Efficacy of Gastrografin® Compared with Standard Conservative Treatment in Management of Adhesive Small Bowel Obstruction at Mulago National Referral Hospital

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Abstract

Introduction: The treatment of adhesive small bowel obstruction is controversial, with both operative and non-operative management practiced in different centers worldwide. Non-operative management is increasingly getting popular, though operative rates still remain high. A study to compare the efficacy of an oral water-soluble medium (Gastrografin®) with standard conservative management, both non-operative methods, in the management of this condition was conducted in a tertiary Sub Saharan hospital.

Methods: An open randomised controlled clinical trial was conducted between September 2012 and March 2013 at Mulago National Referral and Teaching Hospital, Uganda. Fifty patients of both genders, with adhesive small bowel obstruction, in the hospital’s emergency and general surgical wards were included. Randomisation was to Gastrografin® and standard conservative treatment groups. The primary outcomes were: the time interval between admission and relief of obstruction, the length of hospital stay, and the rates of operative surgery.

Results: All 50 recruited patients were followed up and analysed; 25 for each group. In the Gastrografin® group, 22 (88%) patients had relief of obstruction following the intervention, with 3 (12%) requiring surgery. The conservative treatment group had 16 (64%) patients relieved of obstruction conservatively, and 9 (36%) required surgery. The difference in operative rates between the two groups was not statistically significant ($P = 0.67$). Average time to relief of obstruction was shorter in the Gastrografin® group (72.52 hrs) compared to the conservative treatment group (117.75 hrs), a significant difference ($P = 0.023$). The average length of hospital stay was shorter in the Gastrografin® group (5.62 days) compared to the conservative treatment group (10.88 days), a significant difference ($P = 0.04$).

Conclusion: The use of Gastrografin® in patients with adhesive small bowel obstruction helps in earlier resolution of obstruction and reduces the length of hospital stay compared with standard conservative management. Its role in reducing the rate of laparotomies remains inconclusive.

Keywords: Adhesive small bowel obstruction; Non-operative management; Conservative management; Gastrografin®; Laparotomies; Hospital stay

Introduction

Adhesive Small Bowel Obstruction (ASBO) is the leading cause of intestinal obstruction in high income countries, and fast becoming so in low and middle income countries, with up to 40% of all cases of intestinal obstruction in some centres in Sub-Saharan countries [1]. It accounts for 3% of all emergency surgical admissions [2-4], and up to 70% of cases of Small Bowel Obstruction (SBO) worldwide [2-7]. Intrabdominal adhesions developing after surgery are responsible for this clinical entity. These are strands or membranes of fibrous tissue that are attached to the various intra abdominal organs, gluing them together. Aside from SBO, other complications of adhesions include chronic abdominal and pelvic pain, and infertility due to complications in the fallopian tubes, ovaries and the uterus [8,9]. Common surgeries associated with early postoperative SBO are large bowel, rectal, appendiceal and gynaecological surgeries [5,10]. ASBO can be treated by early surgery, but most patients are managed by non-operative conservative management, with good outcome and shorter length of hospital stay [10-13]. This conservative management is indicated when there is obstruction in the absence of bowel ischaemia and peritonitis.

In recent years, an oral water soluble contrast agent, Gastrografin®, has been used in the non-operative management of patients with postoperative SBO based on its biochemical properties and its being non-irritating to gut [13-15]. It acts as an osmotic agent within small bowel, causing decrease in oedema and enhancing bowel motility [16]. It has a normal transit time (stomach to colon) of 30 to 60 mins and shows effectiveness in resolving of features of obstruction, reducing the length of hospital stay and reducing the need for surgery [17-19]. Contrastingly, some studies have failed to demonstrate this therapeutic role [20-22].

