defined as the circumference of the abdomen and measured at the umbilicus. Intra-abdominal pressure was measured via the bladder through the urinary catheter [14, 15]. When measuring the IAP, patients were placed in a supine position and 25mL of saline was instilled into the bladder via a urethral catheter port. The zero reference point was taken as the level of the superior iliac crest at the midaxillary line [16]. NRS (Numerous Rating Scale) was used to evaluate the pain level of patients at 2pm every afternoon.

Ethical considerations

The study protocol was approved by the Ethics Committee of our hospital (Approval No.: B2017-121) and the requirement for informed consent was waived because of the retrospective nature of the study.

Data analysis

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc. Chicago). Data were expressed as mean and Standard Deviation (SD) or proportion and non-normally distributed variables were analyzed using medians and interquartile ranges. Continuous variables were compared by Student's t-test or Mann-Whitney U test and categorical variables were compared by chi-squared test or Fisher's exact test, as appropriate. The comparison of bowel sounds, and defaecation used the chi-squared test or Fisher's exact test as appropriate. The relative risk (RR) is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. Relative risk measures the association between the exposure and the outcome.

The risk difference (RD) is the difference between the risk of an outcome in the exposed group and the unexposed group. The abdominal girth, IAP and NRS of two groups were compared by repeated measures ANOVA; if Mauchly's test was significant, the Greenhouse-Geisser estimates were used to compare the effect of M+L in reducing abdominal girth and IAP in both groups. A $p<0.05$ was considered statistically significant.

Validity and reliability

All patients were treated with the same standard basic treatment, including intensive vital signs monitoring, gastrointestinal decompression on the first postoperative day, vitamin supplement and parenteral antacids. In addition, Lactulose only treatment (N=93) or M+L treatment (N=74) was adopted to treat PGID. External use of Mirabilite was conducting by placing it on the skin of the abdomen. To facilitate immobilization of Mirabilite on the abdomen and prevent the distortion of drainage tube, specially made belly bands with small bags were designed and applied. In the M+L group, 2Kg Mirabilite divided into four times (500g per time) was

administered to patients per day from 9am to 9pm for at least three days. Mirabilite was wrapped in gauze and externally placed on the abdomen by putting them in the bags of belly bands (Electronic Supplement Material 1). Patients in both groups received Lactulose solution (10ml each time) by oral administration or via nasal-gastro tube three times a day, at 8am, 12pm and 4pm, respectively. All these treatments were lasted at least three days.

RESULTS

Patient Characteristics

Finally, 167 patients were enrolled in the study. In total 74 and 93 patients in each group were included in the analysis (Figure 1). Baseline patient characteristics were similar between the two groups. No significant differences were observed in age, gender, APACHE II score. Patients in the M+L group had similar abdominal girth (109.81 vs. 111.49cm, $p>0.05$) and IAP (18.26 vs. 18.71mmHg, $p>0.05$) compared with the L group before treatment (Table 1).

Outcomes

As to the frequency of bowel sounds, 62.16% patients in M+L group recovered their bowel sounds to at least three times/min after 3-day treatment, while only 37.63% patients in Lactulose group recovered ($p=0.002$) and the RR was 1.65 (95%CI, 1.20, 2.27). We found 70.27% patients in the M+L group finally had flatus or defecation compared with 46.24% patients in Lactulose group ($P=0.003$) and the RR was 1.52 (1.17, 1.98). Additionally, we compared accumulative number of patients who recovered their gastrointestinal mobility each day after treatment. The primary outcomes were both showed significant recovery after 2-day treatment. The results showed, more patients recovered the bowel sounds in M+L group

(43.24%) than the L group (26.88%) from day 2 (P=0.033) and the RR was 1.61 (1.05, 2.46) (Table 2).

The mean abdominal girth and IAP of both groups decreased between the start of the treatment and 3 days after the treatment. Although the girth and IAP decreased over time, the repeated measures analysis determined the girth and IAP were significantly different between two groups (Table 3). The line graphs presenting the decreasing trends of girth and IAP in different time points, the girth and IAP in M+L group showed significantly greater decrease (Figure 2). Abdominal discomfort using NRS score significantly decreased in both groups, the repeated measures analysis showed the mean decrease of NRS was significantly greater in the M+L group than in the L group (Table 2). We also compared the duration of hospital-stay between the two groups by calculating the mean and SD. Patients in the M+L group had shorter hospital stay than the Lactulose group; 12.5 (SD 3.51) versus 13.9 (SD 5.14), p=0.05.

