W22: Management of Fecal Incontinence from Bench to Bedside
Workshop Chair: Donna Bliss, United States
12 September 2017 15:30 - 17:00

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**Speaker Powerpoint Slides**
Please note that where authorised by the speaker all PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website [www.ics.org/2017/programme](http://www.ics.org/2017/programme). Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

**Aims of Workshop**
This workshop will provide a comprehensive overview of current approaches for managing fecal incontinence (FI) from bench to bedside. It will explain progress in developing cutting-edge cell-based therapies for FI and provide the latest evidence about behavioral and conservative management strategies as well as surgical modalities. The session will focus on adults and incorporate findings and recommendations of the ICI6-ICS consultation.

**Learning Objectives**
At the end of the session, the participant will be able to:
1. Examine the different types of behavioral therapies and conservative and self management strategies for fecal incontinence (including devices such as an anal plug, anal insert, and vaginal bowel device). Review their evidence, strengths, and limitations, and impact of managing FI on daily life.
2. Discuss the indications and efficacy of surgical procedures in treating fecal incontinence, including sphincter repair, sacral neuromodulation, sphincter replacement and implantable sphincter enhancement device—good with this.
3. Discuss advances in cell-based therapies for fecal incontinence and consequences of their use.

**Learning Outcomes**
1. Understand the impact of managing fecal incontinence (FI) on daily life.
2. Understand that conservative/self management and behavioral therapy (i.e., non-surgical approaches) of FI are the initial strategies.
3. Understand the role of surgery including sphincter repair and sacral neuromodulation (SNM) as well as other new modalities such as an implantable sphincter and a new device to enhance sphincter function in the treatment of FI.

**Target Audience**
Physicians, Nurses and Physiotherapists interested in the latest evidence about comprehensive therapies for fecal incontinence

**Advanced/Basic**
Basic

**Suggested Reading**

Fecal incontinence is a type of bowel leakage associated with emotional distress, reduced quality of life, and often other problems such as odor and skin damage. Management of fecal incontinence among community-living adults begins with conservative or symptom management approaches unless surgery is indicated. Central to conservative management is a focused assessment of lifestyle and previous self-management activities to assess whether they improve or exacerbate leakage and need modification. This session will review the latest evidence, recommendations and algorithm for conservative management of fecal incontinence of adults living in the community per the recent ICS-ICS16 review. Content is applicable to primary care or generalist healthcare providers who are frequently the first contact for conservative management.

Conservative management of fecal incontinence includes ascertaining a patient’s goals for therapy, inquiring about self-management strategies tried, and potentially lifestyle modifications. Studies have revealed a need for improved incontinence-related literacy for the patient and possibly a family caregiver; therefore, education about bowel function, leakage, and available interventions is important part to engage the patient in the conservative management plan. Patients also need information about advances in and selecting absorbent products aimed at containing bowel leakage while reducing associated skin problems. Studies have tested patient education strategies to improve knowledge and use of recommended therapies. This workshop will provide a comprehensive overview of current approaches for managing fecal incontinence (FI) from conservative management and behavioral therapies to surgical approaches. It will also review the latest work in cellular therapies targeted to fecal incontinence.

Conservative Management: Lifestyle
Donna Z. Bliss, PhD, RN, FGSA, FAAN, Professor of Nursing and Nursing Research, University of Minnesota School of Nursing, United States

The management of faecal/anal incontinence in the adult population is multifactorial. The first line therapeutic approach is dietary and lifestyle modifications. The International Consultation on Incontinence recommends patient education...
about the causes of faecal incontinence and a systematic effort to remove barriers to effective toileting is an intervention likely to be beneficial based on the consensus of experts. This is often followed by or given in association with a form of behavioural therapy. In order to change the behaviours associated with faecal incontinence many therapists will use Biofeedback which has also been described as operant conditioning therapy. Biofeedback can take many forms and this can make review of the literature difficult as studies use different protocols cannot be directly compared. The American College of Gastroenterology and the American Gastroenterological Association both recommend biofeedback for the treatment of faecal incontinence. Biofeedback gives the subject immediate feedback about subconscious body processes. Equipment is used to detect and amplify a physiological response. Three main modalities are described in the literature, with many variations and adjunctive measures.

1. Improvement of anal sphincter function – power, endurance co-ordination
   • Intra anal surface Electromyography
   • Intra anal manometry
   • Trans perineal ultrasound
2. Re-training co-ordination of rectal filling sensation with voluntary contraction of anal sphincter
   • Double balloon catheter to evoke rectal sensation and re-train sphincter co-ordination
3. Rectal sensation re-training
   • Use of rectal balloon catheter

Biofeedback is often offered in conjunction with pelvic floor muscle training. In association with Behavioural therapy, the consistency of the stool must also be considered and may require further modification of dietary intake or stool consistency modification via the use of medication as used in the CAPABLE study.

This presentation will review the current evidence regarding behavioural therapy for faecal/anal incontinence in adults and will examine recommendations from the ICS/ICI-6 for this therapeutic area.

Evolving Surgical Treatments for the Treatment of Fecal Incontinence: An Evidence and Case-Based Approach
Holly E. Richter PhD, MD, FACOG, FACS, J Marion Sims Professor Obstetrics and Gynecology and Director, Division of Urogynecology and Pelvic Reconstructive Surgery, University of Alabama at Birmingham, United States

Significant innovative approaches for the surgical treatment of fecal incontinence (FI) have emerged in the past 10 years. In general, surgery should be offered to women who have failed a credible attempt of conservative therapies and viewed as an adjunct to conservative therapies. Surgical therapies include repair of anal sphincter disruption. For most women, sphincter injuries are caused by obstetric trauma in the anterior segment. The etiologies for chronic sphincter disruptions can be due to either unrecognized injuries at the time of childbirth, from a perineal repair breakdown, or persistent injuries after the primary repair. Short-term continence rates have been reasonably good with up to 75% of patients becoming continent to liquid/solid stool. Longer-term results suggest that these results are not robust.

Other surgical modalities include neosphincter approaches such as graciloplasty and artificial bowel sphincter (ABS). Graciloplasty success rates of 38-90% have been reported. However, gracilis muscle transfer has drawbacks; deterioration in effectiveness over time, a long learning curve for surgeons, and high morbidity. Complications include infection and problems related to the defeactory dysfunction. Existing data on ABS success rates and safety vary considerably. Device erosion and infection are the most common reasons for explantation.