Intra-abdominal adhesions affect the quality of life and increase the burden on the meagre health care resources in low income countries. Re-operations are made more difficult, with an increased risk of iatrogenic bowel injury during surgery. Furthermore, repeated laparotomy and adhesiolysis triggers-off yet more adhesion formation [23,24]. Consensus for the ideal management of ASBO has yet to be reached. At Mulago Hospital, most patients with ASBO without complications undergo conservative management for longer periods (a mean of 6 days, ranging from 1 to 29 days) [25] than the estimated standard duration of 48 to 72 hours. Many of these patients eventually

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undergo operative management with bowel resection. In this same centre there is also an increase in length of hospital stay, a mean of 20 days postoperative [25].

There are debatable study inferences on the ideal management of ASBO. In addition, there are also no standard protocols on when to switch from conservative to operative management [3,26,27]. We deemed it worthwhile to compare the efficacy of Gastrografin® with standard conservative management in resolving bowel obstruction, and reducing duration of hospital stay and the rate of laparotomies done among patients with ASBO undergoing conservative management.

Materials and Methods

This was a single-centre, open randomised controlled clinical trial carried out in patients with ASBO. It covered the period between September 2012 and March 2013. It was conducted at Mulago National Referral and Teaching Hospital’s general surgical wards. The hospital, located in Kampala, Uganda’s Capital and largest city, provides comprehensive tertiary health care and is also a university teaching hospital. Ethical clearance was provided by Makerere University College of Health Sciences’ (MakCHS) Research and Ethics Committee and Mulago Hospital’s Research and Ethics Committee.

Patients with ASBO were received at the Accident and Emergency (A & E) Department and admitted to its inpatient’s ward (3BE/S). It is in this ward that patients’ history was taken, examination done, and resuscitation and treatment instituted. They were managed there for the first 24 hours after which they were transferred to the general surgical wards. All issues concerning the care of the patients were coordinated from this unit, including radiological investigations and initiation of the allotted treatment method.

Included were patients of any age, both genders, admitted to A & E ward (3BE/S) with clinical features of ASBO who consented/assented to participate in the study between September 2012 and March 2013. Clinical features referred to symptoms, signs and radiological evidence of SBO, with a history of previous intra-abdominal surgery. These symptoms included: colicky abdominal pain, vomiting, abdominal distension and constipation. In turn, signs were: tachycardia, hypotension, fever, dehydration, abdominal tenderness, high-pitched bowel sounds and an empty rectum. Radiological features were based on plain radiographs. The diagnosis was made through: plain abdominal radiography with the patient in supine and erect postures, and plain chest radiography with the patient in an erect posture. A plain abdominal radiograph was taken to confirm the diagnosis of SBO. An abdominal ultrasound was also conducted if deemed necessary. Written informed consent and assent was obtained from all patients who fulfilled the inclusion criteria. Those who declined participation in the study were still given the appropriate treatment.

Upon establishment of a clinical and radiological diagnosis of ASBO, a Nasogastric Tube (NGT) was inserted, followed by active suction to decompress the stomach. An intravenous (IV) cannula of appropriate size was placed in the cephalic vein (distal portion) of the non-dominant arm to ensure intravenous access for fluids and drugs. Patients were promptly hydrated with intravenous fluids – Ringers Lactate or Normal Saline, basing on the pulse rate, blood pressure and urine output. The standard conservative treatment group continued with its management protocol, while the Gastrografin® treatment group had the intervention initiated.

Gastrografin® administration

Gastrografin® (Schering, Berlin, Germany; diatrizoate meglumine and diatrizoate sodium solution) was the oral contrast medium used for the Gastrografin® treatment group’s patients. It is a palatable lemon-flavored water-soluble iodinated iodopaque contrast medium. Each mL contained 660 mg diatrizoate meglumine and 100 mg diatrizoate sodium, with a pH adjusted to 6.0 – 7.6 with sodium hydroxide. It also contained 367 mg of organically bound iodine per mL, an essential constituent given its relatively high atomic weight making it sufficiently radio-dense for radiographic contrast with surrounding tissues. Administration was conducted by an investigator or trained research assistant (nursing officer), with adults receiving 100mL, children 5 to 10 years old receiving 60 mL, while infants and children less than 5 years old received 30 mL, through a NGT in the sitting position. The NGT was clamped for 2 to 3 hours with the patients kept in a propped-up position. To minimise the chance of aspiration, Gastrografin® was given only using a NGT of appropriate size corresponding to the age of the patient. Side effects monitored for were allergic reaction and aspiration pneumonia.

