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Bone Marrow Cell Therapy in Complex Fistula-In-ANO

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Abstract

Perianal fistula is a worldwide health problem that can affect any person anywhere. Complex perianal fistula is a fistula which has multiple tract, horse shoe tract, suprasphincteric extension or a recurrent fistula & fistula associated with crohn's disease, ulcerative colitis, tuberculosis etc. Surgical management of this type of fistula is not free from risk ; often result in recurrence and high risk of fecal in continence if an extensive surgical debridement is performed. The post operative complication like pain, tenderness, discharge, incontinence, recurrence are more common. In our study we have tried the autologous bone marrow therapy to operative site to prevent such complication. Two group of patient were selected randomly having complex fistula in ano; containing 20 patient in each group. The patient are under contrast group were treated by conventional fistulectomy alone ; where study group were treated by fistulectomy followed by autologous bone marrow cell therapy to operative site. The patient follow up. The post operative pain in control group 9 (45%) but in study nil recurrence. Tenderness persist. 8 (45%) in contrast group; but in study group 2 (10%) and require analgesic. HPE of granulation tissue from floor of ulcer at POD 7 shows more neovascularisation, more no. of fibroblast with inflammatory cell per high power field with minimal necrosis seen in 10 (80%) of study group and (20%) in control group. No incontinence in both group.

Keyword : Autologous bone marrow therapy, fistulectomy, complex fistula.

Introduction

Fistula-in-ano is seen quite frequently and frequency virtually mirrors perianal-perirectal suppuration. situation of the disease, the unmentionable site adds to the morbidity consequent on the reluctant shy patient shying away from the surgeon. Fistula is a chronic granulating track connecting two epithelial lined surface, external opening in the skin on mucosa of the perianal region and internal opening on the modified skin or mucosa of and cannal or rectum above. The wall of tract composed of a thick layer of fibrous tissues.Majority of patient suffer from complication like post operative pain, discharge, tenderness, incontinence, recurrence. Due to these complications the duration of stay in surgery increase many type of surgery done. None of surgery alone is sufficient to prevent such problem. Autologous bone marrow therapy is a new concept which is base on the facts that bone marrow contain mesenchymal stem cells which stimulates the local stem cells. Fibroblast, macrophage for their enhance activity. They also liberate cytokine and growth factors which helps in rapid wound healing and preventing early and late complication.

In this prospective study from August 2016 to March 2018, we have done prospective analysis in the study on the effect of autologous bone marrow therapy to fistula bed to present complication.

Objective

Primary

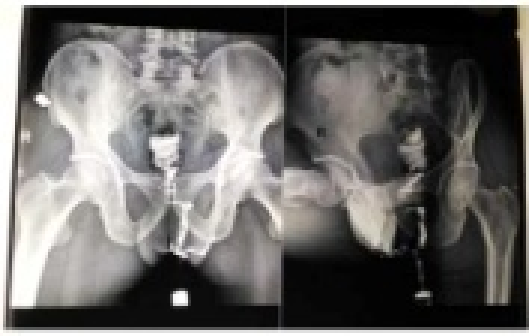
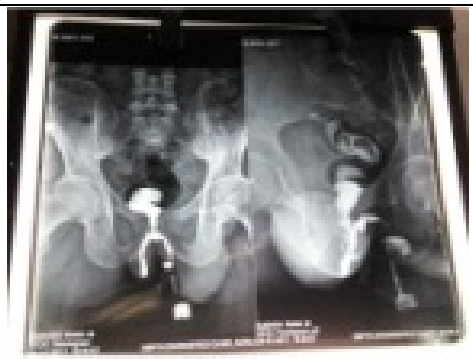
To study the effect of Autologous bone marrow therapy to fistula bed to present early complication.

