Non-drug therapies for the management of chronic constipation in adults: the CapaCiTY research programme including three RCTs

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Scientific summary

The CapaCiTY research programme

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Scientific summary

Background

Constipation is common in adults and children, with up to 20% of the population reporting this symptom depending on the definition used. Some people (1–2% of the population) suffer symptoms that are chronic, disabling and refractory to basic treatments. Such people, who are most commonly female, are usually referred to secondary care, with many progressing to tertiary specialist investigations. Patient dissatisfaction and health-care and societal costs are high in this group.

Management of chronic constipation (CC) is generally stepwise, with first-line conservative treatment, such as lifestyle advice and laxatives (primary care), followed by nurse-led bowel retraining programmes, sometimes including focused biofeedback (secondary/tertiary care). Such treatments are poorly standardised in the UK and far from universally successful. Patients with intractable symptoms and impaired quality of life (QoL) may subsequently be offered irreversible surgical interventions that have unpredictable results.

Objectives

The main aims of the Chronic Constipation Treatment Pathway (CapaCiTY) research programme were to trial the effectiveness of three current and popular interventions for CC.

CapaCiTY trial 1:

- to determine whether or not standardised specialist-led habit training plus pelvic floor retraining using computer-assisted direct visual biofeedback (HTBF) is more clinically effective than standardised specialist-led habit training alone (HT) at 6 months' follow-up
- to determine whether or not outcomes of such specialist-led interventions are improved by stratification to HTBF or HT based on prior knowledge of anorectal and colonic pathophysiology using standardised radiophysiological investigations (INVEST).

CapaCiTY trial 2:

- to compare the impact of transanal irrigation (TAI) initiated with a low-volume and a high-volume system on patient disease-specific QoL after 3 months of treatment.

CapaCiTY trial 3:

- to determine the clinical efficacy of laparoscopic ventral mesh rectopexy (lapVMR) compared with controls at short-term follow-up (24 weeks).

In addition, the programme sought to:

- detail the baseline phenotype of UK patients with CC to identify symptom burden and psychological morbidity
- systematically review the outcomes of all current surgical interventions for CC
- synthesise results of all three trials with current evidence to produce a prototype treatment pathway for health-care decision-makers.

Methods and results

Standardised methodological framework, recruitment and baseline phenotyping

Participants met stringent eligibility criteria. The main inclusion criteria were age 18–70 years, symptom onset > 6 months prior to recruitment, symptoms meeting the American College of Gastroenterology's constipation definition and constipation that failed treatment to a minimum basic standard. The main exclusions were secondary constipation and previous experience of study interventions.

A total of 275 participants were recruited across three trials, representing a major shortfall in the required sample sizes ($n = 808$). This reflected several major process challenges but also low uptake from the 733 patients screened (37.1%). About half of screen failures were because participants failed eligibility and half were because participants declined. There were also problems of participant retention, with higher-than-anticipated loss before primary outcome (actual loss 11–43% vs. anticipated loss 20%).

Trial participants were 90% female (100% in CapaCiTY trial 3) and were a mean age of 45 years [interquartile range (IQR) 33–57 years]. Baseline phenotyping indicated high levels of comorbid medical disorders (> 70%) and a history of previous abdominal and pelvic surgery (> 50%). Risk factors such as psychiatric diagnoses and joint hypermobility were present in ≈ 20% of participants. Around two-thirds of women were parous. Although the criteria for chronicity of constipation was 6 months' duration, mean duration was 6 years and almost all participants with CC had constipation that proved intractable to lifestyle modification and laxatives, which was reflected by referral pattern (80% of referrals were from secondary or tertiary care). Almost 20% of these cases of CC were also refractory to prokinetic drug therapy. Levels of symptom burden were high, with mean Patient Assessment of Constipation Quality Of Life (PAC-QoL) and Patient Assessment of Constipation Symptoms (PAC-SYM) scores of > 2.0 points at baseline. In addition, > 50% of participants had faecal incontinence symptoms, > 30% had urinary symptoms and > 20% (100% in CapaCiTY trial 3) had pelvic organ prolapse symptoms. Levels of psychological morbidity were high. Cut-off points on the self-reported Patient Health Questionnaire-9 items (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) scale suggest that around one-third of participants would have met criteria for a depressive or anxiety disorder. These rates are six times higher than those reported in the general population and are on the higher end of mental comorbidity in patients with medical conditions.