Sacral Neurostimulation (SNS) was first introduced in Europe in 1994 as a minimally invasive treatment for FI.[7] The InterStim® (Medtronic, Inc., Minneapolis, MN) was approved by the US Food and Drug Administration (FDA) for chronic refractory FI in April, 2011. In the 2010 pivotal US multicenter trial including 133 patients undergoing InterStim®, 83% achieved therapeutic success of 50% reduction of FI episodes at 12 months, and 41% had complete continence. Common device-related adverse events are implant site pain (28%), paresthesia (15%), and changes in the sensation of stimulation (12%).

Posterior tibial nerve stimulation (PTNS) for FI has been approved in Europe, but is still under investigation in the US. PTNS treatment uses a 34-gauge needle to stimulate the posterior tibial nerve near the medial malleolus to achieve effects via L4 – S3 nerve roots. PTNS is a minimally invasive outpatient therapy with almost no associated morbidity. Estimated cost is less than 1/10th compared to that of SNS.

Bulking materials into the submucosa or intersphincteric space increase the tissue volume in the high-pressure zone, especially in the proximal sphincter canal, creating a greater seal at rest. In 2011, non-animal stabilized hyaluronic acid/dextranomer (NASHA Dx) was approved by the FDA for the treatment of FI refractory to conservative therapy. Although complete continence may not be achieved, perianal bulking therapy may be an effective and safe option to alleviate symptoms especially in patients with mild to moderate passive FI.

Diversion by colostomy or ileostomy is considered a definitive therapy yet the last option when other treatments have failed. One study reported that both general and disease specific QOL were better in patients with colostomy where higher scores on social function on the SF-36 as well as the coping, embarrassment, lifestyle, and depression scales on the FIQoL compared to patients with FI were noted. Other evolving surgical approaches will also be discussed.

Cell-Based Therapies
Massarat Zutshi, MD, Staff Surgeon; Associate Professor of Surgery Department of Colorectal Surgery
Cleveland Clinic Foundation, United States
Cell-based therapies for injury and inflammatory diseases are an emerging area of interest. A major reason why cellular therapy has become attractive for these diseases is that treatment must be multi-focal and include the ability to stimulate repair, dampen inflammation and minimize opportunistic infection. Fecal incontinence is one such disorder that has attracted various researchers to study cell-based therapies. Mesenchymal stem cells (MSCs) have been utilized for this purpose due to their ability to differentiate into multiple cell types within a variety of organs as well as suppress immune functions. Early clinical trials with MSCs have yielded some exciting therapeutic potential and had good results in animal models. Other cells that have been used are adipose derived stem cells (ADSC’s) and muscle derived stem cells (MDSC’s). Most studies have evaluated regeneration after an acute injury. Fecal incontinence most often presents many years after an injury. This talk explores all cell based option and some non-cellular ones to heal a dysfunctional anal sphincter.

All preclinical animal research involving anal sphincter regeneration have used the model of an acute injury to evaluate cell based therapies including studies that demonstrated an increase in EMG and healing of the defect with muscle; a decrease in anal pressures then an increase after muscle progenitor cell transplant in a rabbit model; and an increase in the muscle fraction area in the groups treated with MSC and also an increase in EMG contraction compared to control but not to the sham. Pathi et al evaluated neurophysiological studies 21 days after injury and reported full recovery in rats treated with direct MSC injection and partial recovery with those treated with an IV injection. Fitzwater et al. did not demonstrate increase in muscle volume between cell and sham treated animals. They reported histological findings but did not quantify the muscle mass. They also reported no beneficial effect in animals where the cut ends were not repaired. We have demonstrated that the sphincterotomy in rats heals at 4 weeks and therefore have used a model which excises part of the anal sphincter which does not heal spontaneously.

References
Pathi SD, Acevedo, JF, Keller, PW, et al., Recovery of the injured external anal sphincter after injection of local or intravenous mesenchymal stem cells. Obstetrics and gynecology, 2012; 119:134-44.
W22: Management of Fecal Incontinence from Bench to Bedside
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Professor, Nursing, USA
Julia H Herbert, Grad Dip Phys. MSc. MCSP, MPOGP
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Holly E. Richter PhD, MD, FACOG, FACS
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Fecal Incontinence
Conservative Management: Lifestyle

Donna Z. Bliss, PhD, RN, FGSA, FAAN
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University of Minnesota School of Nursing
Minneapolis, MN
Chairperson, ICS Nursing Committee

Definitions of Bowel Incontinence

Faecal Incontinence
(the involuntary loss of faeces)

Anal Incontinence
(the involuntary loss of faeces and/or flatus and/or mucous)

Flatus Incontinence
(the involuntary loss of rectal gas or flatus)

Mucous Incontinence
(the involuntary loss of mucous only)

ICI6-ICS, 2016

Clinical Assessment
AI or FI Severity Scales/Scores

8 Common Severity Scales

- 7 score severity of AI or AI+QoL
  - Pescatori
  - Wexner or Cleveland Clinic Scoring Scale
  - Vaizey or St. Mark’s Score
  - Fecal Incontinence Severity Index (FISI)
  - Modified Manchester Health Questionnaire
  - Fecal Incontinence and Constipation Assessment (FICA) (now Fecal Incontinence Symptom Severity Scale (FISS))
  - ICI questionnaire for Bowel (ICIQ-B)
- 1 scores severity of FI + QoL
  - Revised Fecal Incontinence Scale (RFIS)
  - None score FI severity only or FI separate from AI

(Bliss et al, ICI6-ICS 2017)
Empowering Evidence 2014

**Conservative Management**

- **Educate** patient and/or caregiver
  - Individuals with FI and family caregivers have many incontinence literacy needs (B/C)
  - Normal bowel function, alterations in fecal incontinence, management options, absorbent product types, skin care
  - Use of a mnemonic (RELIEF) vs. standard counselling for FI to assist women to remember treatment plan – no differences (Bliss et al. ICI6-ICS 2017)

**Consider Patients’ Goals of Management**

If complete cure is not possible…top goals:

- Decrease frequency of leakage
- Decrease leakage of loose or liquid stool
- Greater confidence in controlling fecal incontinence

(Marhney et al. Western J Nurs Res 2010)

**Initial Interventions**

- **Dietary fiber supplements -- Psyllium**
  - Moderately fermentable and soluble
  - Start at lower amount and increase as needed (3-16 g/d)
  - Mixed with adequate fluid, in baked goods, take with extra fluid
  - Supported by RCTs (Bliss et al. J Water Anal 2014; ICI6-ICS 2017; Mertland et al. Dis Colon Rec 2013)