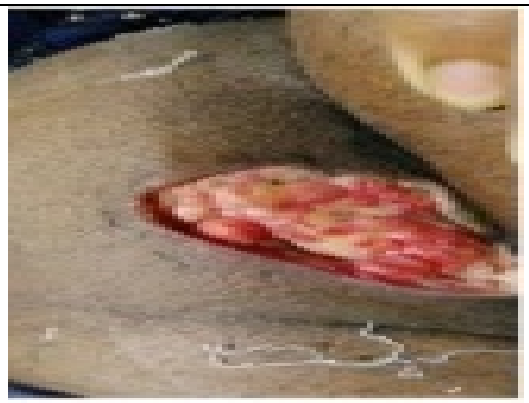
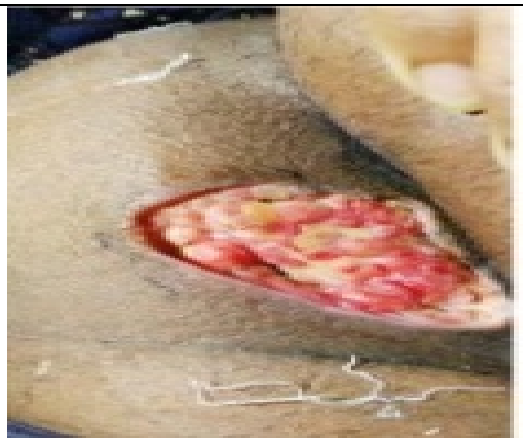
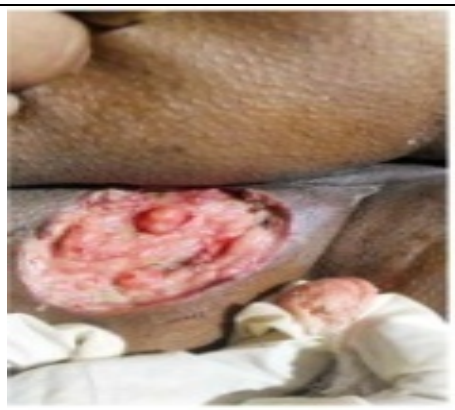
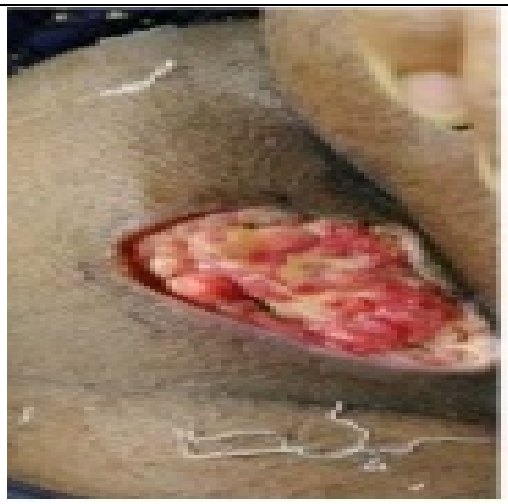
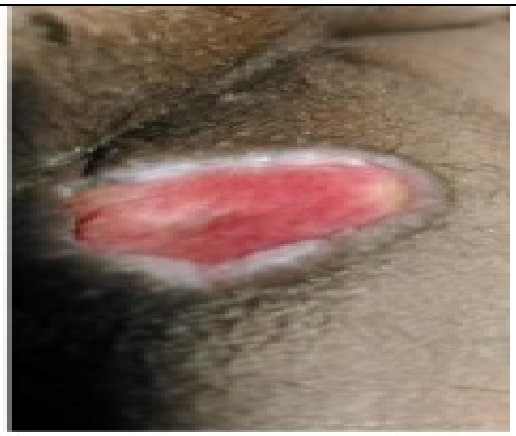
Secondary

To study the effect of Autologous bone marrow therapy to fistula bed to present late complication like recurrence.

