Improved Health-Related Quality of Life After Surgical Management of Severe Refractory Constipation-Dominant Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is the most common of the functional gastrointestinal disorders (FGIDs). Despite its prevalence and health-care costs, there are few effective therapies for patients with severe symptoms. Our objective was to determine whether surgical management would improve health-related quality of life (HRQOL) in severe refractory constipation-dominant FGIDs. From 2003 to 2005, 6 patients underwent total colectomy with end ileostomy or primary anastomosis. They completed Short Form 36 (SF-36) and IBS-36 questionnaires preoperatively and postoperatively. HRQOL was compared with age- and sex-matched Canadian norms using Welch's unpaired *t* test. Preoperative SF-36 physical and mental health summary scores were significantly lower than Canadian norms ($P < 0.0001$), while postoperative scores were not significantly different than Canadian norms ($P = 0.50$ and $P = 0.57$, respectively). After surgical management, HRQOL in patients with severe constipation-dominant IBS improved from drastically below that of Canadian norms to a comparable level. This finding questions the convention of avoiding operations in IBS patients and demonstrates that surgical management may be suitable for the appropriately screened patient.

Key words: Health-related quality of life – Surgery – Irritable bowel syndrome

Irritable bowel syndrome (IBS) is one of 20 functional gastrointestinal disorders (FGIDs). These are a heterogeneous group of chronic disorders in which the presenting gastrointestinal (GI) symptoms cannot be explained by structural or biochemical abnormalities.^{1,2} IBS is characterized by abdominal pain associated with defecation, change in bowel habit, bloating, and distension.^{3,4} The ROME III committee developed a set of diagnostic criteria for each FGID separately.^{3,4} However, it has become increasingly accepted that the FGIDs overlap considerably and therefore, IBS should not be considered as a single entity but rather on a spectrum of related disorders.^{1,5}

IBS is the most common of the FGIDs with a prevalence rate in the United States anywhere from 3% to 20%, with most studies quoting around 10%.^{1,2} Although up to 70% of IBS sufferers in the United States do not seek medical attention, the total health-care costs and burden to the health-care system is substantial.^{5,6} In fact, in the United States, among GI illnesses, IBS was second only to gastroesophageal reflux disease in prevalence in a comprehensive assessment of burden of illness.⁵ In addition, the estimated direct and indirect annual health-care costs of IBS in the United States are \$1.6 billion and \$19.2 billion, respectively.^{1,5} Despite the high expenditure for this illness, there are very limited effective treatment options, and patients continue to demonstrate poor health-related quality of life (HRQOL), which is comparable to that seen in patients with organic disease.^{1,7-12}

Treatment options have largely been directed at symptom relief and vary depending on symptom severity. They include any and all of the following: education and reassurance, diet and lifestyle modification, pharmacotherapy directed at relief of bowel-specific symptoms with medications (such as anticholinergics, antispasmodics, antidiarrheals, and laxatives), as well as antidepressants and narcotics, along with referrals to mental health and pain services.^{2,5,13} A combination of the above therapies has been somewhat effective in patients with mild to moderate symptoms; however, in moderate to severe cases, patients often have symptoms that are refractory and persistent despite exhaustive use of the above modalities.

Patients who suffer from severe symptoms of IBS commonly present with a picture of acute severe abdominal and/or pelvic pain and frequently undergo unnecessary emergent abdominopelvic surgeries.¹⁴⁻¹⁷ As the literature would suggest, these surgeries are often nontherapeutic, and thus it is a

general convention to avoid operating on patients with IBS and other FGIDs for the purpose of symptom control.¹⁴⁻¹⁷ Nevertheless, there are some motility-disordered patients who have such intractable symptoms as to severely diminish their quality of life. These patients have received operative management aimed at ameliorating their symptoms and thus improving their lives. At our tertiary care center, we have identified a group of such motility-disordered patients. Patient accounts of their disease experience relate severe pain and constipation leading to debilitating loss of daily functioning, emotional distress, disability, and impaired quality of life. The objective of this study was to determine whether surgical management of severe refractory constipation-dominant motility disorders in adult patients would result in improved HRQOL.