- **Medications -- Antimotility (Loperamide)**
  - 1-2 tablets (2 mg/tablet) before each meal and bedtime up to 16 tablets/d
  - Effects not improved by supplementing dietary fiber (Laud et al., Colorectal Disease 2006; Bliss et al. ICI6-ICS 2017)

**Modify Diet Intake**

Avoid Aggravating or Gas-Forming Foods

- Spicy, ethnic foods
- Fatty, greasy foods, eggs
- Caffeinated coffee, chocolate
- Dairy products
- Fresh apricots, strawberries, citrus
- Popcorn, nuts, seeds
- Onions, beans
- Cabbage, broccoli
- Alcohol

(Hansen et al. JWOCN 2009; Croswell et al. JWOCN 2010)

**Lifestyle Modifications**

- **Smoking Cessation**
  - Recommended for general health but limited and inconclusive evidence for reducing FI

- **Weight loss**
  - Observational studies in FI (mostly women)
    - More women with FI (36%) were overweight vs. women without FI (19%)
    - Obese women with FI had higher ARM baseline anal resting tone and squeeze pressures vs. normal weight
  - Improvements in UI with weight loss

(Bussen et al. Gastrointest Med Surg 2012; Bliss et al. ICI6-ICS 2017)
Weight Loss -- inconclusive

- No difference in FI after weight loss from dieting
  - Dieting program with higher fiber content (10 g/d) vs. controls (education program)
  - Women on program with dual incontinence lost weight and UI improved
- After bariatric surgery
  - Mixed results after surgical weight loss
  - 1 study: Anal incontinence increased 12.5% 5.6 months after surgery despite weight loss of 40 kg on average
  - Recommended for general health but inconclusive for FI


Establish Bowel Pattern and Bowel Training

- Try to establish regular bowel pattern/habits
  - Eat at consistent times
  - Modify cooking practices depending on diet tolerance -- no frying, mild spices
- Bowel Training
  - Behaviors to achieve a controlled response to urge to defecate
  - Procedure similar to bladder training
  - Progressive delay, reduce anxiety, and build confidence (Cognitive and relaxation techniques)
  - Consensus Best Practice recommendations by ICS Nursing Committee underway

Rectal Emptying

- Purpose: empty rectum, more complete elimination, prevent involuntary leakage
  - Transanal irrigation systems
  - Gauze dressing: Small cotton gauze pad folded lengthwise and placed between the buttocks for small amounts of leakage. No adhesive, tape or straps hold it in place. Underpad: one size that can protect skin from more solid/softer feces. Use with an adhesive strip. Incontinence Guards: Undergarments with an adhesive strip
  - Underpads with a breathable cloth outer layer are placed between the buttocks for small amounts of leakage. No adhesive, tape or straps hold it in place. Gauze dressing: Small cotton gauze pad folded lengthwise and placed between the buttocks for small amounts of leakage. No adhesive, tape or straps hold it in place. Underpad: one size that can protect skin from more solid/softer feces. Use with an adhesive strip. Incontinence Guards: Undergarments with an adhesive strip

(Collins & Norton, Br J Nurs 2012; Risien et al. Colorectal Dis 2011; Bliss et al., ICS-ICS 2016)

Complementary Therapies

- No recommendation
  - Patients use a variety -- inquire about & evaluate
  - Most common: herbs, probiotics (acidophilus)
  - Others: acupuncture, massage, homeopathy, kinesiology, relaxation, reflexology, Chinese medicine
  - Users: consider them safe, natural, allow control

2 FI case reports (women)
  - opposite results
  - Cured FI, ↓ liquid stools, urgency
  - antimicrobial herbs + Lactobacillus probiotic then herbs + bioceutical
  - Aloe vera, Ulmus rubra, Citrus bioflavonoids, apple pectin, Psacca lentscus, glutamine and Curcuma longa) (Lutbeck et al., Aust J Herbal Med 2011)
  - FI developed after bilateral needling of trigger-point acupuncture for pain in MS (McDowell et al., Med Acupunct 2014)

Practical Advice for Coping

- Incontinence absorbent products
  - Types of products
    - Pads, pantiliners, briefs, etc
    - For light to heavy leakage
  - Day vs night
  - Hard copy guide on ICS Nursing Committee “Library” of resources webpage
  - Website for assistance with selecting options Continence Products Advisor: http://www.continenceproductsadvisor.org/

(Biss et al., JWOCN 2013)

Design Changes for Absorbent Products FI

- ~ 1/3 absorbent products users not satisfied with product design for FI
  - Recommended Changes
    - Materials that can protect skin from more solid/softer feces or particulate irritants in liquid feces
    - Better/more absorption in back with low bulking
    - Decrease odor
    - Easier on and off (w/o removing pants), make flushable
    - Decrease leaking of bigger leaks
      - Raised gathers along inside, around legs
      - Package with wipes
    - Trial sampler packs of different types

(Biss et al. JWOCN 2011)
Practical Advice for Coping

- Locating or mapping public toilets -- apps
- Carrying small kits for cleansing and change
- Eat less or skip meal before going out or when in public
- Ask to be seated nearer restrooms
- Use continence aids (C)

(Bliss et al. ICSI-ICS 2017; Peden-McAlpine et al. 2008)

Pros and Cons of Devices

**Pros**
- 40%-80% effective
- ↑ QoL

**Cons**
- Uncomfortable, soreness
- VBD – higher comfort
- Unwanted expulsion
- Fear to defecate/urgency, vaginal irritation, UI/leakage/urgency, cramping
- VBD needs to be sized
- Need to insert and remove, temporary


Secondary Interventions

**Anal plugs, anal inserts, vaginal bowel device**


References


References


Fecal Incontinence
Behavioral therapy for faecal incontinence

Julia H Herbert Grad Dip Phys. MSc. MCSP. MPOGP.
Consultant Physiotherapist
Ellesmere Physiotherapy

Aims of this presentation

Define behavioural therapy
Review types of therapy appropriate for Faecal / Anal incontinence
Review the evidence to support therapy

Behavioural therapy: Definitions

The process of learning new motor patterns through movement patterns in contrast to the old.

Aims to teach the individual to differentiate between old patterns/habits and the new, thus correcting poor habit

Phases: cognitive, associative & automatized (Haugstad, 2008)

Julia Herbert
Affiliations to disclose:

- Clinical Director Femeda Ltd.
- Consultant to deSmit Medical Ltd.
- Consultant to Lucid innovations Ltd.
- Honorarium Astellas

Funding for speaker to attend:

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Sponsored by: Femeda Ltd.

Assessment and conservative management of faecal incontinence

Education

Education about the causes of FI/AI and a systematic effort to remove barriers to effective toileting is an intervention likely to be beneficial based on the consensus of experts.

