RICHIESTA DI PARERE

- **TITLE:**

Prospective controlled randomized trial on Prevention of Postoperative Abdominal Adhesions by Icodextrin 4% solution after laparotomic operation for small bowel obstruction caused by adherences
(**POPA** study: **P**revention of **P**ostoperative **A**dhesions)

- **INVESTIGATORS:**

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- **MAIN CENTER**

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- **SPONSOR**

None

- **BACKGROUND**

Adhesive small intestine occlusion (ASIO) is an important cause of hospital admission and are associated with significant morbidity and mortality, placing a substantial burden on healthcare systems worldwide. Postoperative adhesions account for > 40 percent of all cases of intestinal obstruction, with 60 to 70 percent of those involving the small bowel.[1] Of patients who require abdominal reoperation, 30 to 44 percent have adhesion-related intestinal obstruction. [2] For small-bowel obstruction, the incidence rises to 65 to 75 percent.[3] Mortality rates range from 3 percent for simple intestinal obstructions to 30 percent when the bowel becomes necrotic or perforated.[1]

The cumulative recurrence rate for patients operated once for ASIO is 18% after 10 years and 29% at 30 years. For patients admitted several times for ASIO, the relative risk of recurrent ASIO increased with increasing number of prior ASIO episodes. The cumulative recurrence rate reached 81% for patients with 4 or more ASIO admissions.[4] In USA adhesiolysis is responsible for >300,000 hospitalizations annually, accounting for nearly 850,000 days of inpatient care and $1.3 billion in hospitalization and surgical expenditures.[5]

An increasing number of adhesion-reduction agents, in the form of site-specific and broad-coverage barriers

and solutions, are becoming available to surgical teams to complement optimal surgical techniques. Icodextrin 4% solution (Adept, Shire Pharmaceuticals, UK) is a high-molecular-weight *a*-1,4 glucose polymer that is approved in Europe for use as an intra-operative lavage and a post-operative instillate to reduce the occurrence of post-surgery intra-abdominal adhesions. The icodextrin colloid is absorbed slowly, resulting in the retention of the fluid within the peritoneal cavity for more than 4 days. The solution reduces adhesions by a process of hydroflotation, keeping the peritoneal organs and tissues apart during the critical post-surgery period when the patient is at greatest risk of adhesion formation. [6] Icodextrin has an extensive safety profile and has been used as a 7.5% solution in continuous ambulatory peritoneal dialysis (CAPD) for >50,000 patient-years. [7] In addition, preclinical and preliminary clinical studies have demonstrated the safety and efficacy of icodextrin 4% solution in the reduction of adhesion formation following abdominopelvic surgery [8] .

In literature there are not randomized trials on the use of this solution to prevent adhesions after ASIO operation.

- **AIMS**

The current clinical study evaluates the safety and effectiveness of icodextrin 4% for decreasing the incidence, extent, and severity of adhesions in patients after abdominal surgery for ASIO.

- **DESIGN**

The study project is a prospective, randomized controlled investigation. The study will be performed in the Department of Transplant, General and Emergency Surgery of St Orsola-Malpighi University Hospital (Bologna, Italy), a large teaching institution, with the participation of all surgeons who accept to be involved in together with the Emergency Surgery DPT of Maggiore Hospital (Bologna, Italy). These two institutions serve all surgical emergencies of Bologna city. The study is designed and conducted in compliance with the principles of Good Clinical Practice regulations.

The safety and efficacy of icodextrin 4% is compared to no antiadhesion treatment (control) in a parallel group, prospective, randomized study with a blinded evaluation of efficacy end points. Evaluation of adhesion formation is blinded by use of designated third party individuals who are unaware of the treatment assigned to the patients.

- **HOW RANDOMIZED**

The randomization will be obtained through computer-generated schedule. The result of this randomization will be sealed in numbered envelopes. After small bowel obstruction diagnosis caused by adhesions if the patient fulfils the inclusion criteria the responsible surgeon will disclose the envelope and accordingly to the protocol the patient will sign an informed consent.

The responsible surgeon will record the patient name (and number).

- **SAMPLE SIZE**

The sample size will be 88 patients for each group (176 patients for the whole study).

- **POWER CALCULATIONS**

All randomized patients (Intention to Treat population) are included in the analysis.