Materials and Methods

This study was approved by the institutional research ethics board. The study population was drawn from patients referred to a colorectal motility clinic at a Canadian tertiary care center from 1996 to 2003. These patients were referred for consideration of surgical management for their motility disorder. Between 2003 and 2005, all such patients who underwent surgical management, including bowel resection, were approached to be involved in this study. All patients who met inclusion criteria and gave informed consent were consecutively sampled. Inclusion criteria were the following: adult (age ≥ 18 years), diagnosis of GI motility disorder, and upcoming bowel resection for management of motility disorder. In order to exclude nonmotility disorders or mechanical causes of obstruction, all of these patients were evaluated thoroughly. Work-up included, but was not limited to, upper and lower GI endoscopy, barium swallow, colonic transit studies, and esophageal and anal manometry. Within 1 month before their surgery, all eligible patients completed preoperative Short Form 36 (SF-36) and Irritable Bowel Syndrome 36 (IBS-36) quality-of-life questionnaires. The SF-36 is a generic HRQOL scale that has been well validated in various clinical settings as well as at the population level.^{18,19} It has 8 domains, each scored from 0 to 100. The domains are as follows: physical function, role physical, pain, role emotional, energy/fatigue, emotional well-being, social function, and general health. These domains can be summarized by a Physical Health Summary score and a Mental Health Summary score. The IBS-36 is a well-

Table 1 Patient demographic and clinical characteristics, including CCI

Patient	Age at onset	Sex	Diagnosis	Type (constipation/diarrhea)	Stool frequency ^a	CCI	CCI (age-adjusted)
1	40s	Female	Motility disorder	Constipation	Every 2 weeks	1	2
2	Unknown	Female	Motility disorder	Constipation	Every 3 to 4 days	0	3
3	Teens	Female	Motility disorder	Constipation	Every 3 to 4 days	1	1
4	40s	Female	Motility disorder	Constipation	Requires daily enemas	0	0
5	Childhood	Female	Motility disorder	Constipation	Once a week	1	2
6	Unknown	Female	Motility disorder	Constipation	Every 3 days	1	2

^aAll stool frequencies were reported as occurring with the patients' use of laxatives..

validated condition-specific HRQOL scale that was developed and validated using Canadian IBS patients.²⁰ Postoperatively, these patients again completed the SF-36 and IBS-36 questionnaires between 6 and 9 months after their surgery.

Demographic and symptom-related (*e.g.*, frequency of bowel movements) data were collected prospectively. A Charlson Comorbidity Index (CCI) was calculated for each person using these data. The CCI is a well-validated and widely used prognostic measure; in our study, it was employed to adjust for the burden of preexisting comorbidities and the potential effect it may have played on both preoperative and postoperative HRQOL.^{21–28} The preoperative and postoperative SF-36 Physical Health and Mental Health Summary scores were compared with age- and sex-matched mean scores for Canadians. The Canadian normative SF-36 data were based on a large multi-centered community-based study conducted in 1996–1997 and sampling within a 50-km radius of 9 Canadian cities stretching from Vancouver to St. John's.²⁹ Welch's unpaired *t* test was used to assess for significant differences between Canadian mean Summary Health scores and the mean Summary Health scores of the study population. Although a nonparametric test such as a Mann-Whitney *U* test would have been more appropriate, given the small sample size, the Canadian normative population data were only available in mean $\pm$ SD format and precluded the use of nonparametric tests. Thus, Welch's unpaired *t* test was used; this test does not assume equal variances between samples and is thus more conservative than the Student *t* test. An α of 0.05 was set as the threshold for rejecting the null hypothesis of no significant difference.

Change scores (postoperative minus preoperative) were calculated for IBS-36 and SF-36 Physical Health and Mental Health Summary scores. In order to standardize the change scores against the Canadian normative data, standardized *z* scores

were calculated for each SF-36 Physical Health and Mental Health Summary score in this study population. For example, this was done as follows for the Physical Health Summary score: patient Physical Health Summary score minus age- and sex-matched mean Canadian Physical Health Summary score, all divided by the SD for that age- and sex-matched mean Canadian Physical Health Summary score. Generalized linear models using type-III analysis of model effects were performed with change scores as the scale response (*i.e.*, dependent) variable and the following predictor variables: surgery type and presence of histopathologic abnormalities in resected bowel specimen. Three separate models were performed for the change scores in IBS-36 and SF-36 Physical Health and Mental Health Summary scores. Sensitivity analyses for the SF-36 change scores were conducted by performing generalized linear models with change in standardized *z* score as the dependent variable. All analyses were performed using the SPSS/PASW (SPSS Version 21.0., IBM Corp., Armonk, NY) statistical package.

