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--Manuscript Draft--

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Full Title:	Power Doppler sonography to predict the risk of surgical recurrence of Crohn's disease
Article Type:	Original Paper
Abstract:	Purpose. The aim of this work is to investigate the role of power Doppler sonography as an additional predictor of surgical recurrence in Crohn's disease. Methods. A sample of 33 patients, with ileal or ileocolonic Crohn's disease, that had underwent intestinal resection, were retrospectively enrolled. All patients had bowel ultrasonography 7-16 months after resection. Power Doppler sonography of the preanastomotic ileum was evaluated as a possible prognostication tool to assess the risk of long-term need for reoperation. Results. The absolute incidence of surgical recurrence in those who had a positive power Doppler was 42%, while that of those who had a negative power Doppler was 28.6%. Combining the power Doppler with bowel wall thickness, the surgical recurrence risk grew from 41.2% of those with a positive power Doppler and thickness >3 mm to 55.6% of those with a positive power Doppler and thickness >6 mm. Conclusions. Power Doppler look to be another useful prediction tool for the personalization of patient's care. It could be useful to perform power Doppler in all patients with a wall thickness greater than 5 mm: for those who have a positive power Doppler it may be indicated a more aggressive prophylactic therapy.
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Author Comments:	This is the first serie in the literature in which is studied the predictive power of the color Doppler of surgical recurrence of Crohn's disease; we have found another useful factor for the personalization of patient's care: knowing that the 54.5% of patients who at bowel ultrasound performed within 1 year after operation have a bowel wall thickness > 5 mm and positive power Doppler will be reoperated could select the patients that should undergo colonoscopy for assessing endoscopic recurrence and authorize the use of a more aggressive medical therapy to try to change the natural history of their disease.
Response to Reviewers:	1) the color Doppler imagine has been removed 2) declaration about Conflict of interest, Informed Consent, Human & Animal Studies have been added

Power Doppler sonography to predict the risk of surgical recurrence of Crohn's disease.

Abstract

Purpose. The aim of this work is to investigate the role of power Doppler sonography as an additional predictor of surgical recurrence in Crohn's disease.

Methods. A sample of 33 patients, with ileal or ileocolonic Crohn's disease, that had underwent intestinal resection, were retrospectively enrolled. All patients had bowel ultrasonography 7–16 months after resection. Power Doppler sonography of the preanastomotic ileum was evaluated as a possible prognostication tool to assess the risk of long-term need for reoperation.

Results. The absolute incidence of surgical recurrence in those who had a positive power Doppler was 42%, while that of those who had a negative power Doppler was 28.6%. Combining the power Doppler with bowel wall thickness, the surgical recurrence risk grew from 41.2% of those with a positive power Doppler and thickness >3 mm to 55.6% of those with a positive power Doppler and thickness >6 mm.

Conclusions. Power Doppler look to be another useful prediction tool for the personalization of patient's care. It could be useful to perform power Doppler in all patients with a wall thickness greater than 5 mm: for those who have a positive power Doppler it may be indicated a more aggressive prophylactic therapy.

Keywords: Color Doppler; Inflammation; Small Bowel; Ultrasound.

Introduction

In a previous study [1], we found that bowel wall thickness at the anastomosis >3 mm, detected through bowel ultrasound performed 1 year after surgery, could be added to the list of non-invasive predictors of early recurrence after ileo-colonic resection besides those implying a double risk of recurrence, such as smoking, previous bowel surgery, penetrating behavior of the disease, perianal location, extensive small bowel resection, and absence of prophylactic treatment [2].

In recent years, power Doppler has been proposed as an additional prognostication tool to increase the accuracy of bowel ultrasound in the assessment of disease activity [3-5].

A wide deployment of these additional techniques is impaired by the intrinsic variability. It has been also proposed that the morphological characteristics of the intestinal wall correlate with the histological pattern [6, 7] and with the clinical activity [8-11], although the correlation between the intestinal wall thickness and Crohn's disease activity index (CDAI) is not close [12].