DISCUSSION

For PGID, there are limited effective interventions described in the current evidence base. In our study, we demonstrated that Mirabilite might improve the gastrointestinal mobility in older patients in the ICU after surgery.

External use of Mirabilite place on the skin of the abdomen to stimulate gastrointestinal motility is easier and more comfortable. Some studies reported that applying Mirabilite can help treat severe acute pancreatitis and prevent acute gastrointestinal injury in older patients with severe sepsis[10, 18, 19]. Yang discovered that external use with Mirabilite helps lowering IAP in patients with abdominal compartment syndrome [20]. Besides, combination with other

drugs was also common when applying Mirabilite. Sun[21] combined external use of Mirabilite with Liqitongbian decotion by nasal feeding or enema lowered IAP and reduced the length of hospital stay. Wu[22] applied Mirabilite with Chaishaochengqi decotion to reduce IAP and APACHE II score in critically ill patients. Consistent with previous studies on patients with IAP and severe abdominal compartment syndrome, Mirabilite combined with Lactulose showed great effects on PGID in older patients. Our study showed that external use of Mirabilite + lactulose can greatly elevate efficacy compared with lactulose only. More patients in M+L group had recovered normal bowel sounds and had defecation during treatment than in L group. Moreover, the standard of intro-abdominal hypertension is above 12mmHg and the IAP of patients in the study group decreased to 13.46mmHg which is almost close to normal level. The promotion of bowel sounds also resulting the relieve of abdominal pain. Consistently, the NRS score had greater decrease from the baseline in M+L group than in L group. Although the duration of hospital-stay had small difference between two groups, the results of this study may indicate therapeutic or clinical benefits for these patients; further studies are needed to confirm this. Therefore, our study indicated that the benefits of Mirabilite may help solve the issue of PGID that might bother the older intensive care patients. Notably, to our best knowledge, this is the first study to investigate the efficacy of Mirabilite in older patients with serious PGID.

The biological mechanism of Mirabilite is known as the following two aspects. The crystal osmotic pressure of Mirabilite is significantly higher than human tissue, the external application of Mirabilite can form a hypertonic environment locally and the tissue water can be exuded by the action of osmotic pressure, so that magnesium sulfate and water in the

Mirabilite form hydrated ions to dissolve, thereby reducing swelling and improving local blood circulation[23]. Additionally, Mirabilite can accelerate lymphatic circulation, increase the phagocytic function of reticuloendothelial cells, reduce leukocyte infiltration and promote the absorption of inflammatory cytokines[24]. Although this medicine is commonly used in China, because of its belief in benefitting patients, its effect on health outcomes has been limited investigated by rigorous studies.

According to the Chinese Pharmacopoeia published by Chinese Pharmacopoeia Commission, the basic functions of Mirabilite are helping heat purgation and bowel movement, moistening dryness, softening hard mass and clearing heat for detumescence. But it should not be used for pregnant women[25]. The reported side effects of externally applying Mirabilite is rare, two studies reported local skin rush or pruritus as the side effect[26]. In our study, no serious adverse events were reported.

Limitations

This study was limited by its retrospective nature. Furthermore, both patients and nurses were not blinded to the intervention and we didn't record the nurse's behaviour on measurement, this may contribute to information bias for the results. In addition, this was a single-centre study with a small number of study participants, which may raise the possibility of referral bias. Finally, we did not take the impact of belly band into account which also may have an impact on abdominal girth and IAP. Ideally and in future studies, this limitation can be corrected when using a randomized controlled trial design with a control group having a belly band with a placebo.

Implications for nursing practice

Our study adds new evidence to prove the effectiveness of Mirabilite on the PGID. As there is lack of effective treatment for PGID in older patients, Mirabilite might be an option for nurses to relieve PGID for older patients after abdominal surgeries. **CONCLUSION**

This retrospective study demonstrated that external use of Mirabilite may be associated and beneficial for improving gastrointestinal mobility in older critically ill patients after surgery. Compared with Lactulose alone, Mirabilite combined with Lactulose showed better efficacy to decrease abdominal girth, IAP and promote flatus and defecation. Future research should be conducted in a larger randomized controlled trial to further verified the efficacy and feasibility of Mirabilite including long-term outcomes.