Patients follow up

Patients in both groups maintained a nil-by-mouth status, receiving maintenance fluid and analgesics intravenously. They were closely monitored in their respective wards, 6 to 12 hourly, by

repeated clinical examinations. Supine abdominal plain radiography was done 12 to 24 hours post admission. Patients in both groups were assessed for: resolution of abdominal pain (using the Visual Analogue Scale (VAS) for pain), reduction in abdominal distension (abdominal girth in cm), normalisation of bowel sounds and passage of flatus or stool. Successful management in the Gastrografin® group was considered when the contrast reached the caecum within 12 to 24 hours, along with: reduction in abdominal distension, passage of flatus/stool, normalisation of bowel sounds and pain subsiding. Success in management in the standard conservative group was considered upon fulfillment of all the above features, except that pertaining to contrast medium.

The decision to switch to operative management was made by the attending surgeons. It was based on: persistence of symptoms and signs of obstruction, clinical deterioration with persistent or worsening radiological evidence, or patients showing features of strangulation or peritonitis. In addition, patients who didn’t show improvement within a maximum of 5 days were subjected to surgery. Patients who were free from all obstructive symptoms and signs, and who were able to tolerate a normal diet were discharged. The patients were followed up to the day of discharge only.

Data analysis

Data were collected over a period of 7 months using interviewer administered pretested questionnaires and data entry forms. Entry was into EpiData® version 3.1 prior to exportation to Stata® version 10 (StataCorp, Texas, USA) for analysis. Continuous variables were expressed as means and standard deviations. Categorical variables were expressed as proportions and percentages. Normally distributed data were expressed in graphs and tables. The chi-square test was used to compare duration of hospital stay and time to resolution of symptoms/signs in both groups. A P value < 0.05 was considered significant. The Poisson regression method was used to compare the incidence of laparotomies between the two groups.

Results

Patient characteristics

All 50 patients completed the study and had their data analysed. The entire process is summarised in Figure 1. There were no significant differences between the 2 groups as far as age and sex were concerned (Table 1). All patients presented with abdominal pain (100%), with the least frequent presenting complain being failure to pass flatus (70%) (Figure 2). Any differences between the distribution of presenting complains were not statistically significant, $P > 0.05$. There was a statistically significant difference between the 2 groups concerning those who had had previous episodes of ASBO, $P = 0.039$ (Table 2). Most patients (70%) in the whole population had had one previous operation, with the rest having had 2 or 3 previous surgeries. Intestinal obstruction (42%) was the commonest indication for previous surgeries that patients underwent while appendicectomy (2%) was the least performed. Any differences between the distribution of severity of abdominal pain, number of previous surgeries (Figure 3) and whether the patient had had a previous episode of ASBO or not, were not statistically significant, $P > 0.05$ (Table 2).

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**Patient flow chart**

- **Enrolment**: Assessed for eligibility $n = 102$ (patients with intestinal obstruction)
  - Excluded $n = 52$
    - Did not meet inclusion criteria $n = 7$
    - Refused to participate $n = 0$
    - Other reasons $n = 45$
  - Randomised $n = 50$
- **Allocation**: Allocate to standard conservative management $n = 25$
  - Received intervention $n = 25$
  - Withdrew from treatment $n = 0$
  - Deaths $n = 1$
- **Follow up**: Analysed $n = 25$
  - Withdrew from treatment $n = 0$
  - Deaths $n = 1$
  - Analysed $n = 25$
- **Analysis**: Allocated to Gastrografin meal $n = 25$
  - Received intervention $n = 25$

*Figure 1: Study flow chart.*
Treatment outcomes

The average time to resolution of clinical symptoms and signs was shorter in the Gastrografin® group compared to the standard conservative group and was statistically significant (Table 3). Overall average length of hospital stay was 8.14 days (SD 6.56) for both groups. The duration for the Gastrografin® group was 5.62 days (SD 3.94), while that for the conservative group was 10.88 days (SD 7.73). The difference was 5.26 days with $P = 0.004$, a statistically significant result.