Methodology

We performed a retrospective study on 196 patients that underwent ileal or ileo-colonic resection with ileo-colonic anastomosis between December 1993 and March 2009 (all diagnosis of Crohn's disease was confirmed through histologic examination). All patients underwent bowel ultrasound after at least 6 months from surgery; in this study, we analyzed a total of 33 patients who were evaluated by power Doppler.

The study was reviewed and authorized by the Local Ethical Committee.

Bowel ultrasound was performed using the following ultrasonographic equipments: ESAOTE AU4, ESAOTE Technos, ESAOTE MyLab 70, and TOSHIBA Aplio. A first evaluation of the bowel was made with a convex transducer (frequency 3.5 MHz) and then with a high frequency linear-array transducer (7.5–10 MHz); power Doppler was performed at the preanastomotic ileum.

The four ultrasonographers who performed the examinations were all radiologists with at least 3 years of experience in ultrasound scanning of patients with intestinal bowel diseases and all working in the same department. Each investigation was performed by one radiologist, C. T., S. A, R. D., D. P., who, respectively, performed 11, 10, 7 and 5 investigations. During the procedure, the involved tract wall was examined in a transverse section, from the central hyperechoic line of the lumen to the outer hyperechoic margin of the wall with a linear-array transducer. Wall thickness of the ileo-colonic anastomosis was calculated as the average of at least 3

measurements; at the end of the US investigation, measurements of intestinal wall and power Doppler results at the ileo-colonic anastomosis level were reported on a standardized form. Flow was considered to be present when colored pixels could be constantly reproduced in the area of interest or when flowmetric signals could be documented by spectral analysis of the pulsed color Doppler signal. Color Doppler flow was subjectively characterized either as positive (clearly visible, i.e. numerous color signals distributed within and/or around the inflammatory mass or clear identification of vessel paths or minimally visible, i.e. few and/or scattered color signals) or negative (no color signal obtained either inside the lesion or in the periphery).

Ileocolonoscopy was performed in a little percentage of patients and at a different time than bowel ultrasound (due to the invasiveness of this type of exam in patients with resection of the ileum for Crohn's disease), so it is impossible to prove any correlation.

The CDAI was calculated in the follow-up visits.

Statistical analysis

Statistical analysis was performed by using MedCalc software (version 9.2.1.0). The relative risk was calculated with a confidence interval of 95%.

Results

Clinical characteristics of the study population are reported in Table 1.

Table 1.

Other data: 28 patients were clinically inactive (CDAI < 150 at the time of the bowel ultrasound); bowel ultrasound was performed after a mean time of 13 months (range 7–16 months) after surgery.

The average follow-up was 95 months (range: 25–156 months) after surgery.

Major surgical complications occurred in 5 out of the 33 patients (15%). Clearly, our final analysis refers to the reoperation for the disease recurrence and not to the reoperation for these immediate complications (Table 2).

Table 2.

The rate of surgical recurrence for the whole population was 36.4% (12 of 33 patients), at a mean distance of 50 months from previous surgery (range: 20-144 months).

Discussion

Although a sample of 33 patients is not very a large one, considering that power doppler in real world is usually assessed only in a subgroup of patients that underwent bowel ultrasound and the follow up of 95 months is long enough, this looks to be the first case in the literature in which the predictive power of color Doppler for the surgical recurrence of Crohn's disease is assessed.

Out of 33 patients, 19 of them had a positive power Doppler after surgery and this seems to be linked to the fact that color Doppler in clinical practice is performed mostly in patients with a thickened bowel wall and, thus, with a greater probability of active disease.

The surgical recurrence was found to be 36.4%; this percentage is higher than the 20.4% found in our previous study [1]; this seems linked to the fact that the population in which the power Doppler is normally assessed usually has an increased risk of recurrence (increased thickness of intestinal wall).

Patients with positive power Doppler at the anastomosis run a relative risk = 1.5 (95% CI = 0.6–3.9) of undergoing surgery compared to patients with negative power Doppler.

The RR of surgical recurrence of those with positive color Doppler compared to those with negative color Doppler does not reach the statistical significance, since there is

a selection bias of the population, as there are very few patients with negative power Doppler and physiological thickness of the wall (those who have physiological thickness of the wall generally will not be evaluated by power Doppler in real world, which is the setting of our study).