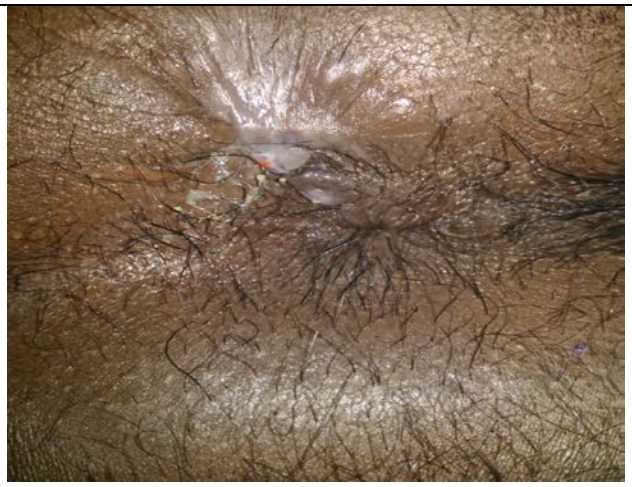
Method

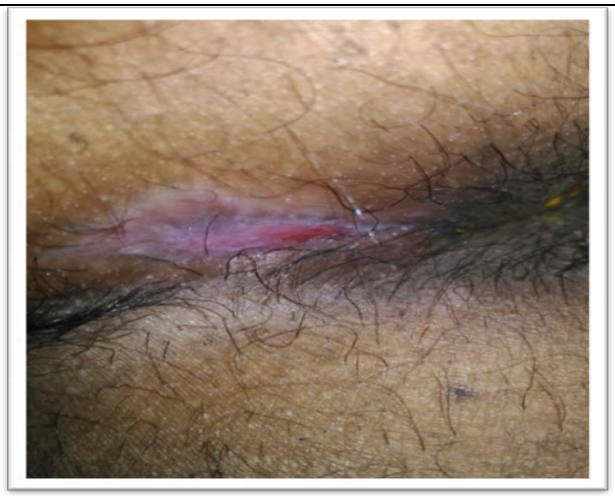
Institutional ethics committee clearance and informed concept of the patients was taken before the study. Then total 40 complex fistula-in-ano patient in this study underwent fistulectomy surgery at VIMSAR, Burla, Odisha in one surgical unit during this year August 2016 to March 2018. Out of 40 patient, 20 patient were kept in this study group and rest 20 control group. Fistulectomy done in both control and study group. But in study group on operative table bone marrow aspirate was kept aside after priming with heparin in a sterile syringe. Then haemostasis maintained all case. Bone marrow was infiltrated to fistulectomy bed. In control betadine, antibiotic soaked gauge pack given. But in study group only normal saline soaked gauze pack given. Postoperatively patient were followed up parameter like pain, tenderness, ulcer status, discharge, recurrence, incontinence were studied.

	Control Group	**Study Group**
Pre-Op.		
Fistulogram		

P O D - 3		
P O D - 5		
P O D - 7		
P O D - 3 week		

POD 8 WEEK

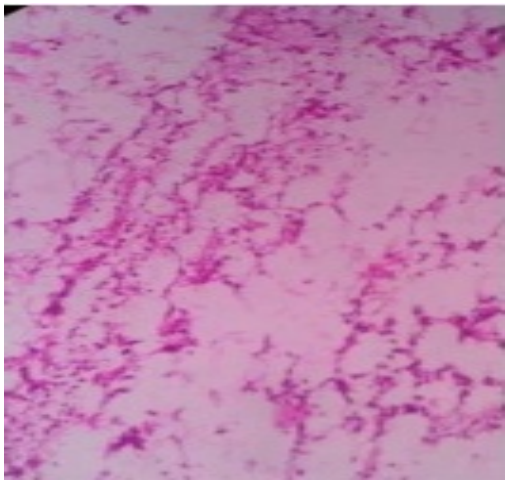


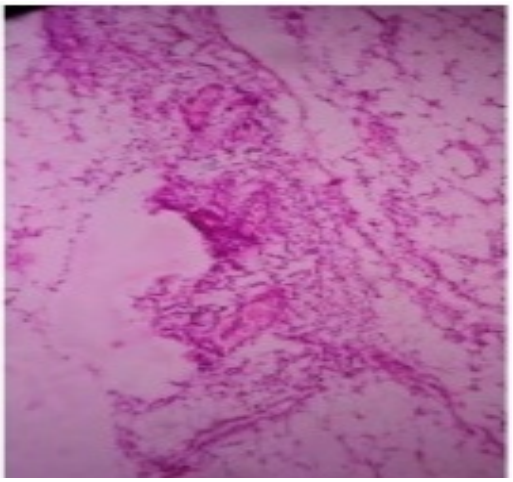


	STUDY	CONTROL
Post op pain	2	16
Persistent tenderness require analgesic	2	8
Recurrence	Nil	4
Post op bleeding	4	8
Granulation tissue biopsy ,more neovascularisation, more fibroblast	16	4
Incontinence	Nil	Nil

CONTROL STUDY

Biopsy (HPE)





BIOPSY STUDY

	CONTROL	EXPERIMENTAL
NECROSIS	MORE	LESS
NEUTROPHIL,LYMPHOCYTE	LESS	MORE
BLOOD CAPILARY	NO	PRESENT
MACROPHASE	LESS	MORE
FIBROBLAST	NO	NO

