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Study of immunological factors in non-inflammatory bowel disease enterocutaneous fistulae

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Registration date	**Overall study status**	[_] Statistical analysis plan
22/12/2010	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
28/09/2018	Digestive System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Study information

Scientific Title
A prospective study single centre comparative study of immunological factors in non-inflammatory bowel disease enterocutaneous fistulae

Study objectives

St. Mark's Hospital in London was founded in 1835 and is a national and international referral centre for intestinal and colorectal disorders. It is one of two national intestinal failure centres in England.

Enterocutaneous fistulae (ECF) are abnormal communications between the gastrointestinal tract and the skin. Although rare, they are associated with considerable morbidity and mortality. Death related to enterocutaneous fistulae remains disproportionately high compared with that associated with other surgical conditions. Studies reported over the past 30 years have shown mortality rates of 6 - 33% in the most recent case series. A retrospective review of ECF in 177 consecutive patients with mean age of 48.7 years (median 49 years) treated over an 8 year period (January 2003 to June 2010) at St. Mark's Hospital has been completed. Results have been compared to a previously reported series from this unit of an 11-year experience of 277 patients.

Fistulae resulted from surgery in 166 of the 177 patients (93.7%). 85 of the 177 patients (48.0%) had a medical history including inflammatory bowel disease (69 Crohn's disease and 16 ulcerative colitis). 150 of the 177 patients underwent definitive surgery (84.7%). The overall healing rate following surgery in the current series was 94.6% compared with 82% in the previous series. Mean delay from previous surgery to current operation was 1 year in the current series compared with 8 months in the previous series. 30 day post fistulae resection mortality was 0% in this current series compared with 3.5% in the previous series.

27 of the 177 patients (15.3%) underwent medical management alone. The overall healing rate following medical management was 46.4% compared to 19.9% in the previous series. The spontaneous closure rate was lower than in many other reported series, perhaps reflecting the complex group of patients, many of whom were referred from other centres after failure of fistulae healing. In addition, the St. Mark's Intestinal Failure Unit has had a long standing interest in inflammatory bowel disease, reflected in the relatively high prevalence of Crohn's disease in this cohort.

The incidence and aetiology of fistulae are highly dependent on the surgical experience and case load at particular institutions, and on patient and disease related cofactors. Moreover, much of the published data relate to experience at specialised centres treating complex cases in particularly unstable patients. It is estimated that 75 - 85% of enterocutaneous fistulae form after operation as a result of bowel injury, inadvertent enterotomy and/or anastomotic leakage. Fistulae formation is more commonly associated with surgery in the presence of malignancy or inflammatory bowel disease, and with attempted division of dense adhesions. In the remaining 15 - 25% of instances, enterocutaneous fistulae form spontaneously secondary to underlying pathology. Inflammatory bowel disease, in particular Crohn's disease, is the commonest cause of spontaneous enterocutaneous fistulation in the developed world, other causes include radiation enteritis, diverticular disease, malignancy, intra-abdominal sepsis and trauma.

Fistulae formation can result in a number of serious or debilitating complications, ranging from disturbance of fluid and electrolyte balance to sepsis and even death. The patient will almost always suffer from severe discomfort and pain. They may also have psychological problems, including anxiety over the course of their disease, and a poor body image due to the malodorous drainage fluid. Post operative fistulae formation often results in prolonged hospitalisation, patient disability, and enormous cost. Therapy has improved over time with the introduction of parental nutrition, intensive post operative care, and advanced surgical techniques, which has reduced mortality rates. However, the number of patients suffering from gastrointestinal fistulae has not declined substantially. This can partially be explained by the fact that with

improved care, more complex surgery is being performed on patients with more advanced or complicated disease that are generally at higher risk. Therefore, gastrointestinal fistulae remain an important complication following gastrointestinal surgery.

A three stage strategy is generally employed in the management of gastrointestinal fistulae based on diagnosis and investigation, stabilisation/conservative treatment, and surgical measures. Optimal therapy is reliant on thorough radiological investigation to determine the potential for spontaneous closure, and classification according to anatomical site and nature of output allowing timely instigation of appropriate management measures.