Norton et al. 2003
Bliss et al. 2013
Defaecation dynamics

Behavioural therapy: Types
Pelvic Floor Muscle Training (PFMT)

Biofeedback (BF)
- addition of electronic or mechanical devices to aid PFMT (strength training)
- sensory training (rectal balloon training)
- Urge resistance training – used in addition to strength and sensory training

Electrical stimulation of the anal mucosa (ES)

Summary of current evidence / Recommendations
PFMT is possibly effective for the treatment of faecal incontinence. Studies comparing PFMT alone to BF augmented by PFMT and ES have shown mixed results and the optimal protocol for teaching PFMT has not been standardised, limiting the generalisability of findings (Level of evidence 2)

Pelvic floor muscle training (PFMT)
PFM exercises are recommended as an early intervention in the treatment of faecal incontinence as part of a conservative management bundle of interventions (Recommendation Grade B)

Assessing the problem
Also assess for the nature and severity of any pain

Biofeedback (BF)
Definition:
Biofeedback therapy is a technique in which physiological activity (neuromuscular and autonomic) is monitored, amplified and conveyed to the patient via visual or acoustic signals

Biofeedback (BF)
Anal probe better than vaginal (Fynnes 1999)
Manometry more specific to anal sphincter function? – Expert opinion
MAPLe EMG – Able to isolate external anal sphincter (Voorham-van de Zalm 2013)
Biofeedback (BF)

There are numerous uncontrolled trials
There is a low morbidity associated with Biofeedback
Those most likely to benefit from Biofeedback for AI are:
❖ Motivated
❖ Have intact cognitive skills
❖ Some rectal sensation
❖ Nearly intact sphincters and innervation
Bo et al. 2014

Rectal sensation training

Single / Double balloon catheter
Air filled syringe
3-way tap
Bols et al 2012
Markland et al 2017

Biofeedback (BF)

Improving biofeedback for the treatment of faecal incontinence
in women: implementation of a standardized multi-site
manometric biofeedback protocol
Bo et al. 2014

Treatment:
Strength training
❖ Improve external anal sphincter (EAS) squeeze pressure
❖ Improve endurance EAS (50% of maximum squeeze)
❖ Improve co-ordination of EAS
Sensory training
❖ Uptrain / downtrain rectal sensation threshold
Urge resistance training

Biofeedback (BF)

Recommendations
Biofeedback +/- PFMT and sensory training with a rectal balloon, is recommended as second line treatment for faecal incontinence after other behavioural and conservative / medical management have been tried and failed to provide adequate symptom relief
(ICI6 - ICS 2017 Recommendation Grade A)

Home Biofeedback using a portable battery-operated device is recommended as an adjunct to biofeedback training in the clinic, especially for younger patients
(ICI6 - ICS 2017 Recommendation Grade B)

Electrical stimulation of the anal mucosa (ES)

Recommendations
Based on current evidence it is not possible to recommend low frequency (100Hz) for FI
Percutaneous tibial nerve stimulation remains an investigational treatment protocol cannot currently be recommended for FI
(ICI6 - ICS 2017 Recommendation Grade B)

Triple therapy (combined biofeedback and 3000Hz stim) appears to be effective but requires further evidence

Electrical stimulation of the anal mucosa (ES)

Further recommendations
ES is useful in a specific group of patients; to improve the voluntary control of the pelvic floor in patients who lack this voluntary control

(Dutch evidence statement for pelvic physical therapy in patients with anal incontinence, 2014)
Thank you
Evolving Surgical Treatment Approaches for Fecal Incontinence in Women: An Evidence and Case-Based Approach

Holly E. Richter, PhD, MD, FACOG, FACS
J Marion Sims Endowed Professor Obstetrics and Gynecology
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Affiliations to disclose:

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Evolving Surgical Treatment Approaches for Fecal Incontinence in Women: An Evidence and Case-Based Approach

WS22
September 12, 2017
Florence, Italy

Learning Objectives
• To appreciate that the optimal treatment regimen for fecal incontinence (FI) may be a complex combination of various non-surgical and surgical approaches
• Surgery is a credible option for the treatment of FI
• Present evidence and case-based surgical treatment approaches for FI

Cochrane Review 2013
Surgery for Fecal Incontinence

The review is striking for the lack of high quality randomized controlled trials with any fecal incontinence surgeries that have been carried out in the last 10 years…..

"Larger rigorous RCTs (including the use of sham treatments) are needed, however, it should be recognized that the optimal treatment regime may be a complex combination of various surgical and non-surgical therapies"

Brown et al 2013

Surgical/Other Procedural Treatments for Fecal Incontinence

Neuromodulation, Artificial Bowel Sphincter, Anal Sling, Investigational

Case 1

• 55 yo female P3013 with 5 year history of FI and ano-rectal urgency
• FI of liquid/solid stool and gas despite a credible attempt at management with behavioral therapy
• Spontaneous vaginal delivery (SVD) X 3 with largest infant weighing 3700 g
• Forceps delivery and a lot of “stitches” with first SVD
• Alternating constipation & diarrhea
• PMH: obesity
• PSH: cholecystectomy

Physical Examination and Diagnostic Testing

• Examination: decreased anal tone, intact reflexes, dove tail appearance, 1.5 cm thickness
• Surface Electrode EMG: reasonable isolation with decreased squeeze pressure activity, good relaxation, no evidence of dysynergia
• Anal Manometry: anal resting tone of 25 mm Hg, squeeze to 55 mmHg, normal sensation, compliance 200 cc, normal RAIR
• Endoanal Ultrasound:
Sphincteroplasty

- The term sphincteroplasty is used to describe secondary or delayed reconstruction of the anal sphincter musculature, injury to which has either not been recognized or the outcome of the repair unsatisfactory.
- Among women who had a sphincter tear repaired at the time of delivery, 35% continued to have IAS gaps and of those women, the majority had concomitant EAS disruptions at 6 and 12-months*

Evidence for efficacy?