The RR of surgical recurrence for patients with positive power Doppler and a bowel wall thickness at the anastomosis greater than 3 mm (18 patients), 4 mm (16 patients), 5 mm (12 patients), 6 mm (10 patients), respectively, compared to patients with negative power Doppler and lower bowel thickness is shown in Table 3.

Table 3.

The RR of patients with positive power Doppler and increased wall thickness does not reach the statistical significance compared to those with negative power Doppler and lower wall thickness because of the smaller sample size compared to our previous study [1] (in fact, only a limited number of patients who underwent bowel ultrasound were assessed using power Doppler).

The absolute incidence of new surgical intervention was: 28.6% in patients with negative power Doppler, 42% with positive power Doppler, 41.2% with positive power Doppler and thickness >3 mm, 46.7% with positive power Doppler and thickness >4 mm, 54.5% with positive power Doppler and thickness >5 mm, and,

finally, 55.6% with positive power Doppler and thickness >6 mm (Figure 1).

Figure 1.

As far as the therapy, the percentage of patients not taking prophylactic therapy of post-surgical recurrence fell from 31.1% of the previous study [1] to 20%; only 12% of patients were receiving steroids and 3% immunosuppressive agents (Figure 2).

Figure 2.

The percentage of patients with positive power Doppler that had taken steroids or immunosuppressants or biologics at the time of bowel ultrasound (2 out of 19, 10.5%) is similar to that of the whole population (5 out of 33, 15%).

Some critical issues should be considered. The retrospective design of the study represents a limitation and this is the reason why the color Doppler has been assessed mainly in patients with thickened bowel wall, but this is exactly what happens in daily clinical practice; in addition, the examinations have been assessed by the same group of radiologists and all patients were treated along the years by the same doctor (A. M.).

In conclusion, it seems we have found another useful factor for the personalization of patient's care: knowing that 54.5% of patients who performed bowel ultrasound within 1 year after operation and showed both a bowel wall thickness >5 mm and a positive power Doppler will be reoperated, this could help selecting the patients that should undergo colonoscopy for assessing the endoscopic recurrence and suggest the use of a more aggressive medical therapy to try to change the natural history of their disease.

A prospective study would also be useful, where the population with bowel wall thickness >5 mm within 1 year after surgery would be assessed by color Doppler: those with positive color Doppler should undergo colonoscopy for assessing endoscopic recurrence and should be treated with more aggressive drugs (topical or systemic steroids, immunosuppressants, biological agents) to modify the disease behavior and to extend their surgical recurrence-free interval.

Conflict of interest

We have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and

with the Helsinki Declaration of 1975, as revised in 2000. All patients provided written informed consent to enrolment in the study and to the inclusion in this article of information that could potentially lead to their identification.

Human & Animal Studies

The study was conducted in accordance with all institutional and national guidelines for the care and use of laboratory animals.

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Fig. 1 Surgical recurrence rate

Fig. 2 Medications at the time of the bowel ultrasound

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Running title: Doppler and Crohn's disease recurrence.

Table 1
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Table 1. Characteristics of the study population (*n* = 33, Crohn's disease patients).

Males/females	18/15
Median age, years (range)	44 (24–72)
Duration of Crohn's disease, years (range)	12 (0–54)
Smoking habit at surgery, n (%)	
Ever smoker	15 (45.5)
Never smoker	18 (54.5)
Previous surgery, n (%)	
Never	17 (51.5)
1	13 (39.4)
2	1 (3.0)
> 2	2 (6.1)
Total length of bowel resection (cm)	
< 50	20 (60.6%)
>= 50	13 (39.4%)
Indication for surgery, n (%)	
Strictures	20 (60.6)
Fistula	5 (15.2)
Refractoriness to medical therapy	6 (18.2)
Perforation	2 (6.1)

Table 2
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Table 2. Major surgical complications.

Patients with major surgical complications	5 (15%)
Complications	
Anastomotic dehiscence	2
Entero-cutaneous fistula	1
Hemorrhage	1
Venous thrombosis	1
Reoperation	2
Number of patients with anastomosis wall thickness >3 mm 1 year after operation	5 (100%)
Number of patients with surgical recurrence	3 (60%)

Table 3
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Table 3. RR of surgical recurrence.

