Review article

Stem cell therapy in fecal incontinence: a narrative review

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Abstract: The main treatment for fecal incontinence is sphincter repair surgery; however, its outcome is not that satisfactory and return of fecal incontinence symptoms is common, especially in long term follow up of the patients. On the other hand, alternative methods such as using mesh or artificial sphincters are not ideal due to high morbidity and probability of device failure and the effect of methods such as injection of bulking agents are limited by numerous factors like absorption of the injected agent, its migration, fat embolism and formation of granuloma. Therefore, tendency to alternative or supplemental treatments such as using stem cells for replacing the lost tissue is increasing. In this study, the aim is to do a narrative review on cellular strategies and their strong and weak points in treating fecal incontinence.

Keyword: Fecal Incontinence; Cell Therapy; Human

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1. Introduction

Fecal incontinence is usually a result of decreased mechanical pressure in the sphincter tissue of the anus and its disability to close the anal canal (1, 2). Epidemiologic studies show that fecal incontinence affects 2–15% of the population (3-5). This statistic increases with age and is significantly higher in women (13-23%) probably due to injuries during labor (6). Fecal incontinence has many negative effects on daily life and the person's social interactions, quality of life, and mental well-being and has no complete and standard treatment yet (3, 7, 8).

Although sphincter repair surgery is the main treatment for fecal incontinence due to anatomic deficiencies of the sphincter (9), its results are not that satisfactory and return of the incontinence symptoms is common, especially in long term follow up of the patients (10-13). On the other hand, alternative methods such as using mesh or artificial sphincters are not ideal due to high morbidity and probability of device failure (14, 15) and the effect of methods such as injection of bulking agents are limited by numerous factors like absorption of the injected agent, its migration, fat embolism and formation of granuloma (16, 17). Therefore, tendency to apply alternative or supplemental treatments such as using stem cells for replacing the lost tissue is increasing. In this study, the aim is to do a narrative review on cellular strategies and their strong and weak points in treating fecal incontinence.

2. Epidemiology

18 million adult individuals over the age of 65 in America are affected with fecal incontinence, more than 50% of which suffer from this problem continuously and without any treatments (18, 19). According to the statistics of a national surveying company, 8.3% of the population is affected with fecal incontinence without visiting health centers (18). There are contradicting reports regarding the association of individuals' race and sex with prevalence of fecal incontinence. In the past, it was believed that its prevalence is higher in women compared to men. Recently, the prevalence of fecal incontinence has been reported to be 8.9% in women and 7.7% in men. There is no significant correlation between fecal

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incontinence and race, ethnicity, level of education or level of income (19). Since many of the patients are shy to reveal their problem, evaluating the effect of this disease on the economic status is hard to judge. The cost of taking care of those with this condition is 55% more than the cost of daily life and more than 11 billion dollars a year is spent on these patients in the United States of America (20). It is estimated that for each individual, 4.110 dollars is spent on research for fecal incontinence each year (21).

3. Diagnosis and risk factors

Taking neurologic, surgery and medical histories and history of using anti-depressants, Parkinson, anti-seizure and anti-psychosis drugs helps a lot in diagnosis of fecal incontinence. Numerous valid surveys exist regarding intestinal health, which are used for determining the type and severity of fecal incontinence. Fecal Incontinence Severity Index (FISI), the Fecal Incontinence Quality of Life Questionnaire (FIQOL) (22) and Wexner Score (23) can be named as 3 of the most famous surveys among them. FISI and FIQOL are calculated based on rate and frequency of intestinal leak and Wexner score is based on stool shape. Other scales such as Bristol stool scale exist that are efficient in planning a treatment plan based on stool shape (v shape) (24). From the most important risk factors of fecal incontinence sex (female), pregnancy, labor trauma, neurologic causes, surgery in perineum region, COPD, diabetes, and smoking can be pointed out (25). The most common curable risk factor in fecal incontinence is diarrhea (26).

4. Treatment

The first step of treatment is usually prescribing a low-sugar, low-caffeine, high-fiber diet (27). Regular exercise is among the efficient treatment plans in control of fecal incontinence, especially in over-weight individuals. Combination of diet and exercise can only control fecal incontinence up to 50% (28) and cannot be counted as a definitive treatment. Therefore, other measures should be taken along with diet and exercise to control fecal incontinence. Among common treatments for fecal incontinence the following can be pointed out:

1- Drug therapy: Antidiarrheal medicines and dietary supplements containing fiber, such as psyllium, significantly control mild and moderate stages of fecal incontinence. Methylcellulose along with loperamide (29), diphenoxylate, and atropine are among the drugs that efficiently control fecal incontinence (30).