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Table 1. Demographic characteristics

Characteristics	M+L Group (n=74)	L Group (n=93)	p value
Female, n (%)	20 (27.03)	35 (37.63)	0.15#
Age in years, mean (SD)	67.35 (7.03)	69.33 (8.07)	0.10*
APACHE II score on ICU admission, mean (SD)	11.04 (4.71)	10.60 (4.67)	0.55*
Surgical type, n (%)			
Liver	1 (1.35)	3 (3.23)	
Gastrointestinal system	43 (58.11)	52 (55.91)	
Pancreas	5 (6.76)	9 (9.68)	
Esophagus	20 (27.02)	25 (26.88)	
Biliary	5 (6.76)	4 (4.30)	
Surgical approach, n (%)			0.26#
Open	50 (67.57)	55 (59.14)	
Laparoscopic	24 (32.43)	38 (40.86)	
Previous surgical intervention history, n (%)			0.10#
Yes	12 (16.22)	25 (26.88)	
No	62 (83.78)	68 (73.12)	
Girth, cm, mean (SD)	109.81 (6.25)	111.49 (7.29)	0.12*
IAP, mmHg, mean (SD)	18.26 (2.55)	18.71 (2.41)	0.24*

M+L=Mirabilite and Lactulose; L=Lactulose; IAP= intra-abdominal pressure. *used the Independent-samples T test; # used the Chi-square test.

Table 2. Comparison of bowel sounds and defecation after treatment

Outcomes	No. (%)		Absolute Rate Difference, %(95% CI)	Relative Risk (95% CI)	P Value
	M+L Group (n=74)	L Group (n=93)			
Bowel sounds ≥3/min					
Day 1[a]	11 (14.86)	8 (8.60)	6.26 (-3.43, 15.96)	1.73 (0.73, 4.08)	0.228*
Day 2[b]	32 (43.24)	25 (26.88)	16.36 (1.88, 30.84)	1.61 (1.05, 2.46)	0.033*
Day 3[c]	46 (62.16)	35 (37.63)	24.53 (9.27, 39.79)	1.65 (1.20, 2.27)	0.002*
Flatus or defecation					
Day 1[a]	7 (9.46)	7 (7.53)	1.93 (-6.53, 10.39)	1.26 (0.46, 3.42)	0.781*
Day 2[b]	30 (40.54)	23 (24.73)	15.81 (1.60, 30.02)	1.64 (1.05, 2.57)	0.031*
Day 3[c]	52 (70.27)	43 (46.24)	24.03 (8.91, 39.15)	1.52 (1.17, 1.98)	0.003*

a: number of patients whose bowel sounds ≥3/min / who had flatus or defecation after 1-day treatment

b: accumulative number of patients whose bowel sounds ≥3/min / who had flatus or defecation after 2-day treatment

c: accumulative number of patients whose bowel sounds ≥3/min / who had flatus or defecation after 3-day treatment

* used the Chi-square test.

Table 3. Repeated measures analysis in girth and intra-abdominal pressure.

Measurement	Girth, cm, mean (SD)		IAP, mmHg, mean (SD)		NRS, median (IQR)	
	M+L Group (n=74)	L Group (n=93)	M+L Group (n=74)	L Group (n=93)	M+L Group (n=74)	L Group (n=93)
Before treatment	109.81 (6.25)	111.49 (7.29)	18.26 (2.55)	18.71 (2.41)	3.30 (2.30, 3.30)	3.30 (2.30, 4.30)
Day 1	108.31 (6.64)	110.82 (7.67)	17.11 (2.68)	18.20 (2.64)	2.30 (1.30, 3.30)	2.30 (1.30, 3.30)
Day 2	107.03 (7.12)	109.37 (7.87)	16.57 (2.93)	17.69 (2.76)	2.00 (1.30, 2.30)	2.30 (1.30, 3.80)
Day 3	104.95 (6.55)	108.03 (7.55)	13.46 (2.14)	15.60 (2.57)	0.65 (0.30, 1.30)	2.30 (0.30, 2.30)
Reduction between	4.86 cm	3.46 cm	4.80 mmHg	3.11 mmHg	2.40	1.11
F (time)	101.30	p<0.001	80.21	p<0.001	58.02	P<0.001
F (time / treatment)	2.61	p=0.070	2.58	p=0.059	3.15	P=0.028
F (between groups)	4.98	p=0.027	10.24	p=0.002	20.93	P<0.001

