Implementation of an Efferent Loop Stimulation Protocol Prior to Ileostomy Closure at La Paz University Hospital.

TITLE: Implementation of an Efferent Loop Stimulation Protocol Prior to Ileostomy Closure at La Paz University Hospital
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BACKGROUND AND CURRENT STATUS

Stoma creation is a surgical procedure used in certain situations in general surgery, especially in colorectal and emergency surgery. There are several ways to bypass intestinal transit during intestinal surgery. The most frequently performed is colostomy, which is defined as the exteriorisation of the colon through the skin, usually on the left side of the abdomen. The colon can be bypassed along its entire length and a stoma can be created and matured in any area of the abdominal wall. In addition to the colon, in certain circumstances the transit can also be bypassed more proximal to the colon, such as the small intestine, and although any area of the intestine is susceptible to bypass, the most frequent is the ileum.

The objectives of creating a stoma are diverse, and may be to prevent the passage of faeces to distal sections to treat an infection, to avoid a high-risk anastomosis in a patient with emergency surgery and haemodynamic instability, or to protect a high-risk anastomosis (such as rectal anastomoses due to the anatomical characteristics of their irrigation). Although the creation of stomas is a life-saving surgical technique, the bypassing of intestinal contents has both pathophysiological and aesthetic-psychological repercussions on patients' lives. Stomas bypass the intestinal transit and therefore cause food to leave the intestine before it completes its digestive transit, altering the absorption of nutrients. The more proximal the bypass is, the more this absorption will be altered. Therefore, ileostomy has more absorption problems than colostomy. This leads to a physiological alteration of the patient, with the more proximal the shunt is, the greater the loss of liquids and intestinal contents.

The creation of ileostomies can be encountered mainly in three scenarios:

- A surgical emergency with the need to abduct the small bowel to the skin either by massive colon resection or by risky anastomosis

- Total or subtotal colectomies for various causes: inflammatory bowel diseases, synchronous or metachronous tumours, peritoneal carcinomatosis, etc.

- Protective ileostomies in elective surgery for colorectal cancer or deep endometriosis with high-risk colorectal resection and anastomosis, either because of the distance to the anal margin or because of the patient's biological characteristics (chemotherapy, radiotherapy, immunosuppression, malnutrition). The latter case is the most frequent.

Stomas can be permanent or temporary. Ideally, most stomas should be temporary and should be used as a bridging tool to obtain the best possible conditions for the patient to undergo anastomosis. The literature provides us with real data that approximately 50% of colostomies are not reconstructed, either due to progression of oncological disease, clinical deterioration of the patient or unclear causes. However, given that the most common case of ileostomy creation is to protect an anastomosis of the intestinal transit to aid healing, ileostomies are reconstructed at a rate of over 90%.

A second intervention is used to perform an ileostomy closure and re-establish normal intestinal transit. For such a closure, it is essential to choose the right time depending on the indications that justified the creation of the stoma and the type of stoma used. However, this closure is associated with a number of postoperative morbidities. The most frequent is postoperative ileus (POI), but there are others such as surgical wound infection, diarrhoea... Several studies indicate that stimulation of the efferent loop, prior to ileostomy closure, shows benefits in the postoperative recovery of patients. The cause of these complications after transit reconstruction is multifactorial and a single cause is unknown, but it is thought that it could be due to the colic mucosa being atrophied and inflamed after a variable period without stimulation, preventing the passage of intestinal contents, which are also nutritional for the mucosa. When previously stimulated, it seems that the colic trophism recovers earlier and is more prepared to receive new intestinal contents after intestinal reconstruction, thus decreasing the inflammation associated with the exclusion of food content. This means that, by stimulating the loop, it loses less of its properties and therefore its functionality when transit is re-established. Some of these benefits, translated into clinical practice, are the reduction of hospital stay and the reduction of post-surgical complications such as postoperative ileus, diarrhoea, anastomotic leaks and surgical wound infection. There is inconsistency about which solution to use for efferent loop stimulation. Some studies use serum and thickener, others use short-chain fatty acids, which are the main source of nutrition for the intestinal epithelial cells, and still others use probiotic substances, hoping to optimise the patient's intestinal microbiota.

There are many doubts about the best way to do this and for how long. The time prior to stimulation is one of the doubts analysed by Grafinkle in a recent study, as there is a great deal of variability in the studies analysed. Some studies performed loop stimulation for 2 weeks (Abrisqueta), others for 10 consecutive days (Ocaña) in a hospital setting, while Grafinkle et al. performed stimulation for 7 random days in the 3 weeks prior to surgery. None of the studies explores the difficulty of surgical planning for these patients to meet the timings set out in their protocols. Grafinkle et al. explores how to optimise the procedure by performing it fewer times, but without losing benefit in terms of outcomes. On this issue, several authors point to the benefit of instructing patients to perform the stimulation themselves, thus reducing hospital visits and thus reducing the use of health care resources. This could theoretically improve patient adherence by facilitating logistics and allowing telephone follow-up to be measured using forms. To date, despite the heterogeneity of study methods, probiotic stimulation has not demonstrated any postoperative benefit. However, there is evidence that the use of saline or short-chain fatty acids reduces complications such as paralytic ileus and diarrhoea. It should be borne in mind that the half-life of fatty acids is very short, storage is complex because it requires optimal temperature conditions for storage and other conditions for use, as well as their

high cost. In order to carry out the procedure at home, it is simpler to use serum if it has been demonstrated that fatty acids are not superior to serum.