2- Physiotherapy: One of the best physiotherapy techniques in controlling fecal incontinence (mild and moderate due to trauma injury of external sphincter muscle of the anus) is biofeedback, beacuse it strengthens the pelvic floor muscles, is affordable and safe (31). This technique is significantly more efficient in controlling fecal incontinence when accompanied by cholestyramine prescription (30).

3- Sacral nerve stimulation: For more than 15 years safety and efficacy levels of this technique were evaluated outside America until in 2011 it received approval from America's food and drug administration for treating patients with fecal incontinence (32).

4- Injection of bulking agents: Injection of these agents, such as hyaluronic acid, under the mucosa of rectum in mild and moderate cases results in partial control of fecal incontinence, yet for maintaining the positive effects of these agents in fecal incontinence, they should be re-injected after a few years. The side effects of injecting these agents include bleeding, abscess and pain (32).

5- Sphincteroplasty: This technique is a surgical intervention and is done in cases of severe damages to external sphincter of the anus. About 85% of the patients are satisfied with stool control after one year, but this rate drops to 48% after 7 years. Since performance of this technique requires general anesthesia there is a risk of mortality and common side effects of this technique include pain, bleeding, infection, not controlling injury and hematoma. To achieve the best results in this case, continuing physiotherapy after the surgery is essential (33).

6- Artificial sphincter: Currently, using artificial sphincters in treatment of fecal incontinence is obsolete due to its numerous side effects and inefficiency in long term follow up. In the initial studies, artificial sphincters were used for severe cases of fecal incontinence, which resulted in the patient being candidate for surgery again in long term follow ups due to side effects such as severe infections and the device being damaged (34).

By evaluating the mentioned treatments 2 points can be concluded:

1- Most of these treatments are effective in mild and moderate cases of fecal incontinence.

2- These treatments are not effective in the long run.

Therefore, by taking these points into account, finding a new alternative treatment to obtain permanent results in long term follow ups seemed necessary. Finding a treatment that could replace the lost muscle tissue, especially in severe cases of fecal incontinence and particularly those due to anatomic disability of the external sphincter of the anus, seemed necessary. With the rise of tissue engineering and using one of the most important pillars of this science, namely stem cells, replacing the lost muscle tissue of external sphincter of the anus using these cells can be considered as a proper replacement method.

5. Stem cells in clinical trial

Since the rise of stem cell science it has been accepted that stem cells are divided into 2 main groups: embryonic stem cells (ESCs) and adult stem cells. Researchers are less interested in ESCs for use in clinical trials due to formation of teratoma and debate regarding the ethical problems. However, since adult stem cells can be isolated from numerous tissues and have a more limited and controlled differentiation they are the most used cells in regenerative medicine (35, 36). Among adult stem cells, mesenchymal stem cells (MSCs) are the most popular and most widely used cells for clinical purposes among researchers because of their unique characteristics (35). MSCs are the main candidate for cell therapy in clinic because of 4 major reasons (37):

1- Ability to differentiate to various cells lines (multipotency) such as: nerve (38-40), bone (41), cartilage (42), fat (43), muscle (44), and hepatocyte (45).

2- Secretion of soluble factors required for cell survival and proliferation of cells (paracrine effect): Cytokine, chemokine, and growth factor secretion. With their paracrine characteristic, MSCs prevent apoptosis and stimulate proliferation and increase in adjacent cells through interaction with their surrounding microenvironment and therefore, lead to regeneration of the injured tissue (46). Among these paracrine agents that are secreted from these cells at high concentration are: proteins of the immune system signaling pathway such as (interleukin-6 (IL-6), IL-8, monocyte chemochemoattractant protein-1 (MCP-1), and transforming growth factor-b (TGF-b)), extracellular matrix proteins like (TIMP metallopeptidase inhibitor 2 (TIMP-2), fibronectin, periostin, collagen, decorin, and metalloproteinase inhibitors), and growth factors and their regulators such as (vascular endothelial growth factor (VEGF), granulocytemacrophage colony-stimulating factor (GM-CSF), bone morphogenetic protein 2 (BMP-2), basic fibroblastgrowth factor (bFGF), and insulin-like growth factorbindingprotein 3 (IGFBP3), IGFBP4, IGFBP7) (47).

3- Regulating the immune response: The most accepted mechanism through which MSCs regulate the immune response is that these cells inhibit T-cells, B-cells, dendritic cells, macrophages and natural killer (NK) cells via cell-cell interaction and secretion of immunosuppressive factors and therefore, have immunomodulatory properties (48, 49).

4- Migration and settlement in the site of injury: Migration and settlement of MSCs at the site of injury is related with transportation proteins in the cell such as chemokines, adhesion molecules, and matrix metalloproteinases (MMPs) (50).

In addition, MSCs are acceptable for clinical studies due to not expressing MHCII, inhibiting T-cell responses by inhibiting NK cells and CD4 and CD8 as well as providing an environment full of prostaglandins and interleukin-10 (IL-10) (51-53).