M+L=Mirabilite and Lactulose; L=Lactulose; IAP=intra-abdominal pressure; IQR=interquartile range; F=repeated measures ANOVA; NRS=numerous rating scale.

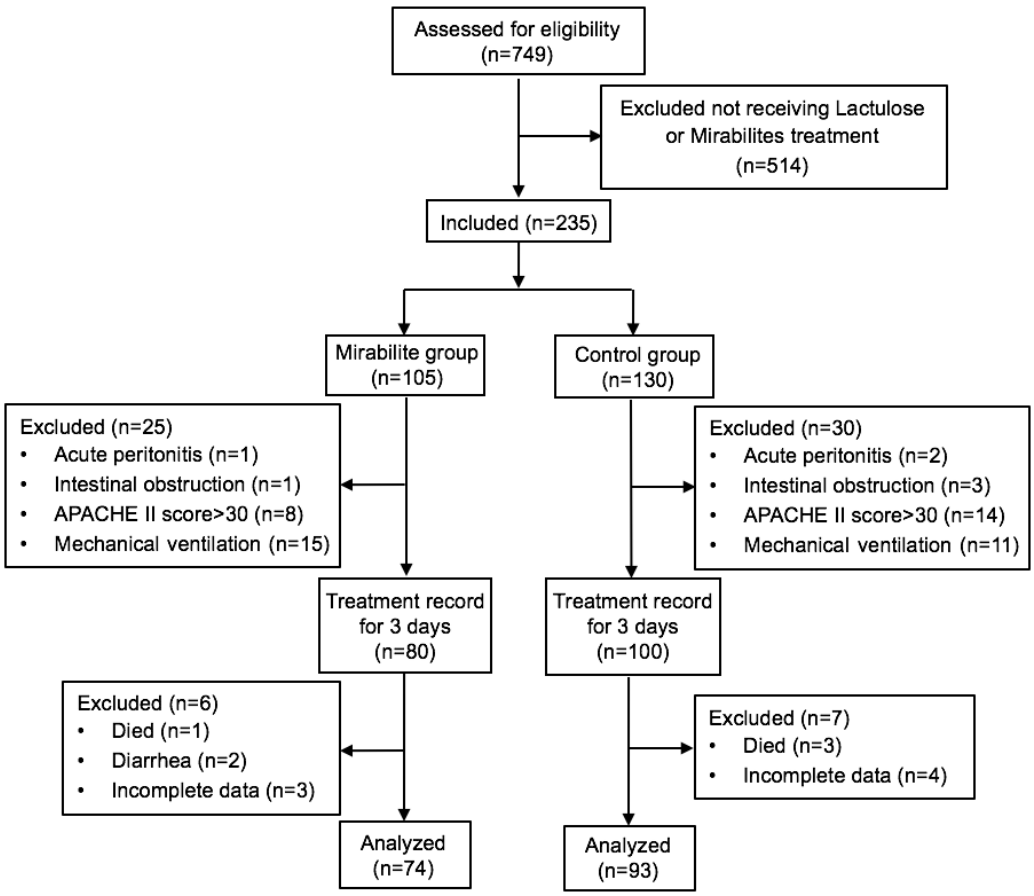

Figure 1. Flow diagram of patient selection

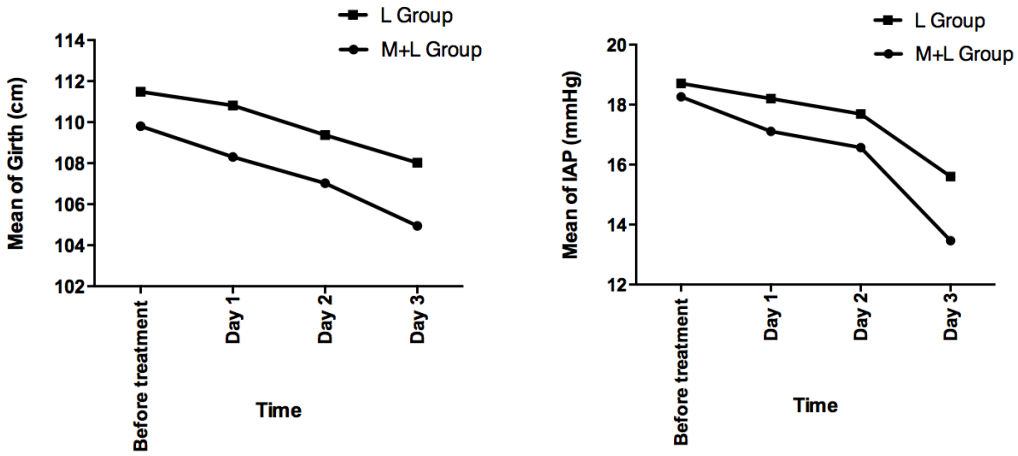

Figure 2. Line graphs presenting the decreasing trends for the abdominal girth and intra-abdominal pressure for the elderly patients after surgery in the Mirabilite + Lactulose and