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Research Article

Trans-Sphincteric Anal Fistula - Treatment by Ligation of Inter-Sphincteric Fistula Tract (LIFT) with Bone Marrow Mono Nuclear Cells (MNCs)

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Abstract

Background :Ligation of Inter-Sphincteric Fistula Tract (LIFT) is a widely popular procedure adopted for the treatment of trans-sphincteric anal fistulas. It is a sphincter functionality-preserving procedure gaining wide acceptance throughout the world. This study is aimed at analyzing the outcomes of anal fistulas undergoing Ligation of Inter-Sphincteric Fistula Tract (LIFT) procedures with or without injection of Bone Marrow Mono Nuclear Cells (BM-MNCs). The outcomes studied include Procedure Time, Time taken for Healing, Post-operative complications, Success Rate, and Recurrences. Complete Healing without any discharge by 6 months is considered the ultimate success of the procedure.

Methods :This is a prospective randomized control trial done in Kanyakumari Government Medical College, Asaripallam, Kanyakumari District, Tamilnadu on patients attending our Surgical Outpatient Department with trans-sphincteric Anal Fistulas from March 2022 to February 2023. Patients were randomly allocated by Odd-Even Method based on Admission into two equal groups. LIFT alone group constituted the Control group while the LIFT with BM-MNCs injection served as the test group. 50 patients were enrolled altogether with 25 patients in each group. The same surgeon and patients operated on all the patients were followed up at 4 weeks, 6 weeks, 10 weeks, and 6 months post-surgery.

Results : Fifty patients (31 male and 19 female) with a mean age of 36.8 ± 8.4 years were included. The mean time to complete healing after LIFT+BM-MNCs was significantly shorter than after LIFT alone (22.8 ± 3.4 vs 30.5 ± 4.5 days, P value-0.003*). The ultimate success rates of both groups were similar (LIFT=64% vs LIFT with BM-MNCs=76%, P value- 0.08). There was no significant difference in the mean operation time or complication rate between the two groups.

Conclusion: In cases of trans-sphincteric fistulas, Ligation of the Inter-sphincteric Fistula Tract along with the injection of Bone Marrow Mononuclear Cells (BM-MNCs) augmented healing and reduced the healing time significantly.

Keywords: Anal Fistula; Bone Marrow; LIFT; Mononuclear Cells; Randomized Control Trial

Introduction

The management of trans-sphincteric anal fistulas remains challenging due to the involvement of the anal sphincter complex and the persistent nature of the condition. The primary treatment goal is to achieve healing without compromising continence, thereby minimizing the impact on quality of life [1]. Park's classification divides fistula into four different types: inter-sphincteric, trans-sphincteric, supra-sphincteric, and extra-sphincteric. Anal fistula is also divided into simple and complex fistula. The American Society of Colon and Rectal Surgeons (ASCRS) divides fistulas into simple types, which include low trans-sphincteric and inter-sphincteric fistulas. These types make up less than 30% of the sphincter complex. However, a complex anal fistula is a trans-sphincteric fistula that includes more than 30% of the sphincter complex [2]. The aim of surgery in complex anal fistula is to

prevent recurrence and avoid incontinence. Different sphincter-sparing techniques were described with variable results, including seton, advancement flap, ligation of the inter-sphincteric fistula tract (LIFT), fistula plug (FP), fistula-tract laser closure (FiLaC), and video-assisted anal fistula treatment (VAAFT). Over the years, sphincter-preserving surgical procedures have emerged, and the Ligation of Inter-sphincteric Fistula Tract (LIFT) procedure has gained wide popularity and acceptance due to its surgical success rates and reduced morbidity rates. LIFT was published by Rojanasakul et al. in 2007, which still stands out. The increased advantage of the LIFT procedure over other procedures is its minimal impact on fecal continence [3]. The LIFT procedure is a good way to treat trans-sphincteric fistula that doesn't damage the sphincter. It also has a good long-term outcome [4,5]. BM-MNCs contain mesenchymal stem cells, which can differentiate into various cell types and promote tissue repair, potentially aiding in wound healing within the fistula tract. BM-MNCs are a rich source of hematopoietic stem cells. BM-MNCs are usually taken from a patient's bone marrow, processed to separate the specific cells needed, and then injected around the fistula site during surgery. Bone marrow mononuclear cells used for external anal sphincter repair strengthen wound healing by transferring cells responsible for healing directly to the site of repair [6,7]. The current study is aimed at assessing the outcome of local injection of bone marrow mononuclear cells (BM-MNCs) in conjunction with LIFT as compared to LIFT alone regarding healing rate, time to healing, and ultimate success rate.