6. Cell therapy in fecal incontinence

For the afore-mentioned reasons, MSCs are the only cell source that has been used in treatment of fecal incontinence in clinical trials. Stem cell transplantation with the goal of treating acute fecal incontinence aiming to repair the muscular tissue of the external sphincter of the anus has been mostly studied in animal models. The history of using this method in clinical trials goes back to a few years ago (Table 1). The first clinical trial in this field has used stem cells derived from the muscles of the patient for treating fecal incontinence. The initiation of this trial has been registered in 2012 by a Canadian research team with Yahira Baez-Santos as the supervisor; however, no preliminary results have been published regarding this study and it is still ongoing. This research team has announced that this project is going to end in 2019. This study has been designed to evaluate the safety and feasibility of transplantation of these cells in 50 patients and the primary outcome studied was incidence of treatment-related adverse events and secondary outcomes consisted of frequency of incontinent episodes, incontinence score, sphincter pressure and quality of life (54). Another study was registered by Abdel-Wahab El-Okby et al. in 2014. Although the finish date of the study is announced to be 2016, its results have not been published yet. This study was designed aiming to assess the effect of MSC transplantation in 50 patients and the primary outcome studied is incontinence score and the secondary outcomes include maximum dry interval, MRI pelvic floor muscles and EMG study (54). Overall, 4 clinical trials have been published to date, the oldest one belonging to 2014. The study was carried out by Frudinger et al. on 10 women who were affected with injury of the external sphincter muscle of the anus and therefore fecal incontinence as a result of labor trauma. In the study, safety and technical feasibility of transplanting the stem cells derived from the pectoralis muscle of the patients to their own injured sphincter muscle was evaluated during a 1-year follow up. Primary outcome of the study included Wexner incontinence score, bowel movements, mean resting pressure, maximum resting pressure, mean squeeze pressure, maximum squeeze pressure, and anal pressure zone. The findings of this study showed that after 1 year, Wexner incontinence score had significantly decreased. Based on the results of the study, Frudinger et al. reported that autologous myoblasts are safe, sustainable, and free of side effects and lead to significant improvement in fecal incontinence symptoms caused by labor damages to the

Table 1: A summary of the clinical trials on using stem cells in fecal incontinence

Authors, year	Sample size	Treatment protocols	Main findings	Limitations
Frudinger, A., et al.,2014	Cell group=10 no control	Anal electrical stimulation + implantation of autologous myoblasts	Wexner incontinent score had decreased by a mean of 13.7 units and anal squeeze pressures did rise significantly at 1 month and 6 months post-injection (p=0.03)	No assessment of physiological change to account for the improvements
Romaniszyn, M., et al.,2015	Cell group=10 no control	50 to 600 × 10^6 stem cells were then administered to the EAS	Squeeze anal pressures and high-pressure zone length increased in all patients. Twelve months after implantation two patients experienced deterioration of continence	A small group of subjects, there was no control group,
Park., et al.,2016	Cell group=3 Control=3	Transplantation of allogeneic-adipose-derived mesenchymal stem cells into the anal sphincter with dose escalation (3×10^7, 6×10^7 and 9×10^7 cells, sequentially).	Study protocol without outcome	Not applicable
Sarveazad., et al.,2017	Cell group=9 Control=9	Transplantation of 6 × 10^6 adipose-derived mesenchymal stem cells.	No significant difference in Wexner scores in the studied groups. The ratio of the area occupied by the muscle to total lesion site showed a 7.91% increase in the cell group compared with the control group.	Heterogeneous patients, small sample size, short follow up period, lack of histopathology assays.

external sphincter muscle of the anus (55). Following this study, Romaniszyn et al. published the results of an experimental pilot study in 2015, in which they evaluated the effect of autologous transplantation of stem cells derived from vastus lateralis muscle on repair of external sphincter muscle of the anus in 10 patients (9 male and 1 female) that were injured due to various reasons during a 1-year follow up. 9 out of the 10 individuals completed the 1-year follow up. Primary outcome of this study included Wexner incontinence score, squeeze anal pressures and high-pressure zone length and Electromyographic (EMG) examination. In 18-week follow up, squeeze anal pressures and high-pressure zone length had increase in all the patients; however, only 6 patients showed a decrease in Wexner incontinence score. After 1 year, 2 out of the 6 patients showed a significant decrease in Wexner incontinence score and this decrease was in line with their manometry and EMG results. Based on the findings of their study, Romaniszyn et al. concluded that autologous implantation of myoblasts has good short term results in objective and subjective evaluations but for a making a definitive decision and getting lasting results in the long run, further studies should be carried out (56). After these 2 studies, in