Results

From 1996 to 2003, 98 patients were referred to the motility clinic for consideration of surgical management. Between 2003 and 2005, 7 patients met inclusion criteria. Of these, 6 patients completed both preoperative and postoperative HRQOL questionnaires.

The patients were all female. Most had disease onset ranging from childhood to their 40s (Table 1). They presented with constipation-dominant symptoms, with frequency of bowel movements ranging from once every 3 to 4 days to once every 2 weeks despite use of laxatives (Table 1). Charlson Comorbidity Indices (CCI) were either 0 or 1; age-adjusted CCIs ranged from 0 to 3 (Table 1). These patients presented with disordered motility in more than one part of their GI tract. Table 2 depicts the results of

Table 2 Patient dysmotility profile following preoperative work-up

Patient	GU dysmotility	Esophageal dysmotility	Gastric dysmotility	Colonic dysmotility	Anal outlet obstruction	Intussusception	Rectocele
1	Yes	Yes	Yes	Yes	Yes	No	No
2	Yes	No	No	Yes	No	No	No
3	Yes	No	Yes	Yes	Yes	Yes	No
4	Yes	No	No	Yes	No	No	No
5	No	No	Yes	Yes	Yes	No	No
6	Yes	No	Yes	Yes	No	No	No

GU, genitourinary.

preoperative work-up. Most patients underwent total colectomy and ileostomy, while 2 patients underwent colectomy and ileorectal anastomosis; one of the patients with ileorectal anastomosis also had a diverting loop ileostomy (Table 3). Histopathologic abnormalities were noted in 2 patients; these were myenteric plexus hypertrophy and melanosis coli (Table 3).

The mean ($\pm$ SD) preoperative SF-36 Physical Health and Mental Health Summary scores were 13.28 (5.93) and 19.74 (10.16), respectively. The mean ($\pm$ SD) postoperative SF-36 Physical Health and Mental Health Summary scores were 50.42 (23.54) and 51.68 (20.95), respectively. The preoperative SF-36 Physical Health and Mental Health Summary scores were significantly lower than the age- and sex-matched mean scores for Canadians (Welch's *t* test $P < 0.0001$ for both). The postoperative SF-36 Physical Health and Mental Health Summary scores were not significantly different from the age- and sex-matched mean scores for Canadians (Welch's *t* test $P = 0.50$ and $P = 0.57$, respectively) (Fig. 1). All but 1 patient had improved postoperative IBS-36 scores (Fig. 2).

The generalized linear model analysis showed that having a colectomy and ileostomy rather than doing an ileorectal anastomosis was also significantly associated with improved postoperative Physical and Mental Health summary scores ($P = 0.02$ and $P = 0.01$, respectively); sensitivity analysis using change in standardized *z* score also showed a significant association ($P = 0.008$ and $P = 0.006$,

respectively). Having a colectomy and ileostomy rather than doing an ileorectal anastomosis was also significantly associated with improved postoperative IBS-36 scores ($P < 0.0001$). Presence of histopathologic findings (*e.g.*, prominent myenteric plexus, melanosis coli) in the resected bowel specimens was also significantly associated with improved postoperative IBS-36 scores ($P = 0.02$).