Patients and Methods

Study Design and Setting

This was a prospective randomized controlled trial on patients with trans-sphincteric anal fistulas. The study was conducted in Kanyakumari Government Medical College, Surgical Department, Asaripallam, Kanyakumari District, Tamil Nadu, from March 2022 to February 2023. After getting signed informed consent, patients were enrolled in the study, highlighting a possible future publication of the data and results. Selection Criteria Patients of both genders greater than 18 years with cryptoglandular trans-sphincteric anal fistula were included. We excluded patients with secondary anal fistula caused by inflammatory bowel disease, malignancy, or irradiation; immunocompromised patients; and pregnant women.

Preoperative Assessment

A detailed history was taken regarding the current complaint and its duration, associated medical conditions, previous surgical operations, constipation, and fecal continence state. The continence status was assessed with the Wexner incontinence score.7 MRI fistulograms were performed for assessment of the type and branching of the fistula tract and localization of the internal opening.

Group Allocation

Patients coming to the surgical outpatient department of Kanyakumari Government Medical College with anal fistulas were examined, and patients with trans-sphincteric fistulas were identified and selected for this study. Patients were counseled on their treatment options and need for surgery with the help of their MRI fistulogram reports. Informed signed consent was obtained from all selected patients, and possible future publications of the results and data were also informed. Patients and surgeons were aware of the nature of the trial and group allocations. Outcome assessors were blinded to the group allocations. Patients could not be blinded to the intervention as they were aware of the aspiration of bone marrow from the iliac spine.

Surgical Intervention

Patients were operated on in the modified lithotomy position under spinal anesthesia. Prophylactic antibiotics in the form of 1 g of cefotaxime and 500 mg of metronidazole were given intravenously at the time of the induction to patients in the two groups. The procedures were performed by a single surgeon in all cases. None of the patients in the two groups had a drainage seton before surgery.

LIFT Technique

The classical LIFT procedure as described by Rojanasakul et al. [5] was performed. The internal opening was localized by injection of methylene blue dye through the external opening and gently probing the fistula tract. The inter-sphincteric plane was entered via a curvilinear incision. The inter-sphincteric fistula tract was carefully dissected using scissors and electrocautery. The inter-sphincteric tract was raised using a small right-angled clamp. The track was then ligated twice, first close to the internal sphincter and then at a distal point with Vicryl 3-0, and then the tract was divided between the two ligatures. The distal tract was surgically excised after the external opening was curetted and adequately drained. The inter-sphincteric incision was loosely sutured with Vicryl 3-0.

Bone Marrow Mononuclear cells

Ligation of the inter-sphincteric fistula procedure was followed by injection of 2 ml of BM-MNCs along the ligated fistula tract in the inter-sphincteric space and the internal opening. The injection of BM aspirate ensured that it was retained inside the tissue and did not escape through sutures. Preparation of the BM-MNCs— One hour before surgery, patients were placed in the left lateral position, and the lower part of the back was prepared with povidone-iodine (10%) and draped. A small stab was made in the skin over the posterior superior iliac spine (PSIS) under local anesthesia, and a