2016, Park et al. in a phase I pilot study evaluated the effect of allogeneic stem cells derived from adipose tissue of human on repair of external sphincter muscle of the anus and fecal incontinence for the first time. The study was done on 12 patients (6 in the cell group and 6 in the placebo group) during a 1-year follow up. Primary outcomes of the study were Wexner score, pressure of the anal sphincter and score of patients' satisfaction. Protocol of this study has been published, yet to date the results of this study have not been published (57). The newest study published to date in the field of repairing external sphincter of the anus aiming to treat fecal incontinence is the preliminary results of a study by Sarveazad et al. in 2017 (58). In this study, the effects of allogeneic transplantation of the stem cells, derived from human adipose tissue, on fecal incontinence has been studied with a 2-month follow up period. This study was carried out on 18 patients (9 controls and 9 cell transplantations) with sphincter deficiencies. Primary outcome of the study consisted of Wexner score, amount of muscle in injury site and EMG assessment. After 2 months, Wexner score showed a significant decrease in both control (2.67±0.62) and cell (6.44±1.08) groups compared to the baseline (6.0±1.18 and 10.33±0.87) (p=0.01). Yet, there was no difference between the 2 groups (p=0.36). The amount of muscle at the site of injury had a significant increase (p=0.02) in the cell group (18.85±5.06%) compared to the control group (11.65±7.75%). EMG findings showed that 5 out of the 9 patients in the cell group had action potential at the site of injury. The results of this study showed that transplantation of human adipose derived stem cells to the damaged external sphincter muscle can replace the fibrose tissue at the site of injury with muscle tissue, which is a big step towards finding an efficient treatment, particularly in the long term. The authors have justified the absence of a difference between the Wexner scores in the control and cell groups 2 month after surgery by saying that the fibrose tissue in the control group can act as a mechanical barrier without a contractile function and lead to a partial stool control. However, it seems that in the long term follow up when the fibrose tissue loses its strength, a significant difference between the Wexner scores of the control and cell groups should be found since the site of injury in the cell group is partially filled with muscle tissue with a contractile function. Therefore, the real results regarding the efficiency of transplanting these cells in treatment of fecal incontinence can be better judged in the long term (58).

7. Limitations

The main limitation of cell therapy for fecal incontinence could be lack of an accurate and standard protocol, because the history of research in this field goes back only 5 years and articles published in this field are all pilot studies to assess the safety and efficacy of this method. The appropriate source, number of cells, cells being allogeneic or autologous, time of injection (before, after, or immediately after surgery) and duration of follow up, which are all the main pillars of an accurate treatment protocol have not been determined yet.

One of the other limitations of assessing the effect of any intervention for treating fecal incontinence including cell therapy is selection of all the patients for eliminating confounding factors and getting reliable results. Since damage to the external sphincter muscle of the anus occurs due to various reasons and in all different levels, even if all of the patients are selected in a way that all have been injured for the same cause, homogenization has not been done, because the injury to sphincter is not controlled and the rate of damage and

Table 2: Strengths and limitations of the stem cells used for treating fecal incontinence

Stem cells	Strengths	Limitation
Autologous myoblast	- Cells derived from muscles are more efficient in differentiation to muscle tissue (external sphincter of the anus). - In autologous implantation of the cells there is no ethical problem or probability of transplant rejection.	- Biopsy for isolating enough of the required cells is an invasive method. - Limitation in the volume of muscle tissue removed during biopsy.
Allogeneic human adipose tissue derived stem cells	- Easily accessible for biopsy -Very high number of cells in a small volume of adipose tissue - Very high level of angiogenic factor	- There are ethical problems and probability of rejection in transplantation of allogeneic cells

the site of injury are different. Among other limitations in cell therapy for treating fecal incontinence is determining the fate of the implanted cells. For evaluating the fate of the cells first they need to be labeled and the common methods of labeling cannot be used in clinical trials due to ethical limitations; and second biopsy from the site of injury is required for histopathology evaluation, which is an invasive method and can lead to more damage at the site of injury and interrupt accurate evaluation of the results. Therefore, in the studies carried out until now evaluation of the cells' fate has not been done (Table 2).

8. Conclusion

By evaluating the existing studies on use of stem cells in treatment of fecal incontinence it can be concluded that: All the studies are in phase I of clinical trials for confirming safety and feasibility of stem cells. From the results of the 4 published studies it can be concluded that using mesenchymal stem cells with 2 sources of muscle and fat, either autologous or allogeneic, with the aim of repairing the external sphincter of the anus and treating fecal incontinence is safe and efficient, and can be a step forward for treating this dysfunction. Yet, it is obvious that further studies should be done in phase II and III of clinical trials with larger sample size, various cell sources and different doses, via autologous or allogeneic cells.

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10. Conflict of interest

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12. Author contribution

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