Power Doppler positive and wall thickness at the anastomosis (mm)	RR
> 3	1.3 (95% CI = 0.5 ÷ 3.3)
> 4	1.7 (95% CI = 0.7 ÷ 4.2)
> 5	2.0 (95% CI = 0.8 ÷ 4.8)
> 6	1.9 (95% CI = 0.8 ÷ 4.5)

Figure 1
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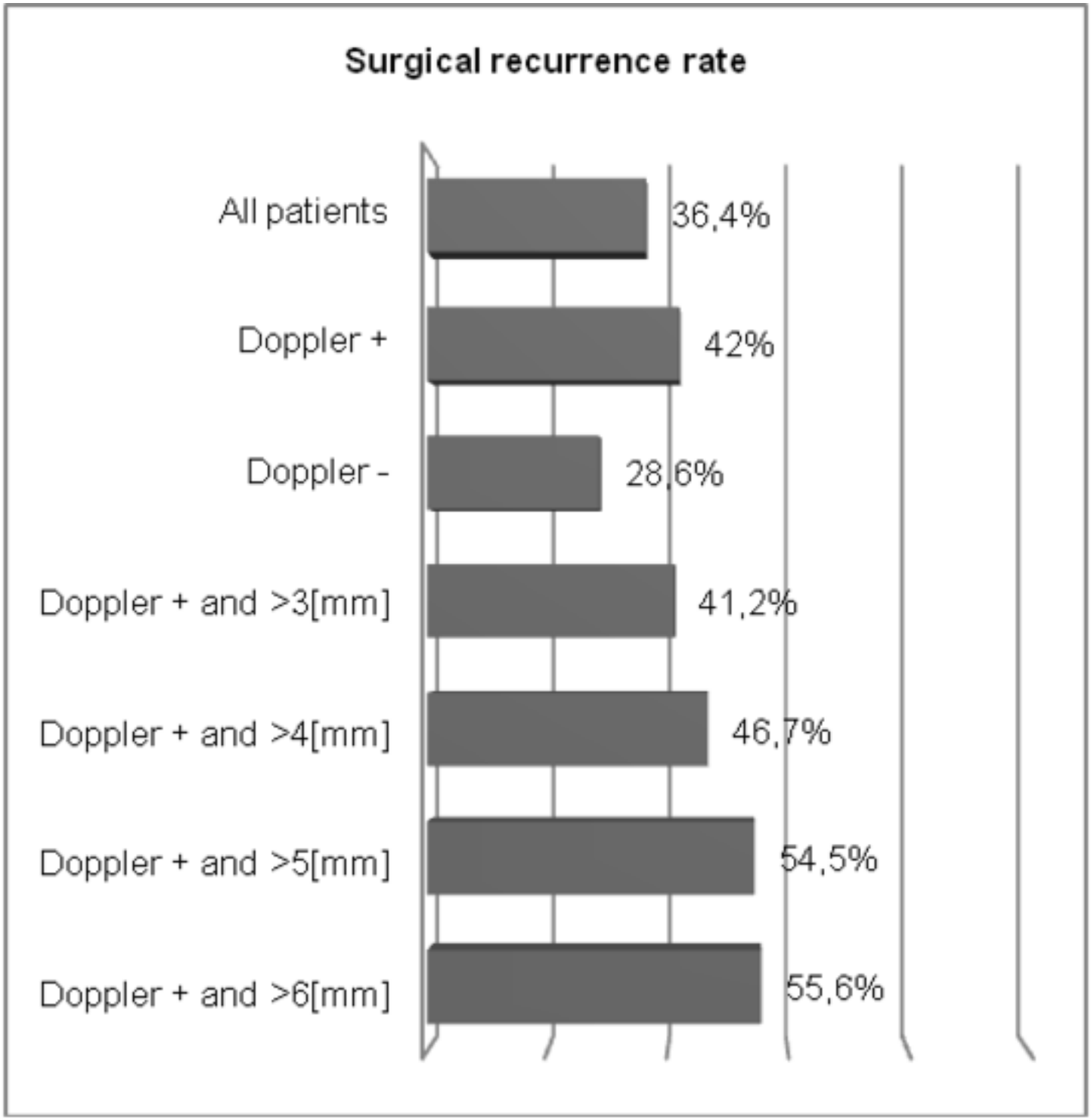