special trocar and cannula (Jamshidi needle) were introduced into the bone marrow cavity of the iliac bone. Ten milliliters of bone marrow were aspirated in a syringe pre-flushed with heparin (1000 units/mL). The stab wound was dressed, and the bone marrow syringe was shaken gently for 5 min. Then it was taken to the laboratory for preparation of BMAC. The MNCs were isolated from the bone marrow using density gradient centrifugation (DGC). Five milliliters of bone marrow were diluted by 5 mL of phosphate buffer saline (PBS) and then added to a 5-mL Falcon tube containing 5 mL of LymphoprepTM. Then, the tube was centrifuged at 4000 rpm (rounds per minute) for 20 min. After centrifugation, the tube contents were separated into 4 layers: plasma on the top, a thin layer of MNCs, Lymphoprep, and then the remaining components of bone marrow at the bottom. MNCs were aspirated and washed three times using PBS (they were put in a new tube, then PBS was added, and the tube was centrifuged at 1000 rpm for 10 min, after which the old PBS was removed and new PBS was added, and the process was repeated). In the end, MNCs were resuspended in 2 mL PBS and were sent to the operation room.

Post-operative Care

Patients in the two groups were discharged on the third day of surgery and were prescribed oral quinolone antibiotics for 3 days and stool softeners for 1 week. Instructions on wound dressing using a sitz bath every 6 hours were given to the patients. Follow-up Patients were followed up at the outpatient clinic at 4 weeks, 6 weeks, 10 weeks, and 6 months postoperatively. At each visit, patients were assessed clinically for fistula healing, continence state using the Wexner incontinence score, and postoperative complications including infection, bleeding, hematoma, and incontinence. Assessments were made by a surgical resident who was not aware of group allocations and by one of the study authors who did not influence the outcome of assessments.

Primary and Secondary Outcomes

The primary outcome was complete fistula healing at 6 months. The secondary outcomes were procedure time, Fecal Incontinence and post-operative complications. The operation time was measured from the onset of the incision until closure of the inter-sphincteric wound. The time taken to obtain and prepare the BM-MNCs was not included in the operation time. Fistula healing was defined as the closure of the internal and external openings without any discharge. Failure of healing was defined if complete closure of the external opening did not occur at 10 weeks after surgery. Recurrence was defined as reappearance of the external opening after complete healing, appearance of new external opening, and recurrence of symptoms after complete resolution on follow-up. Ultimate success was defined as complete fistula healing 6 months after surgery with the absence of recurrence.

Statistical Analysis

Data were analyzed using Excel and SPSS (Statistical Package for Social Science) programs under Microsoft Windows. Quantitative data were expressed as mean and SD or median and range according to data normality. Student t-test was used to analyze quantitative data whereas chi-square or Fisher's exact test was used for categorical data. An intention to treat analysis and per-protocol analysis were performed. Multivariate binary logistic regression analysis of the predictors of failure of healing was conducted. The area under the curve (AUC) of the model used was calculated to determine its discriminatory power. A per-protocol analysis of the study outcomes was used. A P-value less than <0.05 was considered significant.

Results

During the study, 50 patients who fulfilled our study criteria were treated by Ligation of Inter-sphincteric Fistula Tract (LIFT) with or without bone marrow mono nuclear cells injection. Out of the 50 patients 16/25 were males (64%) and 9/25 patients were females (36%) in the LIFT alone group. In the LIFT plus BM-MNCs group 15/25 patients were males (60%) and 10/25 patients were females (40%). The Body Mass Index (BMI) of the patients were calculated and the mean was found to be 27.3 ± 1.3 for the LIFT alone group and was 26.8 ± 2.3 for the LIFT plus BM-MNCs group. 3 patients in the LIFT alone group had previous anal surgeries while 2 patients had undergone previous anal surgeries in the Test group. The patient characteristics are shown in the Table 1.