Discussion

The preoperative SF-36 Physical and Mental Health Summary scores were found to be significantly below that of Canadian norms ($P < 0.001$ for both). The change between preoperative and postoperative scores was quite large in most patients. More important, the postoperative SF-36 Physical and Mental Health Summary scores were not significantly different than Canadian norms ($P = 0.50$, and $P = 0.57$, respectively). Similarly, most patients showed an improvement in their IBS-36 score after surgery. Although the minimally important difference (MID) in SF-36 score has not been validated in this population, a change of 3 to 5 points on the summary score is considered a robust MID for the SF-36 across many different conditions.^{30,31} With the exception of the Mental Health Summary score for 1 patient, all change scores exceeded the MID of 3 to 5 points. There are no data on the MID for the IBS-36 scale. Our finding that the HRQOL of patients with

Table 3 Type of surgery and histopathology of surgical specimen

Patient	Surgery	Bowel histopathology
1	Colectomy and ileostomy	No reported abnormalities
2	Colectomy and ileorectal anastomosis	Melanosis coli
3	Colectomy, ileorectal anastomosis, diverting ileostomy	No reported abnormalities
4	Colectomy and ileostomy	No reported abnormalities
5	Colectomy and ileostomy	Normal
6	Colectomy and ileostomy	Prominent myenteric plexus

Fig. 1 Preoperative and postoperative SF-36 scores depicted with age- and sex-matched Canadian norms $\pm$ SD. (A) Physical Health Summary scores ($P < 0.0001$ and $P = 0.50$, respectively). (B) Mental Health Summary scores ($P < 0.0001$ and $P = 0.57$, respectively). PH, physical health; MH, mental health.

FGIDs is markedly lower than national norms is consistent with the literature.^{1,7–12}

Our findings also suggest that surgical management aimed at ameliorating symptoms of severe refractory motility disorders may result in significantly increased HRQOL. Furthermore, not only does this increased HRQOL appear to be clinically significant but it also appears to be elevated to a level that is comparable to age- and sex-adjusted Canadian norms.

In the generalized linear model analysis, we found a number of predictors of improved postoperative HRQOL. It has been conventional thought that motility disorders are functional in nature and do not have an organic pathophysiology behind their presence. However, we found that a predictor of improved HRQOL postoperatively was the presence of some form of histopathologic abnormality within the resected specimen. Thus, our findings suggest that an identifiable histopathologic abnormality is associated with improvement of HRQOL after surgery for management of severe motility disorders. Of interest, there has been recent work looking into the possibility of abnormalities within the enteric neurohormonal system that could be associated with the disorder, specifically changes in the myenteric plexus, number of glial cells, and

Fig. 2 Preoperative and postoperative IBS-36 scores, where a lower score indicates a better HRQOL.

interstitial cells of Cajal.^{32–34} Although currently there have been no conclusive data showing an association, there is ongoing research. Identification of histopathologic abnormalities that are associated with motility disorders and improved postoperative HRQOL could potentially allow for screening of this challenging patient population and allow for targeted surgical management in those most likely to benefit.

Our findings also suggest that colectomy and ileostomy result in better postoperative HRQOL than a colectomy and ileorectal anastomosis. This suggests that, contrary to patients' usual preoperative desires, patients with an ileostomy tend to have better HRQOL than those who have intact intestinal continuity. Anecdotally, this finding is generally reflected in patients managed in our clinic prior to and following this study period. In general, patients tend to abhor the idea of an ostomy when it is first presented to them and, in some cases, refuse to consider the functional benefits of an ileostomy over an ileorectal anastomosis. In some patients, the functional consequences (*e.g.*, constant washroom trips, fecal/flatal incontinence, persistent nausea and vomiting) of an ileorectal anastomosis eventually lead to conversion to an ostomy. In these patients, their quality of life tends to improve, although these are anecdotal observations and have not been subjected to standardized pre- or post-assessment. Of interest, our finding of better HRQOL with an ileostomy rather than an ileorectal anastomosis is apparent and detectable even at this early point (*i.e.*, within the first post-op year). Based on our anecdotal experience, we would expect a more pronounced difference in quality of life 2 or 3 years after surgery. Often, we have observed that patients with ostomies are still trying to come to terms with having an ostomy in the year or 2 following surgery and thus may appear to have a

diminished HRQOL as compared with those without ostomies. Conversely, patients without ostomies are so glad to have avoided an ostomy that they initially ignore or minimize the undesirable functional consequences of their ileorectal anastomosis.