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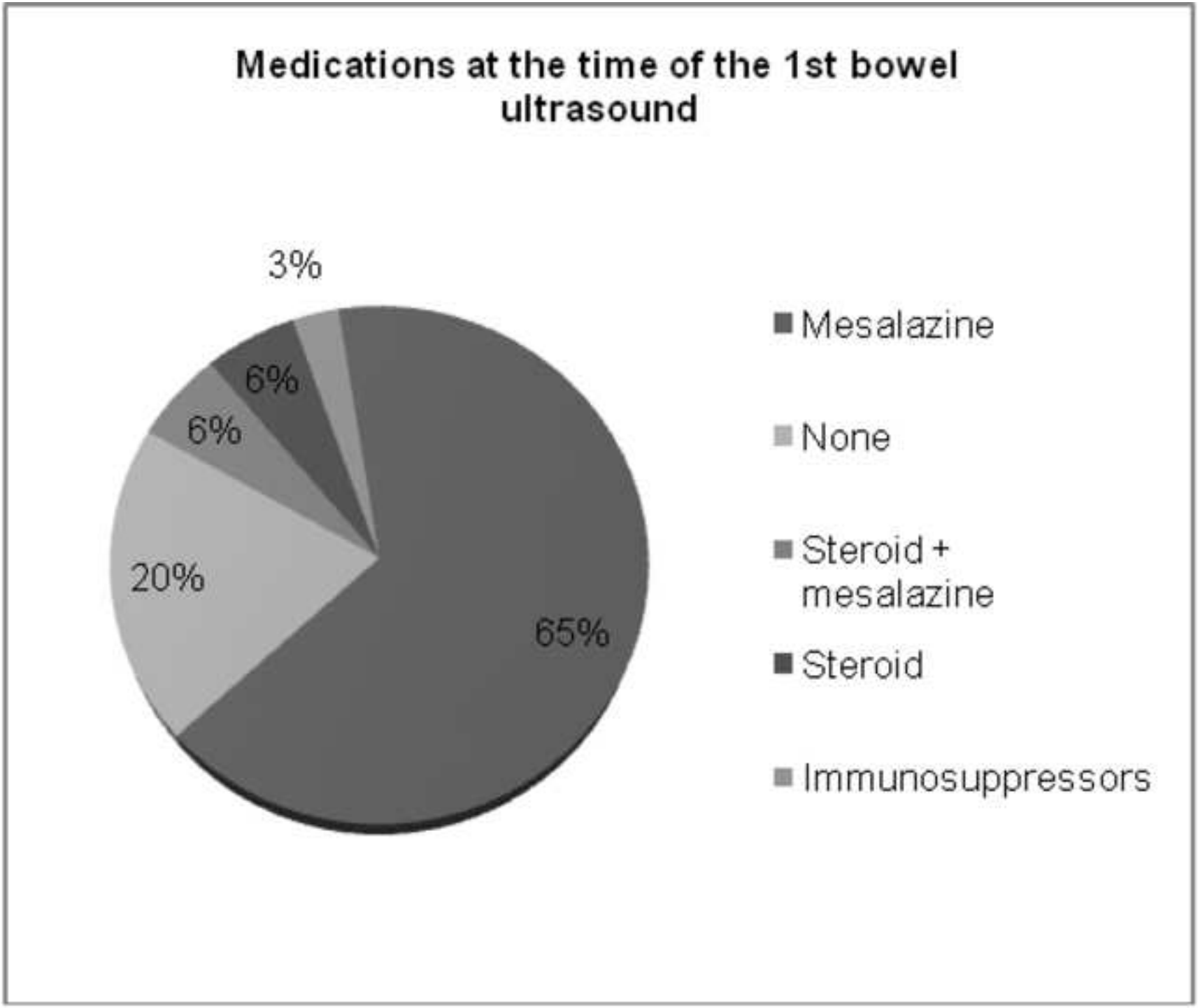

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