Currently, there is no protocol in place at La Paz University Hospital to perform this procedure, which could be of great benefit as it is a simple, cheap procedure that could hypothetically reduce complications and hospital stay, improving the patient's postoperative period and could be of economic benefit to the system.

RATIONALE OF THE STUDY

The aim of this study is to demonstrate the benefits of efferent loop stimulation prior to ileostomy closure for any previous cause, and to develop a practical, simple protocol that can be adapted to complex daily surgical planning, at the Hospital Universitario La Paz, in the General and Digestive System Surgery Department. With the current evidence, we know that there is a real benefit of pre-stimulation, although there are scientific gaps in knowledge about how long to stimulate beforehand and the optimal type of substance to use. Furthermore, with a good organisation of the protocol, it could be possible to perform it at home with the aforementioned benefits.

We know that complications of ileostomy closure are very frequent (estimated at around 40%). The most frequent is postoperative paralytic ileus, but there are many others such as diarrhoea, anastomosis dehiscence, surgical wound infection, etc. All of these prolong the patient's hospital stay, increasing the use of resources that all these complications entail, such as possible re-interventions or the use of medication. The consequences of these complications for the patient involve a deterioration of their functional capacities, especially in fragile patients, by increasing the number of days of hospitalisation and complications. Therefore, if by applying a reproducible and simple protocol of prior stimulation we can reduce post-surgical complications and thus hospital stay, we could improve the lives of these patients.

HYPOTHESIS: Stimulation of the efferent loop (EAE) in ileostomy patients with saline and thickener 2 to 4 weeks prior to surgery for transit reconstruction recovers intestinal transit sooner, reduces hospital stay and post-surgical complications.

OBJECTIVES

Primary Objective	**Primary Endpoint**
To demonstrate the efficacy of efferent loop stimulation in reducing hospital stay compared to historical controls at 30 days after reconstruction surgery.	Difference in mean number of days of hospital stay between control and case group at 30 days after reconstructive surgery
Secondary Objectives	**Secondary Endpoints**
1. To assess whether EAE reduces paralytic ileus 2. To assess whether EAE reduces postoperative diarrhoea	1. Percentage of patients diagnosed with paralytic ileus during admission in the case group compared to the control group

3. To evaluate whether SEA reduces surgical wound infection 4. To evaluate the degree of implementation of this clinical protocol in the General and Digestive Surgery Department of Hospital La Paz 5. To evaluate whether SEA reduces postoperative blood C-reactive protein values measured in the postoperative period	2.Percentage of patients diagnosed with diarrhoea during admission in the case group compared to the control group. 3. Percentage of patients diagnosed with surgical wound infection 30 days after surgery in the case group compared to the control group 4. Percentage of the number of patients included in the protocol compared to the total number of ileostomies reconstructed since the protocol was implemented 5. Percentage of the mean blood CRP value on the second and fourth day of patients undergoing EAE compared to the mean blood CRP value on the second and fourth day of patients without EAE.

MATERIALS AND METHODS

Inclusion Criteria:

1. Subjects must be able to understand the purpose and risks of the study, giving informed consent and authorising the use of confidential health information.
2. Subjects Patients over 18 years of age who, regardless of the cause, are ileostomy patients and have a medical indication for transit reconstruction by a general surgeon.
3. Subjects able and willing to participate and to be followed up for the duration of the study.

Exclusion Criteria

1. Subjects with an ileostomy who do not wish to undergo reconstruction.
2. Subjects who are unable to perform at least two weeks of efferent loop stimulation prior to reconstruction surgery.
3. Subjects who do not consent to participate in the study.

Study Design: Prospective Cohort Study with Historical Controls at a single centre

Study Population: Patients over 18 years of age who, regardless of cause, are ileostomy carriers and have an indication for transit reconstruction.

Intervention:

- Arm Cases: Prospective patients with daily stimulation of the efferent loop at least two weeks prior to surgery with saline and thickener.

- Control Arm: Retrospective data from patients who did not undergo pre-ileostomy closure stimulation prior to the introduction of the efferent loop stimulation protocol.

Once the patient is included in the study, their clinical treatment will be carried out in accordance with standard clinical practice, to which a series of visits and procedures without risk to the patient will be added:

1. The start of the efferent loop stimulation will be performed the day after the anaesthesia consultation prior to surgery to receive the information, material and established follow-up of the patient.