VARIABLE	LIFT	LIFT-BM-MNCs	P VALUE
Number	25	25	-
Mean age in years	36.3 ± 9.2	37.0 ± 8.3	0.4
Males %	16 (64%)	15 (60%)	0.789
Females %	9 (36%)	10 (40%)	0.65
Body mass index in kg/m²	27.3 ± 1.3	26.8 ± 2.3	0.08
Previous anal surgery	3 (12%)	2 (8%)	0.67

LIFT- Ligation of Inter-sphincteric Fistula Tract; BM-MNCs- Bone Marrow Mono Nuclear Cells.

Table 1: Patient characteristics in LIFT alone group and LIFT plus BM-MNCs groups.

Fistula Characteristics

Overall there were 7 anterior fistulas in LIFT alone group (28%) and 8 patients with anterior fistula in LIFT plus BM-MNCs group (32%). There were 6 (24%) and 4 (16%) posterior and lateral fistulas respectively in LIFT alone group. In the LIFT-BM-MNCs group there were 5 (20%) and 3 (12%) posterior and lateral fistulas. Multiple openings and previous fistula surgeries and previous abscess drainage histories were noted. The characteristics of the Fistula are tabulated in Table 2.

VARIABLE	LIFT	LIFT-BM-MNCs	P VALUE
	(n=25)	(n=25)	
Fistula Position			
- **Anterior**	7 (28%)	8 (32%)	0.65
- **Posterior**	6 (24%)	5 (20%)	
- **Lateral**	4 (16%)	3 (12%)	
Secondary Extension	1 (4%)	2 (8%)	0.87
Horse-shoe	1 (4%)	1 (4%)	0.79
Multiple Openings	3 (12%)	4 (16%)	0.67
Previous Fistula Surgery	2 (8%)	1 (4%)	0.32
Previous Abscess Drainage	1(4%)	1 (4%)	0.28

Table 2: Fistula characteristics in LIFT alone group and LIFT plus BM-MNCs groups.

Primary Outcome

The primary outcome of the study is to find the ultimate success after 6 months post-surgery among the two groups. The Mean healing time in days among the two groups are calculated. Healing at 4 weeks, 6 weeks, 10 weeks and ultimately at 6 months are tabulated to find the superiority among the procedure groups. Out of the 25 patients in the LIFT group healing at 10 weeks was found in 15 patients (60%) whereas in the LIFT plus BM-MNCs group 18 patients out of the 25 patients had healing (72%). Ultimate success of the procedures at 6 months post-surgery was found to be 64% (16/25) in the LIFT alone group while the success rate was found to be 76% (19 out of the 25 patients) in the LIFT plus BM-MNCs group. The mean healing time in days was found to be 30.5 ± 4.5 in the LIFT alone group while it was found to be 22.8 ± 3.4 in the LIFT plus BM-MNCs group. P value was found to be 0.003 and is statistically significant. Hence the healing time is quicker for trans-sphincteric fistulas treated with LIFT plus bone marrow mono nuclear cells injection. The primary outcome values are tabulated in Table 3.

VARIABLE	LIFT (n=25)	LIFT-BM-MNCs (n=25)	P VALUE
Mean healing time in days	30.5 ± 4.5	22.8 ± 3.4	0.003**
Healing at 4 weeks (%)	12 (48%)	16 (64%)	0.04*
Healing at 6 weeks (%)	14 (56%)	17 (68%)	0.53
Healing at 10 weeks (%)	15 (60%)	18 (72%)	0.45
Ultimate success at 6 months (%)	16 (64%)	19 (76%)	0.08

Table 3: Healing Time in LIFT alone group and LIFT plus BM-MNCs groups.