Lactulose only groups on each of the four measurements: before treatment, day 1, day 2 and day 3.

Electronic Supplement Material 1:
Belly Band (Fig. 1) and Mirabilite (Fig. 2)

Figure 1. specially-made belly bands with small bags were designed and applied to facilitate abdominal fixation of Mirabilite

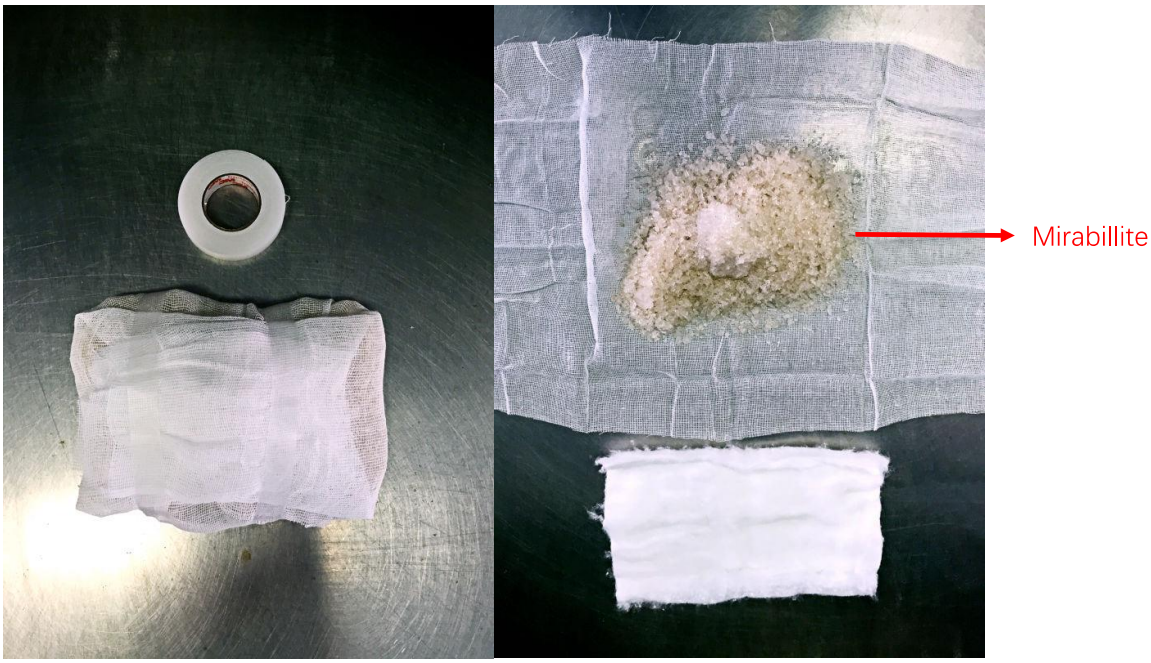

Figure 2. 2kg Mirabilite was wrapped in gauze and externally placed on the abdomen by putting them in the bags of belly bands