The major weakness of this study is the small sample size. However, considering the large effect seen in this study, it would be prudent to follow this study with a larger one. One of the barriers to larger sample sizes is the low incidence of patients that would receive these surgeries for the management of severe motility disorders. Thus, a multi-centered approach would be required. Another barrier is the resistance of surgeons to offer this modality of treatment because of the belief that patients will universally have bad outcomes. The results presented here may provide enough doubt to that assumption that surgeons may be willing to participate in a study examining the efficacy of this treatment strategy.

Another weakness of this study was the use of Welch's unpaired *t* test. Although a nonparametric test such as a Mann-Whitney *U* test would have been more appropriate, given the small sample size, the Canadian normative population data were only available in mean $\pm$ SD format and precluded the use of nonparametric tests. Thus, Welch's unpaired *t* test was used; this is a parametric test, like the Student *t* test, except that it does not assume equal variances between samples and is thus more conservative. Although the use of a parametric test in this instance was suboptimal, the mitigating factor is that the *P* values were starkly on either side of significance (*i.e.*, the significant *P* values were both <0.0001 , and the nonsignificant ones were >0.5). Thus, there were no *P* values at or around $P = 0.05$, where we would worry that having done another test may have tipped it over the threshold in either direction.

Finally, this patient population represents a group of individuals who have endured debilitating symptoms with no benefit from medical therapy. On presentation for surgical assessment, they are aware that surgical therapy is the last option available and are desperate for symptom alleviation. Given this scenario, it may be possible that the benefits seen after operative management represent a placebo effect. To elucidate whether the improved HRQOL seen with surgical management is related to the surgery itself versus a placebo effect, a study would have to incorporate a control group of patients who receive sham surgery. However, at present, there is insufficient evidence to ethically

justify a controlled trial with the use of sham surgery. Nevertheless, the risk of bias introduced by a potential placebo effect is an important consideration that should be addressed in future studies.

In conclusion, HRQOL of patients with severe constipation-dominant motility disorders refractory to medical management is drastically below that of age- and sex-matched Canadian norms. Our findings suggest that surgical management, specifically total colectomy and ileostomy, aimed at controlling refractory symptoms was successful in improving HRQOL to a level comparable to age- and sex-matched Canadian norms. Our findings suggest that an identifiable histopathologic bowel abnormality is associated with improvement of HRQOL after surgery for management of severe motility disorders. Although it has been common practice in the past to avoid operations in patients with FGIDs, the results of this study suggest that specific surgical management may in fact be a suitable treatment option in the appropriately screened patient. However, as this study is small, our findings, although statistically and clinically significant, are not sufficient to drive changes in clinical practice. Larger studies are needed. More important, we need to challenge the assumption that all patients with FGIDs are devoid of organic disease and thus should never be offered surgical management. A significant barrier to accruing larger sample sizes for this study was the resistance of surgeons to offer this modality of treatment because of the belief that patients will universally have bad outcomes. The findings of this small study may call that assumption into question enough that surgeons may be more willing to selectively offer this management modality in the context of a study.

References

1. Talley NJ. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol Motil* 2008;**20**(1):121–129
2. Ringel Y, Sperber AD, Drossman DA. Irritable bowel syndrome. *Annu Rev Med* 2001;**52**:319–338
3. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterol* 2006;**130**(5):1377–1390
4. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterol* 2006;**131**(2):1480–1491
5. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterol* 2002;**123**(6):2108–2131