- Systematic Review of FI studies 1991-2010
- 16 studies selected with 900 patients

Outcome Data

- Data reflects effectiveness in the short-term where 70-80% of patients report symptom improvement
- Long-term success deteriorates over time: 20-67% by 5 years, 0-40% at 10 years

Anandam 2014; Sung et al 2007; Tjandra et al 2003; Garcia et al 2005
Sphincteroplasty-Summary

• Approximately 2/3 of patients report improvement
• Based on patient recall, little prospective data
• Defined by "good", no standardized outcomes used until recently
• No factor significantly associated with a worse outcome (age, severity, duration, previous repair and pudendal nerve delay implicated)

• Still an appropriate first line therapy for women with major sphincter defects
• Restore sphincter to circumferential configuration-although MRI data may dispute this
• Build up perineal body

Most common complication: wound infection (2.2-35%)

Potential Reason for Lack of Efficacy:

Example of distal MRI sphincter pre-pregnancy and corresponding diagram displaying how external sphincter (EAS, white arrows) is not anatomically contiguous across the midline at 12 o’clock or 6 o’clock, but sends fibers to other structures in the perineal body (black arrows) by turning antero-lateral. In contrast, the internal anal sphincter (IAS) is a cylindrical structure that is continuous across the midline posteriorly and anteriorly.


Case 2

• 67 yo female with a 7-year history of FI
• FI of liquid/solid stool, 3-times per week necessitating constant pad use and scared to leave her home
• Has had a sphincter repair, tried behavioral therapy including pelvic muscle exercises, other PT strategies, attention to diet, and use of medications with some improvement, but still room for improvement
• Recent 2 week diary revealed nearly daily bowel movements with leakage 2 times the first week and 3 times week 2
• PMH: hypertension
• PSH: hysterectomy

Physical Examination & Diagnostic Testing

• Examination: decreased rectal tone, intact reflexes
• Surface Electrode EMG: reasonable isolation with good subjective squeeze pressure activity, good relaxation, no evidence of dysynergia
• Anal Manometry: anal resting tone of 40 mm Hg, squeeze to 70 mmHg, normal sensation, compliance 100 cc, normal RAIR
• Endoanal Ultrasound: intact external and internal anal sphincters

She is considering colostomy- what surgical options are available?

Sacral Nerve Stimulation

How Does It Work?

• Many potential neurologic targets
  • Voluntary somatic
  • Afferent sensory
  • Efferent autonomic

• Rectal blood flow increased with stimulation as measured by doppler flowmetry-effect was reversible1
• Decreased episodes of spontaneous sphincter relaxation2
• Electrical stimulation of the sacral nerves causes:
  • Modulation of neural reflexes
  • Interrupts constant sensory input from rectum

1Kenefick, Br J Surg 2003; 2Vaizey, Gut 1999
- Staged testing
- Simple outpatient procedure done under local anesthesia with IV sedation
- 2-4 week bowel diary prior to placement, then 2-4 week stimulation trial with diary

Show Me the Data!

SNS Data Summary
Short, Medium, Long-term

- When reviewing short (<12 months), medium (12-36 months) and long-term (>36 months) success (success defined as a 50% reduction in FI episodes):
  - ITT median (range) rates of 63% (33-66%), 58% (52-81%), 54% (50-58%), respectively
  - Per protocol median (range) rates of 79% (69-83%), 80% (65-88%) and 84% (75-100%), respectively

Matzel et al, 2009

SNS Adverse Events

- Most AEs occur within 1st year of implantation
- Common events include: device pain (28%) and paresthesia (15%)
- Meta-analysis reported lower rate of implant site pain (6%)*
  - With advancements in lead design and techniques, explantation rarely necessary (3-4%)*
- Infection rate 3-11%**

*Tan et al 2011; **Wexner et al 2010; Mellgren et al 2011

Other Procedural/Surgical Treatment Approaches for Treatment of Fecal Incontinence
Artificial Bowel Sphincter (ABS)

- Severe, refractory FI
- Efficacious
- High morbidity

ABS Results

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Follow-Up (mo)</th>
<th>Preoperative Score</th>
<th>Postoperative Score</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleveland Clinic Score*</td>
<td>26</td>
<td>19</td>
<td>14.9</td>
<td>2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dereser et al.</td>
<td>56</td>
<td>26.5</td>
<td>17</td>
<td>4</td>
<td>0.001</td>
</tr>
<tr>
<td>Lehur et al.</td>
<td>13</td>
<td>20</td>
<td>17</td>
<td>4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O’Brien et al.</td>
<td>14</td>
<td>6</td>
<td>19</td>
<td>4.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Ortiz et al.</td>
<td>20</td>
<td>18</td>
<td>18</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>6</td>
<td>10</td>
<td>19.5</td>
<td>4.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

American Medical Systems Score†

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Follow-Up (mo)</th>
<th>Preoperative Score</th>
<th>Postoperative Score</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altham et al.</td>
<td>28</td>
<td>10</td>
<td>19.9</td>
<td>5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Casal et al.</td>
<td>50</td>
<td>24</td>
<td>19.9</td>
<td>19.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Druin et al.</td>
<td>8</td>
<td>10.5</td>
<td>90</td>
<td>93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lehur et al.</td>
<td>24</td>
<td>20</td>
<td>106</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lehur et al.</td>
<td>16</td>
<td>25</td>
<td>105</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>112</td>
<td>12</td>
<td>106</td>
<td>48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Williams et al.</td>
<td>17</td>
<td>60</td>
<td>50</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Cleveland Clinic Score — scale of 0 to 30: 0 = complete continence and 30 = complete incontinence.††
† American Medical Systems Score — scale of 0 to 120: 0 = complete continence and 120 = complete incontinence.††
‡ Williams Score — scale of 1 to 6: 1 = complete continence and 6 = complete incontinence.‡‡
¶ Cleveland Incontinence Scoring System — scale of 0 to 120: 0 = complete continence and 120 = complete incontinence.

ABS Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Experts (%)</th>
<th>Revision (%)</th>
<th>Erosion (%)</th>
<th>Infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altham et al.</td>
<td>18</td>
<td>25</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Casal et al.</td>
<td>30</td>
<td>10</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Christensen et al.</td>
<td>41</td>
<td>35</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Dereser et al.</td>
<td>23</td>
<td>30</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Druin et al.</td>
<td>26</td>
<td>Not stated</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Lehur et al.</td>
<td>31</td>
<td>62</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Lehur et al.</td>
<td>33</td>
<td>38</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Lehur et al.</td>
<td>31</td>
<td>13</td>
<td>6</td>
<td>Not stated</td>
</tr>
<tr>
<td>O’Brien et al.</td>
<td>23</td>
<td>31</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Ortiz et al.</td>
<td>41</td>
<td>27</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Parker et al.</td>
<td>40</td>
<td>64</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Valdez et al.</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>35</td>
<td>65</td>
<td>25</td>
<td>38</td>
</tr>
</tbody>
</table>

TRANSFORM Study

ClinicalTrials.gov identifier: NCT01080739

- TOPAS (AMS) sling for FI
- Prospective, multi-center (12 sites)
- Single-arm, open-label, two-stage, adaptive study with one planned interim analysis
- N=152
- The mesh sling placed via the transobturator approach

Anal Slings-investigational, TOPAS® System

- Self-affixing Type-I Polypropylene Sling
- Minimally invasive trans-obturator post-anal sling

Caution: Investigational device. Limited by Federal (United States) law to investigational use.