Sample size has been calculated to reach a confidence level of 95% with a power of 80%.

A sample size of 88 patients each group (65 analyzable) is calculated supposing that the SIO patients (first, second, third or fourth operation for ASIO) have a mean risk of 50% to develop a further episode of ASIO and this risk can be decreased by 25 % (from 50% to 25%) with the use of icodextrin 4%

- **INCLUSION AND EXCLUSION CRITERIA**

Inclusion criteria are:

- Adult patients (>18 years)
- Submitted to laparotomic surgical procedures for ASIO
- Clinical and radiological evidence of adhesive small intestine obstruction
- ASA I-III patients
- Informed consent

Exclusion criteria

- Intrabdominal cancer
- Peritoneal contamination
- IBD
- Positive history of radiotherapy
- Patients with an intra-operative findings of different pathology will be excluded from the study

- **INTERVENTION**

Preoperative data collected include patient demographics and comorbid conditions (genitourinary, cardiac, pulmonary, gastrointestinal, renal, or rheumatologic) and a detailed history of previous occlusions and surgical procedures.

A decompression with nasogastric tube is carried out. The average nasogastric tube output of each patient (total amount of drainage/ duration) is calculated. For patients submitted to Gastrografin administration before surgery only the output before the procedure is considered. Intravenous fluid therapy is performed. Plain abdomen X-ray are done and maximal small intestine diameter is calculated. Duration of symptoms before admission and number of previous operations are also evaluated.

Subjects with surgical indication to laparotomy are enrolled and randomized. A written informed consent is obtained. Laparotomic surgical procedure is carried out and existing abdominal cavity adhesions are documented. Subjects are submitted to adhesiolysis with bowel resection if necessary with or without anastomosis. The first group receive traditional treatment (control group) whereas the second group is treated

with icodextrin 4% before abdomen closure. The use of irrigants during surgery is not allowed. Peritoneal contamination is evaluated with cultures.

Per protocol the abdominal fascia is closed with a running PDS suture and the skin is closed with sutures or skin staples.

Only one abdominal drainage in allowed in case of bowel resection and it has to be removed 7 days after the operation.

In case of bowel leakage the patient will drop out from the study.

For all patients, perioperative parameters are recorded, including blood loss, total length of the midline incision, method of anastomosis, method and timing of incision openings and closures, corticosteroid use. Operative wounds are classified as clean, clean contaminated, and contaminated as described by Schwartz *et al*.[9]

Morbility, mortality and postoperative stay are registered. A flow chart showing the protocol is illustrated in figure 1.

The patients are followed- up for 5 years.

In case of reoperation for ASIO the procedure is carried out by a third party blinded to the patient's previous antiadhesive treatment: this surgeon evaluates incidence, location, severity, and extent of adhesions. The incidence of adhesions is assigned a severity score of 0 (no adhesions), 1 (filmy thickness, avascular), 2 (moderate thickness, limited vascularity), or 3 (dense thickness,
vascularized).

Adverse events (AEs) are collected for the duration of the study, beginning at the time of randomization. AEs are identified and described by the primary investigators.

- **IS THERE A PLACEBO?** No

In the control group, patients will be treated as in our daily surgical practice.

- **INFORMED CONSENT TO BE SOUGHT?** Yes (see below: Case Report Form)

- **INFORMED CONSENT FORM OR INFORMATION SHEET?** Yes (see below: Case Report Form).

In the informed consent form, patients will receive all the information about the study protocol, the confidential nature of personal data and will fill up a questionnaire before signing or refuse.

There will be not inconveniences caused to the patients. No incentives are planned for the patients regarding the operation or the follow-up.

All the medical informations obtained from the patients will be kept confidentially among the research scientists conducting the study.

The patients will be free to withdraw from the study, whenever they want without any obligation.

- **ETHICAL APPROVAL** *Under evaluation by the ethical Committee of the S'Orsola-Malpighi Hospital, Bologna, Italy*

- **STOPPING RULES**

In case of newly discovered statistically significant advantages.

- **PRIMARY ENDPOINTS**

The primary endpoints of our study will be:

A) To evaluate the therapeutic role of icodextrin 4% to reduce ASIO incidence

B) To reduce adherences rate (in case of reoperation for ASIO)

The onset of any other complications will be recorded intraoperatively, postoperatively, at discharge, at 7-days, 1-month, 6-months, every year up to 5 years follow-up.