Secondary Outcomes

The mean operation time in minutes of the both groups were analyzed and found to be 32 ± 2.5 for the LIFT alone group where as it was 33 ± 3.2 for the LIFT plus BM-MNCs group. P value was found to be 0.87. There was no much difference between the two groups and was statistically not significant. Post-surgical Infection was found in 1 patient in the LIFT alone group on POD 2 and 1 patient in the LIFT plus BM-MNCs group on POD 2. Both were managed conservatively with antibiotics and sterile dressings. No in-continence state was observed in any of the patients in the two groups with a median postoperative Wexner incontinence score of zero. Patients in the BM-MNC group did not have any adverse effects of BM aspiration, except for mild pain at the aspiration site that was relieved with analgesics. None of our patients showed Recurrence. The secondary outcomes are tabulated in Table 4.

VARIABLE	LIFT (n=25)	LIFT-BM-MNCs (n=25)	P VALUE
Mean Operation Time in minutes	32 ± 2.5	33 ± 3.2	0.87
Complications			0.76
- **Infection**	1 (4%)	1 (4%)	
Incontinence	0	0	----

Table 4: Secondary Outcomes in LIFT alone group and LIFT plus BM-MNCs groups.

Discussion

In light of previous literature on LIFT [8-12], the success rate of LIFT ranged between 47% and 79% with a mean success rate of 60%. Hence, we tried the injection of BM-MNC to increase the success rate, and we got favorable results in our study with a success rate of about 76%. Popular combined techniques include the LIFT plus procedure, bio-LIFT, and LIFT plug. For LIFT plus, classical LIFT is done first, and then the external part of the fistula tract is cored out. For bio-LIFT and LIFT plugs, a bio-mesh or a plug-in is placed in the inter-sphincteric space or the external tract to help close the fistula tract even more [13-15] .A different version of the LIFT procedure used a human acellular dermal matrix as a bioprosthetic plug. This had a 95% success rate and a median healing time of 4 weeks [16,17]. Another concept devised to improve the outcome of LIFT was to inject certain materials in the inter-sphincteric space to hasten and enhance healing. In 2017, Madbouly et al. divided 98 people with trans-sphincteric fistulas into two groups: those who only got LIFT and those who also got an injection of Platelet-Rich Plasma (PRP) in the space between the sphincters. Patients who underwent LIFT-PRP had a significantly shorter time to heal and a higher ultimate success rate than the control group (85.7% vs. 65.3%). This study tried to improve the results of LIFT by injecting BM-MNCs at both the internal opening and along the tract in the space between the sphincters. We included 50 patients with trans-sphincteric fistula, primarily middle-aged males. Both groups had similar demographics and fistula characteristics, so there was little selection bias and excellent randomization in the patients in both groups. The primary outcome was to study the healing of anal fistula after the procedure. The secondary outcomes were procedure time, post-op complications, incontinence, and recurrence. BM-MNC injection served to accelerate healing after LIFT significantly owing to the healing-promoting properties. The group that underwent both LIFT and the BM-MNCs injection experienced a significantly shorter mean healing duration. Another study reported that some technical factors may also contribute to failure after LIFT. This area between the sphincters wasn't draining well

enough; there was still necrosis; there were infected tissues in the groove between the sphincters; the internal anal sphincter and anal canal mucosa were hurt; and the fistula tract wasn't completely closed off [18]. The clinical observation of our study indicates that faster healing has a positive impact on the patient's recovery and quality of life. Also, accelerated healing reduced the daily need for dressing and sitz baths, which caused patient inconvenience and financial burdens. This study's positive results pave the way for larger, multicenter studies with longer follow-up.

Conclusion

For trans-sphincteric fistulas, ligating the inter-sphincteric fistula tract and injecting Bone Marrow Mononuclear cells (BM-MNCs) sped up healing and cut the time it took to heal by a large amount. In trans-sphincteric fistulas, the LIFT procedure with BM-MNC injection may be better than LIFT alone, even though there wasn't a big difference in the overall success rate or healing. It is recommended that more research is done to make the protocol work better for the BM-MNC application and to look into the underlying mechanisms that lead to better healing outcomes.

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