Baseline data formed the basis of a subsequent standardised (for all three trials) panel of outcomes, including several validated symptom-scoring instruments, cost-effectiveness variables [i.e. individual-level patient costs from diaries and EuroQol-5 Dimensions, five-level version (EQ-5D-5L), scores to calculate quality-adjusted life-years (QALYs)] and qualitative methodology to determine participant experience (through a total of 45 interviews). The primary clinical outcome was mean change in validated PAC-QoL score. Secondary clinical outcomes included a range of validated disease-specific (PAC-SYM), generic [Measure Yourself Medical Outcome Profile 2 (MyMOP2)] and psychological [GAD-7, PHQ-9, Brief Illness Perception Questionnaire for Chronic Constipation (BIPQ-CC)] scoring instrument values.

CapaCiTY trial 1: habit training with direct visual biofeedback compared with habit training alone in adults with chronic constipation

We sought to answer the question of whether or not, in unselected participants with CC, a more time-consuming, expensive and invasive procedure (namely, instrument-directed visual biofeedback) added benefit to that achieved by a more basic programme of nurse-led bowel education – namely, habit training. We compared HT with HTBF. In addition, because of strongly held views (mainly in the USA) that biofeedback works only for a subset of patients with CC who have dyssynergic defaecation (a specific functional disorder), we used a battery of UK-standardised specialist tests of anorectal and colonic function (INVEST) to stratify participants to one treatment or the other. Both treatments were provided by trained NHS specialist colorectal nurses or physiotherapists.

To answer both research questions concurrently required a sample size of 394 participants (based on 3 : 3 : 2 randomisation to HT, HTBF and INVEST treatment, respectively). Unfortunately, the CapaCiTY trial 1 recruited only 182 participants, and only 103 participants provided primary outcome data at 6 months after cessation of therapy. With the caveat that all results were underpowered, there was no evidence that HTBF conferred additional benefit over HT {HT: PAC-QoL score at baseline, 2.26 points [standard deviation (SD) 0.69 points], vs. at 6 months post treatment, 1.49 points [SD 0.85 points]; HTBF: PAC-QoL score at baseline, 2.41 points [SD 0.81 points] vs. at 6 months post treatment, 1.65 points [SD 1.03 points]; treatment difference −0.03 points, 95% confidence interval (CI) −0.33 to 0.27 points; $p = 0.8445$}. Secondary outcomes also reflected equal beneficial effects of both HT and HTBF on a range of symptom and QoL outcomes (e.g. mean PAC-SYM scores decreased from 2.2 points at baseline to 1.5 points at 6 months and weekly laxative use decreased fourfold). Global satisfaction was 65%, reflecting participants who liked or disliked both interventions for a number of reasons. Similar results were obtained for INVEST vs. no INVEST, with no difference in primary outcome [INVEST: mean PAC-QoL score at baseline, 2.33 points (SD 0.74 points) vs. at 6 months post treatment, 1.56 points (0.93 points); no INVEST: mean PAC-QoL score at baseline 2.36 points (0.78 points) vs. at 6 months post treatment, 1.81 points (1.03 points); treatment difference 0.22 points, 95% CI −0.11 to 0.55 points; $p = 0.1871$]. Participants provided reasons for liking INVEST, for example greater knowledge of their condition (and knowing that their condition was not 'all in their mind'), and described disliking the invasiveness of, and embarrassment caused by, the tests. Given similar changes in EuroQol-5 Dimensions, five-level version (EQ-5D-5L), scores for all interventions, cost-effectiveness analyses favoured the simpler (i.e. HT and no INVEST) strategies as the dominant strategies. For both HTBF and INVEST, cost increases were significant (HTBF vs. HT: £239, 95% CI £133 to £354; INVEST vs. no INVEST: £543, 95% CI £403 to £685) and QoL was actually reduced compared with HT (HTBF: −0.010 QALYs, 95% CI −0.053 to 0.03 QALYs; INVEST: −0.047 QALYs, 95% CI −0.093 to −0.001 QALYs). The probability that HT is cost-effective was a *p*-value of 0.83 at a willingness-to-pay (WTP) threshold of £30,000 per QALY.