Primary Outcome

- 50% reduction in the number of FI episodes from baseline to 12 months post-operatively on a 14 day bowel diary.

Secondary Outcomes

- Decrease in Fecal Incontinent Days and Urgency Episodes
- Symptom Severity: Cleveland Clinic Incontinence Scores
- Quality of Life: Fecal Incontinence Quality of Life (FIQOL)
- Safety
• Mean surgical time = 33 minutes (range 11-71)
• Mean EBL = 13 cc (range 0-50)
• Mean hospital stay = 11 hours (2-57)
• NO visceral injuries or perforations
### Secondary Outcomes

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Median</th>
<th>12 mos.</th>
<th>Median</th>
<th>Range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCIS (Wexner)</td>
<td>13.9 (mean)</td>
<td>9.6 (mean)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FI Episodes per week</td>
<td>9.0 (2-40.5)</td>
<td>2.0 (0-40)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FI Incontinent Days</td>
<td>5.0 (1.5-7)</td>
<td>2.0 (0-7)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FI with Urgency</td>
<td>2.0 (0-7)</td>
<td>0 (0-26)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Treatment Related Adverse Events

- Pelvic pain: 47 events, 41 patients (27.0%)
- Infection: 26 events, 22 patients (14.5%)
- Incision site infection: 9 events, 9 patients (5.9%)
- Abscess: 2 events, 2 patients (1.3%)
- Other infection problem: 15 events, 14 patients (9.2%)
- Urinary problems: 6 events, 6 patients (3.9%)
- Worsening urinary incontinence: 2 events, 2 patients (1.3%)
- Other urinary problem: 4 events, 4 patients (2.6%)
- Pelvic organ prolapse: 8 events, 6 patients (3.9%)
- Pelvic organ prolapse (de novo): 4 events, 3 patients (2.0%)
- Pelvic organ prolapse (worsening): 4 events, 3 patients (2.0%)
- Bleeding: 1 event, 1 patient (0.7%)
- Defecatory dysfunction: 2 events, 2 patients (1.3%)
- Other: 14 events, 14 patients (9.2%)

**Total:** 104 events, 66 patients (43.4%)

17 no treatment
29 treated with medical therapy
1 sciatica surgery
10 persistent at 1 year
None classified as SAEs by FDA standards

**NO mesh erosions or extrusions**

### SECCA® Efficacy Data

- Long-term* (5 year) study, mean Wexner incontinence score improved from 14 to 8, p<0.0003
- 80% subjects had 50% improvement
- N=19
- Other studies limited by short-term follow-up and small sample sizes (N=8-50)
- No comparative data
- Main AEs rectal bleeding and pain

* Takahashi-Monroy et al 2008
PTNS

- The largest prospective study including 115 patients with a median follow-up of 26 months (range, 12 – 42) reported 52% of patients achieving a ≥ 50% reduction in FI episodes as well as improving QOL.*
- First multi-center RCT (the CONtrol of Faecal Incontinence using Distal Neuromoulation (CONFIDeNT)) in the United Kingdom was recently published
- This trial included 227 patients to evaluate the efficacy and cost-effectiveness of PTNS (n=115) comparing to sham electrical stimulation (n=112)
- Interestingly, the study reported no difference between the PTNS and sham groups in efficacy at 12 weeks: 38% in PTNS versus 31% in sham achieving a ≥50% reduction in the number of FI episodes per week, adjusted ratio 1.28 (95%CI 0.72-2.28; p=0.40). **

*Hoturas et al 2014; **Knowles 2015

Non-Animal Sodium Hyaluronate-NASHA Dx

- Dextranomer microspheres and sodium hyaluronic acid – Identical to Deflux
- Administered via anoscope to the proximal anal canal
  - Out-patient setting
  - No anesthesia
  - Four 1ml blebs of Solesta

Pivotal Trial

- Only large scale trial in the literature – injectable bulking agent vs. sham
- 206 patients
  - 13 sites in U.S. and EU
  - 80% female
- Three part primary endpoint
  - Superiority over sham at 6 months
  - Threshold responder rate at 6 months
  - Durability of effect to 12 months

Graf et al, Lancet 2011

Pivotal Trial: Results

- All 3 success criteria were met
  - Responder rates superior to sham at 6 months
    - Above the predetermined threshold
  - Durability of effect out to 12 months: 57.4% Responder%

Most Common Related AEs - Solesta Patients Pivotal Study Through 18 Months

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Events</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proctalgia</td>
<td>41</td>
<td>17.3</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>16</td>
<td>8.1</td>
</tr>
<tr>
<td>Rectal hemorrhage</td>
<td>15</td>
<td>7.6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>6.6</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>10</td>
<td>5.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>4.1</td>
</tr>
<tr>
<td>Anal hemorrhage</td>
<td>9</td>
<td>4.1</td>
</tr>
<tr>
<td>Anorectal discomfort</td>
<td>8</td>
<td>4.1</td>
</tr>
<tr>
<td>Rectal discharge</td>
<td>7</td>
<td>3.6</td>
</tr>
<tr>
<td>Proctitis</td>
<td>5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Majority of AE’s were mild and self limited

Magnetic Anal Sphincter

- Fenix™, Torax Medical; sold to J&J
- Series of titanium beads with magnetic cores linked together with independent titanium wires
- To defecate, the force generated by straining separates the beads to open up the anal canal
- The technique of implantation is simple with no requirement of adjustments
FENIX® Continence Restoration System

FENIX Device
Titanium beads with magnetic cores
Range of Sizes: 14-20 beads
Double suture joining mechanism

FENIX Sizing Tool
Assists in selection of proper FENIX device
Single use

FENIX Introducer Tool
Assists in placing the sizing tool and device
Reusable

FENIX Implant Procedure

<table>
<thead>
<tr>
<th>Pre Op Testing</th>
<th>Patient Procedure</th>
<th>Supplies / Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoanal Ultrasound</td>
<td>~60 minutes</td>
<td>Standard colorectal surgical tray</td>
</tr>
<tr>
<td>Manometry</td>
<td>Perineal incision</td>
<td>Electro-cautery &amp; Suction</td>
</tr>
<tr>
<td>Defecography</td>
<td>Peri-anal tunnel</td>
<td>Portable fluoroscopy</td>
</tr>
</tbody>
</table>