2. The determination of ileostomy closure shall be recorded in the operating room and shall be objectified in the surgical protocol or operative sheet when performed.

3. The patient will be reviewed daily during admission by the corresponding medical team, carrying out anamnesis, physical examination and serial analyses on days 2 and 4 with the necessary parameters for follow-up according to standard clinical practice.

4. On-site review with anamnesis and physical examination at 1 and 6 months to assess the patient's general condition.

Once the patient is included in the study, the management of the stimulation will be monitored with telephone and face-to-face follow-up once a week.

During their hospital stay after ileostomy closure, their clinical management will be carried out in accordance with standard clinical practice, and they will be discharged from hospital when the established criteria are met.

The criteria for discharge from hospital care are considered to be met when the patient meets the following

1. Tolerance to oral diet
2. Absence of abdominal distension
3. Adequate pain control
4. Absence of fever
5. Absence of signs of surgical site infection requiring hospital care
6. Independent mobilisation
7. Presence of vent or stool

SAMPLE SIZE

The primary variable is defined as the difference in mean hospital length of stay between the control and case groups within 30 days following reconstructive surgery. Assuming a

mean of 5.84 days, a standard deviation of 3.04 days, a minimum detectable difference of 2 days, and a one-tailed hypothesis test:

With an alpha error of 0.05 and a power of 0.8, and accounting for a potential dropout rate of 0.15%, a sample size of 68 patients is proposed, with 34 in each arm.

Duration: 1 year (extendable depending on sample size requirements)

STATISTICAL ANALYSIS

A univariate descriptive analysis will be conducted for all study variables. Qualitative variables will be presented as absolute and relative frequencies, while quantitative variables will be summarised using measures of central tendency and dispersion (mean, standard deviation, median, interquartile range, etc.). The Kolmogorov-Smirnov test will be employed to assess the normality of the variables.

For the analysis of the primary outcome and intergroup comparisons, Pearson's Chi-square test will be used for qualitative variables (or Fisher's exact test for 2x2 tables and likelihood ratio test for m×n tables, if necessary). For quantitative variables, the Student's t-test and ANOVA will be applied, or their non-parametric equivalents, the Mann-Whitney U test and the Kruskal-Wallis test, respectively.

Subsequently, a multivariate model will be fitted including all variables found to be statistically significant in the univariate analysis. The final model will be selected using a backward elimination approach, with optimal model determination based on the Bayesian Information Criterion (BIC).

The level of statistical significance is set at 0.05. Statistical analyses will be performed using R software (version 4.3.1).

ETHICAL CONSIDERATIONS

All participants will receive detailed information regarding the study, including its objectives, procedures, potential risks, and benefits. Sufficient time will be provided for consideration, and participants will have the opportunity to ask questions prior to signing the informed consent (IC) form. This process ensures that consent is given voluntarily and is fully informed.

Written IC, specifically designed for this study, will be obtained and signed by the patient. Personal and medical data will be treated with the utmost confidentiality, in accordance with Data Protection regulations. Data will be stored securely, accessible only to the research team, and anonymised to safeguard participant identity.

Participant selection will be fair and equitable, based on clearly defined inclusion and exclusion criteria. Vulnerable groups will not be exploited, and equality will be promoted in the recruitment process.

Participants may withdraw from the study at any time without any negative consequences. They will be informed about the withdrawal procedure and the handling of their data upon withdrawal.

The study has been reviewed and approved by the Research Ethics Committee of La Paz University Hospital, ensuring compliance with all relevant ethical and legal standards.

Study findings will be communicated transparently and accessibly. Participants will be informed of the results, which will also be published in scientific journals and on publicly accessible platforms.

RISK-BENEFIT ASSESSMENT

This study has been designed to ensure that the potential benefits outweigh the risks. A risk assessment has been conducted and measures have been implemented to minimise them, while ensuring that the potential benefits are meaningful.

CONFIDENTIALITY

Data collected for the study will be identified using a code, and only the study physician or authorised collaborators will be able to link this information to the patient and their medical records. Therefore, individual identity will not be disclosed, except in cases of medical emergency or legal requirement.

Should the data from this study be used for future research with different objectives, patient consent will be requested at that time, using a separate information sheet previously approved by the relevant Research Ethics Committee (REC).

The processing, communication, and transfer of personal data will comply with the provisions of the Organic Law 15/1999 of 13 December on the Protection of Personal Data. In accordance with this legislation, participants may exercise their rights to access, rectify, oppose, or cancel their data by contacting their study physician. Data transferred to third parties or other countries will not include any information that could directly identify the participant (e.g., name, initials, address, social security number, etc.). Should such a transfer occur, it will be solely for the same purpose as the present study, and confidentiality will be safeguarded in line with current national legislation.

Access to personal information will be restricted to the study physician, collaborators, authorised personnel, the Clinical Research Ethics Committee, and competent authorities when necessary to verify study data and procedures. Confidentiality will be maintained at all times in accordance with applicable laws

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