Discussion

MSCs were initially isolated from bone marrow but are now shown to reside in almost every type of connective tissue [16]. MSCs are characterized as a heterogeneous population of cells that proliferate in vitro as plastic adherent cells able to develop as fibroblast colony forming-units [17]. MSCs are distinguished from hematopoietic cells by being negative for the cell surface markers CD11b, CD14, CD34, CD45 and human leukocyte antigen (HLA)-DR but expressing CD73, CD90 and CD105. Importantly, the capacity to differentiate into multiple mesenchymal lineages including bone, fat and cartilage is used as a functional criterion to define MSCs [18]. MSCs are clearly capable of responding and modulating their function when exposed to the cells and biochemical factors that are characteristic of an injury environment. Human MSCs migrate preferentially to regions of inflammation [19] and express several chemokine receptors that are necessary to coordinate their homing ability [20]. Furthermore, MSCs have demonstrated chemotaxis toward a variety of wound healing cytokines in vitro, including platelet-derived growth factor, insulin-like growth factor-1, IL-8 and TNFα [21,22]. These data suggest that bone-marrow-derived MSCS or endogenous cells resembling MSCs, such as pericytes, are likely to migrate to and participate in the response to tissue injury.

Studies have shown that mesenchymal stem cells (MSCs) derived either from bone marrow or fat can express LEC markers (prox-1, VEGF-C, VEGF-A) and that stimulation of these cells in cultured media with recombinant VEGF-C, even for brief periods of time in vitro, markedly increased their ability to promote neovascularization in vivo [23, 24]. In our study we have observed more quality granulation tissue in study group than control group at post op day 5 by biopsy report. Our this finding supports the above literature there by suggesting the role of autologous bone marrow therapy in early healing of tissue. MSCs produce basic FGF and VEGF-A, which provide powerful mitogenic cues to promote proliferation, migration and differentiation of microvascular endothelial cells [25,26]. MSCs also express paracrine factors to promote vascular stability and vasoprotection [27,28], including adrenomedullin [29]. It has been hypothesized that these functions are unique to MSCs due to their possible perivascular origin, and they are able to exploit these functions to recreate their perivascular niche as the process of vasculature remodeling is concluded [30]. Enhancement of vascular formation by bone-marrow derived MSCs has been demonstrated in vitro [31] and to facilitate the development of long-lasting functional vasculature as perivascular progenitor cells [32]. Thus autologous bone marrow therapy may facilitate neovascularisation. In our study we have seen recurrence in 4 out of 20 patients in control group and 0 out of 20

patients in study group and post-op pain in 16 out of 20 patients in control group and 2 of the patients in study group. Though such finding is not statistically significant still relatively we have seen patients experienced very less post-op pain as compared to control group may be due to the anti- inflammatory activities of mesenchymal stem cells. MSCs have anti-inflammatory effects because they inhibit dendritic cell [DC] maturation and B and T cell proliferation and differentiation, that they attenuate natural killer [NK] cell killing, and that they also support suppressive T regulatory cells [Tregs][33-35]. MSCs also decrease the amount of IL-10 and TNF-α secreted by DC cells, and increase the amount of the anti-inflammatory IL-4 produced by T cells [33-35]. MSCs provide significant benefit during dermal wound healing, as they can,

1) Accelerate the rate of wound closure and re-epithelialization,
2) Improve the quality and strength of the regenerated tissue,
3) Recover wound healing pathologies that might otherwise result in a chronic, non-healing wound.

In adult cutaneous wound healing, inflammatory cells are recruited to the wound and produce proinflammatory mediators such as monocytechemotactic protein-1 (MCP-1), macrophage inflammatory protein-1 beta (MIP-1β), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). These mediators can not only induce additional inflammation but also contribute to excess extracellular matrix (ECM) deposition and fibrosis. Moreover, the inflammatory cells can produce growth factors such as transforming growth factor-beta 1 (TGF-β1) and platelet-derived growth factor, which stimulate fibroblast proliferation, myofibroblast differentiation, and excess ECM deposition, leading to scar formation. We have not seen any recurrence and it need to be studied more to prove the healing effects of mesenchymal stem cells . This study is purely clinical and we have only seen the effects of autologous bone marrow therapy and the rationale behind them are still being studied at molecular level. At present our sample size is small and we will continue our research in more number of patients in future.

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