The management of enterocutaneous fistulae continues to present a considerable challenge to surgeons, gastroenterologists and allied professionals, and this has resulted in a variety of different management strategies. Patients have frequently undergone several operative procedures, and their physiological and nutritional reserves are often severely compromised. Management should focus initially on correction of fluid and electrolyte disturbances, aggressive treatment of sepsis and control of fistulae output. Nutritional requirements must be addressed and attention paid to skin care and psychological support. Only after these issues have been dealt with adequately, and if the fistulae persists after conservative measures, should further surgery be contemplated.

Although many enterocutaneous fistulae close spontaneously, if the fistulae remains open after 2 months surgical intervention is likely to be needed as spontaneous closure is unlikely after this interval. Major abdominal surgery stimulates the formation of dense adhesions, especially when complicated by intra abdominal sepsis. This reaction is most severe between 3 weeks and 3 months after operation, and further surgery during this time is more likely to be complicated by fistulae recurrence. Operative repairs should be performed when spontaneous closure does not occur, but it should be delayed for at least 3 months.

The local production of tumour necrosis factor alpha (TNF-a) is thought to have a key role in the initiation and propagation of Crohn's disease. Production of TNF-a in the intestinal mucosa, serum and stool is increased in patients with Crohn's disease. There are numerous biological activities that are attributed to TNF-a. Some of these include; induction of proinflammatory cytokines such as interleukin (IL) 1, IL 6 and enhancement of leukocyte movement or migration from the blood vessels into the tissues by increasing the permeability of endothelial layer of blood vessels. In animal models, antibodies to tumour necrosis factor alpha (antiTNF-a) prevent or reduce inflammation suggesting that therapy with such antibodies may be useful for disorders in which chronic inflammation may be due to an increase in cytokines produced by the T helper 1 subclass of T cells.

Infliximab is a genetically constructed IgG1 murine human chimeric monoclonal antibody that binds both the soluble subunit and the membrane-bound precursor of TNF-a. Infliximab inhibits a broad range of biological activities of TNF-a, presumably by blocking the interaction of TNF-a with its receptors, and it may also cause lysis of cells that produce TNF-a. Infliximab has been approved for treating ankylosing spondylitis, Crohn's disease, fistulising Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, and ulcerative colitis. Infliximab is also prescribed (out of indication) for the treatment of Behçet's disease, and infusions of infliximab have been used successfully in the treatment of sciatica due to slipped discs. Infliximab was first used for closure of fistulae in Crohn's disease in 1999. In a phase II clinical trial with 94 patients who had draining abdominal or perianal fistulae, the researchers showed that Infliximab was effective in closing fistulae in 56 - 68% of patients. A large 296 patient Phase III clinical trial (ACCENT 2 trial) showed that infliximab was additionally beneficial in maintaining closure of fistulae, with almost two-thirds of all patients treated with the 3 initial doses infliximab having a

fistula response after 14 weeks, and 36% of patients maintaining closure of fistulae after a year, compared with 19% who received placebo therapy.

It is likely that persistent inflammation prevents adequate healing of these fistulae and that TNF-a and the subsequent stimulation of the pro-inflammatory cascade promotes their existence. A case series of three patients has reported patients with persistent enterocutaneous fistulae not associated with inflammatory bowel disease to of healed following single infusion of infliximab. A review of the literature reveals no further studies to asses immunomodulatory therapies, such as infliximab, for patients with enterocutaneous fistulae not associated with inflammatory bowel disease. There are also no studies to measure TNF-a levels in serum or mucosa of patients with enterocutaneous fistulae not associated with inflammatory bowel disease.

We will examine the types of pro and anti-inflammatory immune cytokines and hormones which are present in the blood stream and fistulae, that cause the fistulae to persist rather then to heal. If this study can show the presence of TNF-a in the fistulae tract then there would be a potential for a novel therapy for patients with persistent enterocutaneous fistulae not associated with inflammatory bowel disease. This would be an alternative option and benefit an already surgically challenging group of patients associated with a high morbidity and mortality where it is deemed conservative management has failed. We aim to show that immunological factors and their interactions are in operation within non-inflammatory bowel disease enterocutaneous fistulae.