FENIX® Feasibility Study
Study Design

- Prospective, observational, open label
- Non-randomized, single-arm, multi-center
- First-in-man use, safety and efficacy
- 35 patients from sites in Europe and the US
- Followed for five years

Sugrue J. et al. Dis Colon Rectum, 2017; 60:87-95

FENIX Feasibility Study
2 Primary Endpoints

Safety Endpoint
Descriptive analysis of device or procedure-related adverse events, summarized by incidence and severity

Efficacy Endpoint
Proportion of patients achieving a 50% or greater reduction in FI episodes per week as compared to baseline:
- Tool: 20-day bowel diary completed by the patient
- Timeline: Baseline, 6, 12, 24, 36, 48 and 60 months after surgery

Primary Efficacy Endpoints
Improved Continence Post-Implant Reported by Patients on Bowel Diaries

<table>
<thead>
<tr>
<th>Reduction in FI Episodes, FI Days, and Urgency Episodes From Baseline at 1 – 5 Years of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome (per week)</td>
</tr>
<tr>
<td>% (n/N)</td>
</tr>
<tr>
<td>12 Months</td>
</tr>
<tr>
<td>≥50% reduction in FI episodes</td>
</tr>
<tr>
<td>≥50% reduction in FI days</td>
</tr>
<tr>
<td>≥50% reduction in urgent episodes</td>
</tr>
</tbody>
</table>

FENIX Feasibility Study
Safe Surgical Option

No long-term sequelae associated with device explants

7 Explants Due To:
- %3 for infection
- %1 for lack of effect
- %3 erosion

N=28 (93%)
FENIX device remaining implanted

N=3 for infection
N=1 for lack of effect
N=3 erosion
Final Consideration

• Fecal Diversion

Fecal Diversion

• Considered “last resort”
• One case-control and two cohort studies
• Results in improved QOL
• More cost effective at 5 years than artificial AS and dynamic graciloplasty
• Usually an end sigmoid colostomy without proctectomy (rectal stump)
• Laparoscopic approach, safe and effective


Conclusions

• Cause of fecal incontinence (a lecture unto itself) is often multi-factorial
• 1st line treatment is...
  • Education
  • Pelvic Floor Muscle Exercises
  • Medications
  • Normalization Of Stool Consistency
  • Bowel Habits
  • Devices*
• Surgery helpful for many women
• Need to be able to discuss all options with patients and individualize care

Conclusions

• Sphinteroplasty has reasonable short-term but reduced long-term results
• Neuromodulation therapy helps those with refractory FI
• Other therapies needed-recent data on devices; need RCTs!
• Individualization of treatment

Select References

• Rao SSC. Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation. Clin Gastroenterol Hepatol 2010;8:910-919.e2
Select References

- Meyer I, Richter HE. Impact of Fecal Incontinence and Its Treatment on Quality of Life. Women's Health 2015; 11:226-38
Why do tissues not regenerate completely at the time of injury?

- Cytokine expression in the tissues that are injured is often short-lived; expression levels are not elevated enough to sustain effective cellular migration.
- The acute injury in the anal sphincter is recognized infrequently and patients become symptomatic many years after initial injury.
- Age-related factors may worsen this problem.
- We have evolved to scar and not regenerate.

What can we do about it?

- Cytokine expression increased to reestablishing homing by exogenous introduction of chemokines in the area of injury or using a conditioning injury.
Why do stem cells work?

Mesenchymal Stem Cells (MSC)
- Differentiation
- New spotlight: Paracrine & autocrine effects

Singer et al., Annu Rev Pathol Mech Dis, 2011

Autocrine: Hormone binds to receptors on and affects the function of the cell type that produced it.

Paracrine: Hormone has effect only in the vicinity of the cell secreting it.

Mesenchymal Stem Cells (MSC)
- Bone marrow, skeletal or adipose derived
- Give rise to cells of mesodermal origin
- Commonly used in models of injury
- Immune privileged
  - Low rejection potential
  - Allogeneic sources

Now termed medicinal signaling cells (Caplan) who says MSC’s are pericytes that reside in the vasculature and are the first line of defense.

When do stem cells work?
1. Signals at site of repair should last.
2. Stem cells should reach the site of intended repair.
3. Cells should be in sufficient numbers to initiate and sustain repair.

SDF-1
Stromal-cell-derived factor 1 (CXCL12) + CXCR4
- MSC showed significant chemotaxis to CXCL12, chemokines preferentially expressed in the area of inflammatory bone destruction.
- Cardiogenesis, primordial germ cell migration, and the recruitment of endothelial-cell progenitor cells to ischemic tissue.

Systemic overexpression of CXCL12 can lead to stem-cell mobilization.

MCP-3

- Monocyte chemoattractant proteins, now known as CC chemokine ligands (CCL)
- Regulates the recruitment of monocytes to sites of inflammation
- Critical for host defense by attracting cells through activation of their cognate receptor CCR2.
- CCL7 (MCP-3) /CCR2 is critical for monocyte mobilization from bone marrow.
- Over-expression of CCL7 in urethral sphincter and serum in a mouse model of simulated birth trauma-induced urinary incontinence.


Cytokines

- Expression of SDF-1 and MCP-3 after anal sphincterotomy

Bone marrow derived MSC: Acute injury models

Treatment of Experimental Injury of Anal Sphincters with Primary Surgical Repair and Injection of Bone Marrow Derived Mesenchymal Stem Cells.


Potential of human umbilical cord matrix and rabbit bone marrow-derived mesenchymal stem cells in repair of surgically incised rabbit external anal sphincter.


Recovery of the injured external anal sphincter after injection of local or intravenous mesenchymal stem cells.

Sujatha D. Pathi, MD, Jesus F. Acevedo, BA, et al. 2012 Obs and Gyn 119, 134-144

MSC–Acute injury models

Functional outcome after anal sphincter injury and treatment with mesenchymal stem cells.


Mesenchymal stem cells can improve anal pressures after anal sphincter injury.


Skeletal muscle cells: Acute injury models

Sphincter contractility after muscle derived stem cells autograft into the cryoinjured anal sphincter of rats


Functional external anal sphincter reconstruction for treatment of anal incontinence using muscle progenitor cell autografting.


Effect of myogenic stem cells on contractile properties of the repaired and un repaired transsected external anal sphincter in an animal model.


Effect of myogenic stem cells on contractile properties of the repaired and unrepaird transsected external anal sphincter in an animal model.