Only 12 (24%) patients underwent surgery while the other 38 (76%) patients had successful treatment non-operatively. Adhesions were present in all operated patients. Resection of gut was done in 6 patients, the indication being total obstruction of gut and the presence of...
colonic tumours. Colonic tumours, alongside adhesions, were present in 2 patients in the Gastrografin® group; one of them had a caecal tumour, while the other had a rectosigmoid tumour. Any differences between the 2 groups in distribution of laparotomy findings were not statistically significant, $P > 0.05$ (Table 4). The incidence of operations was higher in the standard conservative group with an incidence rate of 0.03 compared to the Gastrografin® group, with an incidence rate of 0.02. The Incidence Risk Ratio (IRR) 1.30 was not statistically significant, $P = 0.670$ (Table 5).

There were 2 deaths during the study, one from each group. On the one hand, the death from the Gastrografin® group occurred a few hours after operation. On the other hand, the death from the conservative group occurred suddenly, one week after admission. The patient had apparently been recovering well. This represented a 4% mortality rate.

Discussion

All the 50 patients who were randomised, were also present at the end of the study. There were no cases of discontinuation of treatment. Gastrografin® treatment reduced the duration of hospital stay compared to standard conservative treatment, 5.62 days versus 10.88 days ($P = 0.04$) respectively. It also reduced the time from hospital admission to resolution of signs and symptoms of bowel obstruction; 22.20 hours for Gastrografin® versus 67.52 hours for standard conservative treatment, $P = 0.001$. These outcomes showed statistical significance. In addition, there were fewer operations done in the Gastrografin® group compared to the standard conservative treatment group, 3 and 9 patients respectively. This gave an IRR of 1.30, which was not significant ($P = 0.67$). The overall mortality rate was 4%.

Concerning the participants’ characteristics, 27 (54%; CI 40.4 – 67.0) patients were ≤ 50 years, not presenting a significant majority. We can only deduce that since all of them had had previous surgery, there is a risk of adhesion formation post-surgery, though not related to age. On the side of gender, males were more than females, 35 (70%) and 15 (30%) patients respectively. The number of patients is rather small to give conclusive comments about prevalence of adhesions in this setting. Overall, the two study groups were similar regarding age and sex. Of all patients, 76% had their obstructive symptoms resolving without surgery, an observation higher than that in some previous study reports, with ranges of 27% to 42% [21,19,28]. Our inclusion of only partial bowel obstruction could partially account for this. Patients with complete obstruction, with or without strangulation, were not included during enrolment. Such patients would surely be refractory to non-operative treatment. On the other hand, the overall operative rate was 24% which is within the range reported by other studies [12,16,21,29].

ASBO can occur following any type of abdominal surgery with no single cause having been established as the leading cause of postoperative adhesions. Other studies have reported that gynaecological/obstetrics and colorectal surgeries, and appendicectomy are the procedures that most commonly caused postoperative SBO [2,3]. Our results showed that surgery of small and large gut, for intestinal
obstruction, was the commonest (42%) cause of post operative adhesions. This is quite different from a study in the same centre, 3 years ago which reported 28.8% of ASBO as being due to obstetrics and gynecologic surgeries [25]. Vakil et al., contrastingly described appendicectomy as the commonest preceding surgery (34.3%) [30]. These observations are plausibly accounted for by the RCT nature of our study and its inclusion criteria. These differing previous studies were typical prevalence studies, with longer durations, and involved more patients. They also included completely obstructed patients. The higher occurrence of postoperative adhesions following surgery on small and large gut, in this study, is ostensibly because these operations are some of the commonest general surgical procedures conducted in emergency settings in Uganda. However, though we had patients with one, two and three previous surgeries, there was no statistical correlation between the number of previous surgeries and the previous number of episodes of ASBO.