6. Longstreth GF, Yao JF. Irritable bowel syndrome and surgery: a multivariable analysis. *Gastroenterol* 2004;**126**(7):1665–1673
7. Spiegel BMR. The burden of IBS: looking at metrics. *Curr Gastroenterol Rep* 2009;**11**(4):265–269
8. Lea R, Whorwell PJ. Quality of life in irritable bowel syndrome. *Pharmacoeconomics* 2001;**19**(6):643–653
9. Longstreth GF, Bolus R, Naliboff B, Chang L, Kulich KR, Carlsson J *et al.* Impact of irritable bowel syndrome on patients' lives: development and psychometric documentation of a disease-specific measure for use in clinical trials. *Eur J Gastroenterol and Hepatol* 2005;**17**(4):411–420
10. El-Serag HB, Olden K, Bjorkman D. Health-related quality of life among persons with irritable bowel syndrome: a systematic review. *Aliment Pharmacol Ther* 2002;**16**(6):1171–1185
11. Gralnek IM, Hays RD, Kilbourne A, Naliboff B, Mayer EA. The impact of irritable bowel syndrome on health-related quality of life. *Gastroenterol* 2000;**119**(3):654–660
12. Luscombe FA. Health-related quality of life and associated psychosocial factors in irritable bowel syndrome: a review. *Qual Life Res* 2000;**9**(2):161–176
13. Camilleri M, Bueno L, de Ponti F, Fioramonti J, Lydiard RB, Tack J. Pharmacological and pharmacokinetic aspects of functional gastrointestinal disorders. *Gastroenterol* 2006;**130**(5):1421–1434
14. Longstreth GF. Avoiding unnecessary surgery in irritable bowel syndrome. *Gut* 2007;**56**(5):608–610
15. Hasler WL, Schoenfeld P. Systematic review: abdominal and pelvic surgery in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2003;**17**(8):997–1005
16. Cole JA, Yeaw JM, Cutone JA, Kuo B, Huang Z, Earnest DL *et al.* The incidence of abdominal and pelvic surgery among patients with irritable bowel syndrome. *Dig Dis Sci* 2005;**50**(12):2268–2275
17. Li S, Yu Y, Prakash R. Possible pathogenetic roles of abdominal surgery in irritable bowel syndrome. *Med Hypotheses* 2011;**76**(4):497–499
18. Brazier JE, Harper R, Jones NMB, O'Cathain A, Thomas KJ, Usherwood T *et al.* Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992;**305**(6846):160–164
19. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**(6):473–483
20. Groll D, Vanner SJ, Depew WT, Dacosta LR, Simon JB, Groll A *et al.* The IBS-36: a new quality of life measure for irritable bowel syndrome. *Am J Gastroenterol* 2002;**97**(4):962–971
21. Charlson ME, Pompei P, Ales K, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;**40**(5):373–383
22. Singh B, Bhaya M, Stern J, Roland JT, Zimble M, Rosenfeld RM *et al.* Validation of the Charlson comorbidity index in patients with head and neck cancer: a multi-institutional study. *Laryngoscope* 1997;**107**(11):1469–1475
23. Fowler JE, Terrell FL, Refroe LC. Co-morbidities and survival of men with localized prostate cancer treated with surgery or radiation therapy. *J Urol* 1996;**156**(5):1714–1718
24. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998;**280**(11):975–980
25. Hall W, Ashesh JB, Ryu JK, Narayan S, Vijayakumar S. The impact of age and comorbidity on survival and treatment patterns in prostate cancer: using the Charlson Comorbidity Index to improve outcomes. *Prostate Cancer Prostatic Dis* 2005;**8**(1):22–30
26. Firat S, Bousamra M, Gore E, Byhardt RW. Comorbidity and KPS are independent prognostic factors in stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;**52**(4):1047–1057
27. Birim O, Maat APWM, Kappetein AP, van Meerbeeck JP, Damhuis RA, Bogers AJ. Validation of the Charlson comorbidity index in patients with operated primary non-small cell lung cancer. *Eur J Cardiothorac Surg* 2003;**23**(1):30–34
28. Rieker JR, Hammer E, Eisele R, Schmid E, Hogel J. The impact of comorbidity on the overall survival and the cause of death in patients after colorectal cancer resection. *Langenbecks Arch Surg* 2002;**387**(2):72–76
29. Hopman WM, Towheed T, Anastassiades T, Tenenhouse A, Poliquin S, Berger C *et al.* Canadian normative data for the SF-36 health survey. *CMAJ* 2000;**163**(3):265–271
30. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. *Arthritis Care Res* 2001;**45**(1):384–391
31. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med* 2001;**33**(5):350–357
32. Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A *et al.* Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterol* 2002;**122**(7):1778–1783
33. Kellow JE, Azpiroz F, Delvaux M, Gebhart GF, Mertz HR, Quigley EMM *et al.* Applied principles of neurogastroenterology: physiology/motility sensation. *Gastroenterol* 2006;**130**(5):1412–1420
34. Tornblom H, Lindberg G, Nyberg B, Veress B. Full thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. *Gastroenterol* 2002;**123**(6):1972–1979