- **PLANNED SUBGROUP ANALYSES?** No.

- **SIDE EFFECTS QUANTIFICATION?** Yes

Complications from the employ of icodextrin 4% are very rare.

- **IS THERE AN ANALYSIS PLAN?** Yes

All the above mentioned data will be recorded in the Case Report Form (annexed to this proposal) and later stored in computer database. At the end of the study the final statistical examination will be carried out.

- **ARE THERE PLANS FOR INTERIM ANALYSIS?** Yes

An interim statistical examination of the data will be done every 3 months during the period of patients' inclusion in the study. Then at the end of every completed follow-up period.

- **ARE THERE AN INDEPENDENT DATA-MONITORING COMITTEE?** No

- **TYPE OF ANALYSIS**

The statistical analysis will be carried out using Epi Info 2000, Version 1.1 software package (Dean AG, Arner TG, Sangam S, Sunki GG, Friedman R, Lantinga M, Zubieta JC, Sullivan KM, Smith DC. Epi Info 2000, a database and statistics program for public health professionals for use on Windows 95, 98, NT, and 2000 computers; Centers for Disease Control and Prevention, Atlanta, Georgia, USA, 2000)

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- **STATISTICS TEST STATED**

The data generated by this study will be analysed in two ways. The continuous numerical data were subjected to analysis of variance (ANOVA), this method being applicable to the discrimination of two

continuous populations. Discrete data will be analysed by the chi-squared test or Fisher exact test, as appropriate. Statistically significant differences between study treatments were based on $p < 0.05$.

- **INDEMNITIES SPECIFIED**

No incentives are planned for the patients regarding the operation or the follow-up.

- **FINISHING DATE**

The study will take approximately 2 years for the inclusion period. According to the number of ASIO menaged monthly by each surgeon in our Department, the duration of the inclusion period can be approximately of 2 years to reach the number of about 176 enrolled patients.

- **REPORTING DATE**

An interim report is planned at the end of any completed follow-up period.

- **IS THE STUDY CLINICALLY NECESSARY?** Yes

ASIO is a common disease. Any improvement in this field will benefit many patients reducing the re-operative rate. All our patients will be informed about the study and an informed consent will be obtained. There will not be inconveniences caused to the patients. All the medical informations obtained from the patients will be kept confidentially among the research scientists conducting the study. The patients will be free to withdrawn from the study, whenever they want without any obligation.

Table 1.

EpiInfo Version 6: Statcalc November 1993
Unmatched Cohort and Cross-Sectional Studies (Exposed and Nonexposed)
Probability that if the two SAMPLES differ this reflects a true difference in the two POPULATIONS (Confidence level or 1-Ó): 95.00 %
Probability that if the two POPULATIONS differ, the two SAMPLES will show a "significant" difference (Power or 1-ß): 80.00 %
Ratio (Number of Unexposed : Number of Exposed): 1 : 1
Expected frequency of disease in unexposed group: 30 %
Please fill in the closest value to be detected for ONE of the following:

- Risk ratio (RR) or relative risk--closest to 1.00: 0.25
- Odds ratio (OR)--closest to 1.00: 0.21
- Percent disease among exposed--closest to % for unexposed: 5 %

EpiInfo Version 6: Statcalc November 1993
Unmatched Cohort and Cross-Sectional Studies (Exposed and Nonexposed)
Sample Sizes for 30 % Disease in Unexposed Group:

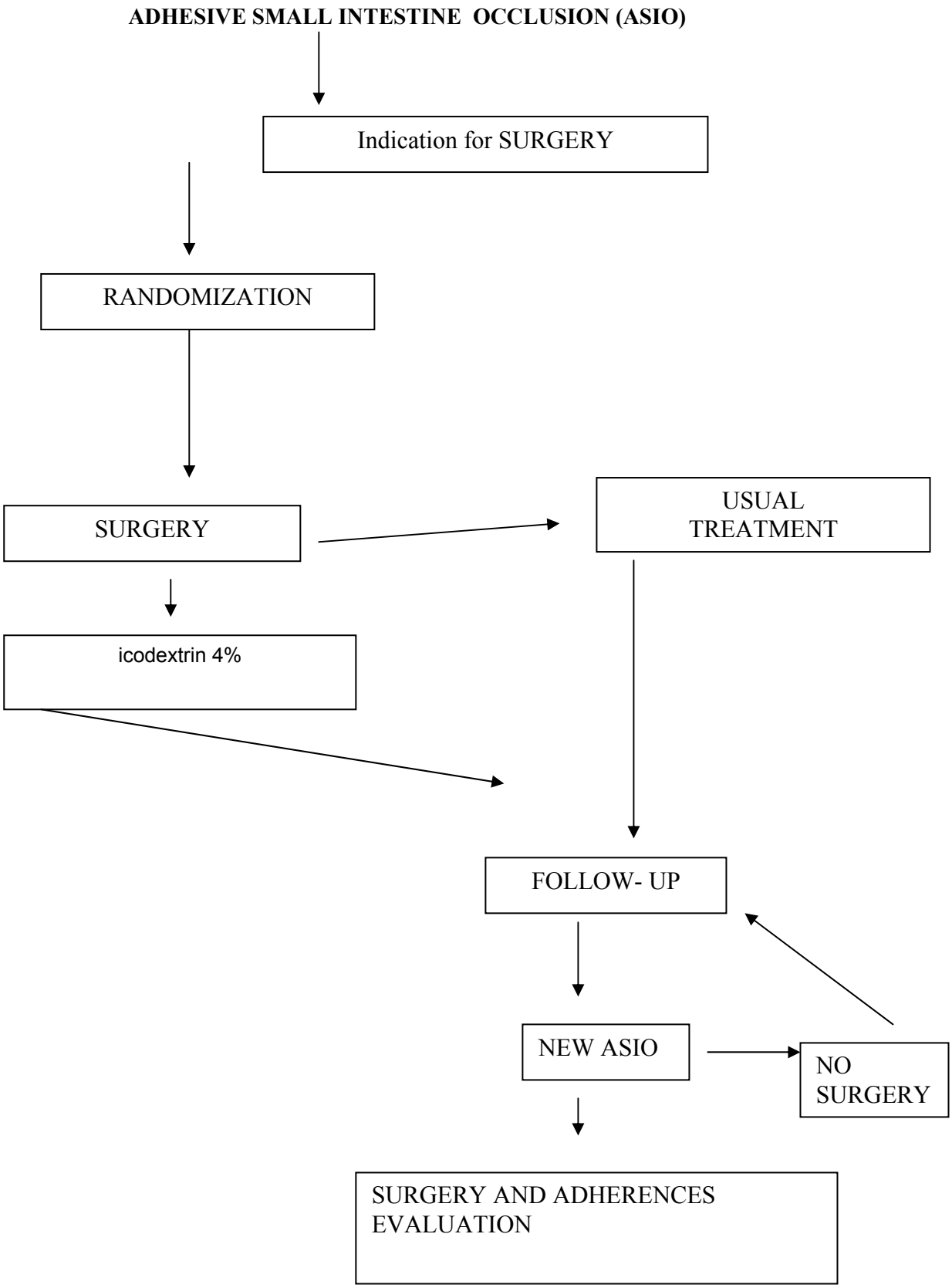
						Sample Size		
Conf.	Power	Unex:Exp	Dis. in Exp.	Risk Ratio	Odds Ratio	Unexp.	Exposed	Total
95.00%	80.00%	1:1	30%	0.25	0.21	88	88	176

Il sottoscritto Sperimentatore Responsabile s’impegna ad attivare la sperimentazione secondo quanto disposto dal D.M. 15 luglio 1997 e soltanto dopo aver ricevuto formale comunicazione di parere favorevole del Comitato Etico e l'autorizzazione da parte della Direzione Sanitaria

Firma dello Sperimentatore Responsabile	*Firma del Responsabile dell'Unità Operativa*

Luogo e data

FIGURE 1


ADHESIVE SMALL INTESTINE OCCLUSION (ASIO)
Indication for SURGERY
RANDOMIZATION
SURGERY
USUAL TREATMENT
icodextrin 4%
FOLLOW- UP
NEW ASIO
NO SURGERY
SURGERY AND ADHERENCES EVALUATION

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