Considering the primary outcomes, Gastrografin® treatment reduced the duration of hospital stay when compared to standard conservative adhesions. This is plausibly explained by Gastrografin® treatment yielding an earlier resolution of the signs and symptoms of ASBO. The mechanisms of action of Gastrografin® ultimately explain this. It is hyperosmotic thereby promoting shifting of fluid into the bowel lumen and increasing the pressure gradient across the site of obstruction. This fluid shift also dilutes the bowel content and allows easier passage of bowel content through a narrowed lumen. Gastrografin® also decreases oedema of the bowel wall and enhances bowel motility [16]. Clinical symptoms are gradually ameliorated.

This was illustrated by a reduction in the mean time from admission to the first stool motion, 52.20 hrs in the Gastrografin® treatment group versus 124.17 hrs in the standard conservative treatment group. A previous clinical trial by Assalia et al., reported similar findings of shorter mean time of passage of first stool, 6.2 hrs in the Gastrografin® group versus 23.3 hrs in a conservative group (P < 0.0001) [20]. Patients in the Gastrografin® group were also able to start and tolerate oral feeding much earlier, within a mean duration of 72.52 hrs versus 117.75 hrs in the conservative group, with a mean difference of 45.23 hrs (P = 0.023). This enabled the patients in the Gastrografin® group to stay shorter in hospital, as the criteria for discharging patients was: patients free from obstruction and those who were able to tolerate a normal diet.

Given that similar outcomes are also noted in other studies in varied settings, there may be uniform benefit of Gastrografin® use worldwide. This finding in our study is similar to that of previous studies which also showed that Gastrografin® treatment significantly reduced length of hospital stay [19-22]. One study, however, did not find any advantage in relation to the length of hospital stay [31]. There were no adverse effects of Gastrografin® during the study, making it safe to use so long as caution is taken during its administration.

Regarding the incidence of laparotomies, several studies with different designs have investigated the role of Gastrografin® in reducing them among patients with ASBO. These studies have come up with contradictory results. One of the prominent setbacks of these studies was the lack of uniform study designs including: unclear patient populations and characteristics, unclear study protocols and non-specific amounts of Gastrografin® administered. Our study revealed that the likelihood of performing operative surgery was not higher in the conservative treatment group compared to the Gastrografin® treatment group, illustrated by the IRR of 1.30 which was not statistically significant (P = 0.670). This finding in our study could have resulted from use of a smaller sample size. Notably, some studies which showed that Gastrografin® reduced the need for surgery, had bigger sample sizes; Mohamed et al., [32], Di Severio et al., [17] and Assalia et al., [20]. Interestingly, Gastrografin® still reduced the need for surgery even in a study done with a smaller sample size than ours [33]. A recent study to consider an institutional management model for predicting the need for surgical exploration in cases of SBO, concluded that Gastrografin® decreased the need for exploration in patients not meeting the criteria for immediate operation [34].

More previous studies have recorded no advantage of the use of Gastrografin® in reducing the need for surgery. In a meta-analysis conducted by Abbas et al., it was reported that Gastrografin® did not reduce the need for surgical intervention, but reduced hospital stay for patients who did not require surgery [22]. This was echoed by Biondo et al., who also demonstrated that water-soluble contrast reduced the hospital stay but did not reduce the need for surgery [21]. Feigin et al., did not find any advantage in terms of reduction of operative rate.