Recovery of the injured external anal sphincter after injection of local or intravenous mesenchymal stem cells.

Sujatha D. Pathi, MD, Jesus F. Acevedo, BA, et al. 2012 Obs and Gyn 119, 134-144

In vivo recovery of the injured anal sphincter after repair and injection of myogenic stem cells.


Skeletal Muscle cells - Safety

Safety assessment of myogenic stem cell transplantation and resulting tumor formation.


No evidence of cell migration to liver or lung was found. 2 transplanted rats developed abnormal foci of growth, i.e. tumors, from the external anal sphincter-raising further safety questions.
Skeletal muscle cells: Injection at a normal site


Cryoinjury 90 degrees.

Intralesional and at the borders injection was equally effective but opposite to the lesion were not.

Zutshi lab : Ultimate goal

- Prove that the effect of cell/non cell therapy lasts over time.
- Find the right factor to allow stem cells to home to the entire anal sphincter.
- Find the right factor to correct neuropathic incontinence

Currently we are evaluating the SDF-1 plasmid with and without MSC in a chronic large injury in a pig model

Another study is evaluating SDF-1 in anal fistula in a rat model of Crohn’s disease.

Stem cells: MDSC Human trial


- 10 women. Electrical stimulation preop 21 days
- Autologous myoblasts were cultured from a pectoralis muscle biopsy
- Injected under ultrasound control
- At 12 months the Wexner incontinence score had decreased by a mean of 13.7 units (95% CI, -16.3 to -11.2), anal squeeze pressures were unchanged, and overall quality of life scores improved by a median of 30 points (95% CI, 25 to 42).
- At 5 years patients still did well

Electrical stimulation and stem cell retention

- We have reported upregulation of CXCL12 and CCL7 expression with both acute injury as well as low current ES.
- Selected ES parameters also achieved the significant MSC retention in the anal sphincter of normal rat.

Results: Anal manometry resting pressure after E stim and MSC injection in an injury model

ES with single direct MSC injection significantly improved the resting pressure in a rat model of chronic anal sphincter injury (*p<0.05).
Muscle regeneration in various groups

Re-establishing the microenvironment using SDF-1 plasmid

Study Design

Anal pressure measurement over time

Conclusion

- In a rat model of chronic large anal sphincter defect, daily ES with a single local MSC delivery given 3 weeks after injury significantly improves both anal sphincter pressure and new muscle formation in the area of injury.

- The injection of MSC directly into the anal sphincter at the site of injury following ES may be an easily accessible delivery option.
**Results : Histology - Masson's staining**

In the area of the defect, all treatment groups showed filling of the defect with muscle. The pSDF-1+MSC group showed the most organization of fibers, the IA group however, showed patchy filling of the defect with a disorganized architecture. This was sustained at 8 weeks.

**Quantification of muscle at the site of the defect**

Compared to the IA group, all three groups receiving the plasmid had significantly greater muscle percentage at the site of the defect at 4 weeks and the SDF-1 plasmid alone had significantly more muscle at 8 weeks.

**Results : Histology – Immunohistochemistry using Desmin**

**Interpretation of results**

- In a rat model of a large anal sphincter excision, local injection with SDF-1 plasmid achieved higher resting pressures, a greater percentage of muscle and less fibrosis at the site of defect 8 weeks post treatment.

- SDF-1 plasmid alone or in conjunction with MSC resulted in regeneration of both skeletal and smooth muscle with no change in their ratio compared to normal tissue.

- There was no significant difference in functional outcome or CXCR4 or Myf5 expression among the 3 groups receiving the SDF-1 plasmid.
Conclusions

- SDF-1 alone without stem cells resulted in sustained muscle regeneration in the long term.
- The function recovered to pre-excisional (normal) levels with morphological evidence of both smooth and skeletal muscle regeneration.
- CXCR4 / Myf5 cytokines were not involved in this effect.

Neo-Anal sphincter ???

- Is there a role?
- Easy to create and implant: Wake Forest University.
- Neural control

Bioengineered Internal anal sphincter

- Previously bioengineered model
- Implanted, intrinsically innervated bioengineered human IAS tissue preserved the integrity and physiology of myogenic and neuronal components.

Restoration of GI motility using autologous cell sources

Contractile response of the constructs

Relaxation of the constructs

Zakhem, E. et al. SCTM (2016)

Zaghari, E. et al. SCTM (2016)
Medically Engineered Functional Anal Sphincters Using Composite Tissue Engineering and Novel Electrode Interfaces
S E. Feinberg, DDS, PhD M G. Urbanchek, PhD University of Michigan

Implant bipolar electrodes on neoanal sphincter. Implant battery and controller modulator subcutaneously.

Clinical trials ongoing
A Prospective Nonrandomized Study of Autologous Muscle Derived Cell (AMDC) Transplantation for Treatment of Fecal Incontinence
- UK
- Cook Myosite
- 50 patients

Treatment of Fecal Incontinence by Injection of Autologous Muscle Fibers Into the Anal Sphincter
- Denmark
- 15 patients . Muscle biopsy from leg

Study, Double Blind, Randomized, Comparing Two Groups to Evaluate the Safety and Efficacy of Autologous Mesenchymal Stem Cells From Adipose Tissue (CMMAd) in the Treatment of the Fecal Incontinence Spain
- 16 patients (not enrolling)

Muco-cutaneous Construct

Skin
Oral Mucosa

Neocutaneous and Neurocutaneous Stabilization

NeoAnal Sphincters of Rat Latissimus Dorsi Muscle with Cells and Alloplast in the Sphincter

Top
Bottom

Top
Bottom

Neo Sphincter with cells explanted POD 0

Neo Sphincter with cells explanted POD 2wk

Native sphincter

Neo Sphincter

Clinical trials ongoing

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Summary

• Many new innovations in the future
• Devices as well as cellular/non cellular therapy will change how we treat fecal incontinence
• Stem cells will be an option only if they can be guided to the anal sphincter at a time remote from injury to heal the entire anal sphincter.
• Bioengineered anal sphincter may be an option with engineering of both IAS and EAS

So, will stem cells be available in the near future?

• That is the hope.
• If not stem cells it may be a cytokine
• Or it may be a ready to use scaffold with cells which can be implanted
• Or maybe a bioengineered anal sphincter
• The possibilities are vast

Funding is however limited

A word of caution

Clinical trials
Injecting stem cells is easy –must have a scientific basis for it.

Questions to be asked
What do stem cells do when injected in normal tissue or in scar tissue or at a time distant from injury?
What can go wrong? Tumors/ tissue in excess?
How do we gauge success?

Thank you