CapaCiTY trial 2: pragmatic randomised controlled trial of low-volume compared with high-volume initiated transanal irrigation therapy in adults with chronic constipation

A total of 65 participants were randomised (low-volume TAI, $n = 30$; high-volume TAI, $n = 35$) from a target sample size of 300 participants. At 3 months, there was a modest reduction in PAC-QoL scores in the low-volume TAI group, from a mean of 2.4 points to a mean of 2.2 points (SD −0.2 points); there was a greater reduction in mean score in the high-volume TAI group, of 0.6 points (difference −0.37 points, 95% CI −0.89 to −0.15). Substantially greater crossover from low-volume to high-volume TAI over the follow-up period ($n = 18$) than from high-volume to low-volume TAI ($n = 6$) indicated a preference for high-volume TAI. Compared with low-volume TAI, high-volume TAI had similar costs (−£8, 95% CI −£240 to £221) but was associated with significantly greater QoL (0.093 QALYs, 95% CI 0.016 to 0.175 QALYs). Qualitative analysis reflected the view that the increased clinical effectiveness of high-volume TAI outweighed concerns about the slightly increased duration and discomfort.

CapaCiTY trial 3: stepped-wedge randomised controlled trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation

Seven high-quality systematic reviews of CC surgery with graded practice recommendations based on European consensus were published in 2017 confirming lapVMR as an evidential need. A total of 28 participants were randomised from a target sample size of 114 participants, and lapVMR resulted in substantial short-term reduction in PAC-QoL scores (−1.09 points, 95% CI −1.76 to −0.41 points) and beneficial changes in all other outcomes that were maintained to 72 weeks. There were few adverse events. However, significant increases in cost (£5012, 95% CI £4446 to £5322) resulted in only modest increases in QoL (0.043 QALYs, 95% CI −0.005 to 0.093 QALYs), with an incremental cost-effectiveness ratio of £115,512 per QALY at 48 weeks. Participant experiences were mixed, including participants who were globally satisfied, participants experiencing partial or transient benefits and participants who felt that it was not the 'miracle' cure they were looking for.

Conclusions

Firm conclusions are limited by significant under-recruitment. However, synthesis of clinical effectiveness and cost-effectiveness data with qualitative experience provides themes and suggestions for a CC pathway of care:

- In unselected CC patients, HT helps the majority, and the more costly, time-consuming and invasive intervention of HTBF should be reserved for special situations (specific diagnoses or perhaps failure of HT).
- Expensive and invasive radiophysiological investigations cannot be recommended early in the care pathway.
- The default for TAI should be high volume, with low volume reserved for special cases or patient preference.
- Care needs to be exercised in recommending surgery because, although surgery reduces constipation symptoms greatly in the short term, there was no evidence that surgery improved general QoL beyond 1 year.
- Future interventions should focus on incorporating psychological methods alongside HT to address psychological comorbidity.

Future research

It is not recommended that others try to repeat the CapaCiTY trials in their current form. First, it is unlikely that the main conclusions would vary despite further recruitment; second, lessons learned in respect of recruitment should deter others from trying to deliver parallel-group randomised controlled trials in this population, even with less explanatory designs. Future research could focus on better understanding the profound psychological comorbidity in the CC population and, if new interventions are to be trialled (including those co-addressing psychological and behavioural problems), these might be best suited to a design that incorporates experimental evaluations in a longitudinal cohort of participants, for example trials within cohorts studies. Such trials should seek to maximise pragmatism by sacrificing standardisation of specialist investigations and interventions in favour of uptake and recruitment; they would also benefit from an expanded network of centres (including outside the UK) to ensure timely recruitment and a greatly simplified and flexible follow-up regimen that could exploit advances in technology for remote follow-up.

Trial registration

These trials are registered as ISRCTN11791740, ISRCTN11093872 and ISRCTN11747152.

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