![Table 4: Operations and intraoperative findings.](image)

<table>
<thead>
<tr>
<th>Laparotomy findings</th>
<th>Intervention Group</th>
<th>Conservative, n (%)</th>
<th>Total, n (%)</th>
<th>CI (75%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastrografin, n (%)</td>
<td>Conservative, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22(88.0)</td>
<td>16(64.0)</td>
<td>38(76.0)</td>
<td>62.5 – 65.8</td>
<td>0.138</td>
</tr>
<tr>
<td>Yes</td>
<td>3(12.0)</td>
<td>9(36.0)</td>
<td>12(24.0)</td>
<td>14.2 – 37.6</td>
<td></td>
</tr>
<tr>
<td>Intra-operative findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adhesions</td>
<td>3(100)</td>
<td>7(77.8)</td>
<td>10(83.3)</td>
<td>54.0 – 96.5</td>
<td>0.273</td>
</tr>
<tr>
<td>Adhesions + gangrenous gut</td>
<td>0</td>
<td>2(22.2)</td>
<td>2(16.7)</td>
<td>3.5 – 46.0</td>
<td></td>
</tr>
<tr>
<td>Surgery done</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adhesiolysis</td>
<td>0</td>
<td>6(66.7)</td>
<td>6(50.0)</td>
<td>25.4 – 74.6</td>
<td>0.679</td>
</tr>
<tr>
<td>Adhesiolysis* gut resection</td>
<td>3(100)</td>
<td>3(33.3)</td>
<td>6(50.0)</td>
<td>25.4 – 74.6</td>
<td></td>
</tr>
</tbody>
</table>

*IR – Incidence rate
**IRR – Incidence Risk Ratio

![Table 5: Incidence of laparotomies and Incidence Risk Ratio (IRR).](image)
resolution of symptoms and hospital stay [31]. Chen et al., demonstrated that the presence of contrast (Urografin) in the colon within the first 24 hours predicted a successful non-operative treatment [35]. However, in a further study, no significant differences were observed in the incidence of non-operative resolution and duration of hospital stay, between contrast and control groups.

Equally, a number of studies, some mentioned earlier, give a definite advantage of the use of Gastrografin®. Choi et al., reported that its use significantly reduced the need for surgery by 74% [36]. A more recent 2012 study reported reduced duration of hospital stay as well as low rates of laparotomy, though it was of cross-sectional design [37]. A trend among previous studies giving a mixed picture can be seen - Gastrografin® reducing duration of hospital stay with no effect on rate of laparotomy on the one hand, while reducing both duration of hospital stay and rate of laparotomies on the other hand.

We postulate that our study finding of Gastrografin® having no effect in reduction of number of laparotomies is partly explained by the fact that the patients included in our study (in Gastrografin® group) who were operated had colon tumours (caecal and rectosigmoid tumours) and complete intestinal obstruction (1 patient). These conditions are out rightly treated operatively, though they were not immediately diagnosed with these diseases at admission. They could have as well been randomised to the standard conservative treatment group. This could have tilted the 'significant difference' balance. Continued Gastrografin® or conservative management would not have cured these patients without the intervention of surgery.

There were some shortcomings during the study. We had a relatively small sample size. This may bring in bias in the presence of other underlying causes of obstruction like colonic tumours. These were randomised to the Gastrografin® group. Also, the grouping of patients into those below and above 50 years may not be the most appropriate method for sub-grouping.

In conclusion, the use of Gastrografin® in patients with ASBO helps in earlier resolution of obstruction and reduces the length of hospital stay compared with standard conservative management, without causing any adverse effects. Its role in reducing the rate of laparotomies still remains inconclusive. We recommend the use of Gastrografin® in the management of partial ASBO in the absence of other complications.

**Conflict of Interest**

The authors declare that they have no competing interests.

**Authors' contributions**

CH conceptualised the idea, conducted procedures, collected and analysed the data, and co-wrote the manuscript. PAO designed and wrote the manuscript, TK edited the manuscript. All authors read and approved the final manuscript.

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