Ethics approval required
Old ethics approval format

Ethics approval(s)
National Research Ethics Service, North London REC 1 approved on the 26th July 2010 (ref: 08 /H0717/24; protocol no.: CRO1043)

Study design
Prospective study single centre comparative study

Primary study design
Interventional

Study type(s)
Screening

Health condition(s) or problem(s) studied
Study of immunological factors in non-inflammatory bowel disease enterocutaneous fistulae

Interventions
An eligible patient will be detected at referral or seen in clinic or the ward and offered participation in this study. The study will be explained, discussed and patients encouraged to ask questions for discussion. A trial information sheet will be provided. Patients who decide to enter the study will be required to sign a consent form. The patients who decline to enter the study, will be treated with the normal standard of clinical care provided.

For patients who enter the study:
At the time of operation or on the ward or in outpatients, biopsies will be taken under local anaesthetic from the enterocuaneous fistulae tracts of non-inflammatory bowel disease and inflammatory bowel disease patients (groups i and ii).

A biopsy of the enterocutaneous fistulae tract will be taken to assess for baseline pro- and anti-inflammatory cytokine markers including TNFa levels. Biopsy forceps will be used to take tissue samples under direct vision from the fistulae tract. We will only take five 2 mm samples.

Healthy patients undergoing screening colonoscopy or sigmoidoscopy with normal mucosa endoscopically and histologically will be used as controls. A maximum of ten biopsies will be taken from the colon and/or small intestine in addition to those required for clinical evaluation (group iii).

Peripheral blood (2 - 50 ml) will be obtained, taken by a clinician or other trained person from all three groups (groups i, ii and iii).

All the patients will have the intervention on one occasion only. Patients will not be followed up after this as the study will not directly affect their outcome, hence follow up is not applicable.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
Cytokine profiles in the mucosa from all three groups will be assessed using multiplex bead analysis. Cytokine blood tests machine analyser will be used to simultaneously analyse the following cytokines, chemokines and growth factors: IL-1a, IL-1b, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-a, IFN-y, MCP-1, EGF and VEGF.

Samples will be collected and stored. Once all the samples have been collected, they will be assessed using the multiplex analyser in one go. This helps to reduce bias, rather then performing the tests one by one with different quantities of reagents each time. The timepoint to perform this test will hence depend on when all the patients have been recruited.

Key secondary outcome(s)
No secondary outcome measures

Completion date
07/10/2011

Eligibility

Key inclusion criteria
Non-inflammatory bowel disease enterocutaneous fistulae participants (group i):
1. Consent to the study
2. Male or female
3. Aged 18+ years
4. Single or multiple enterocutaneous fistulae for at least 3 months duration as a result of non-

inflammatory bowel disease, and not responding to standard treatments
5. Enterocutaneous fistulae confirmed to be due to non-inflammatory bowel disease by radiography, endoscopy or pathological examination

Inflammatory bowel disease enterocutaneous fistulae participants (group ii):
1. Consent to the study
2. Male or female
3. Aged 18+ years
4. Single or multiple enterocutaneous fistulae for at least 3 months duration as a result of inflammatory bowel disease and not responding to standard treatments
5. Enterocutaneous fistulae confirmed to be due to inflammatory bowel disease by radiography, endoscopy or pathological examination
6. Patients with stable inflammatory bowel disease

Normal bowel mucosa participants (control group/group iii):
1. Consent to the study
2. Male or female
3. Aged 18+ years
4. Healthy volunteers
5. Normal endoscopic examination of the bowel
6. No prior history of inflammatory bowel disease or enterocutaneous fistulae

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Group i and iii:
1. Current sepsis or abscess
2. Previous treatment with infliximab, investigational agents or any medication which reduces the concentration of TNF-a
3. History of Crohn's disease or ulcerative colitis

Group ii:
1. Current sepsis or abscess
2. Previous treatment with infliximab, investigational agents or any medication which reduces the concentration of TNF-a
3. Patients taking steroids for inflammatory bowel disease within 1 month prior to start of the study
4. Patients with acute flare up of inflammatory bowel disease

Date of first enrolment
01/12/2010

Date of final enrolment
07/10/2011

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Consultant Colorectal and Intestinal Failure Surgeon
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Sponsor information

Organisation
Imperial College London (UK)

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Charity

Funder Name
Bowel Disease Research Foundation (BDRF) (UK) - an independent charity, BDRF functions as the research arm of the Association of Coloproctology of Great Britain and Ireland (ACPGBI)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2017		Yes	No
Protocol article	protocol	27/05/2011		Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes