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## OBJECTIVES

In hemophiliacs recurrent episodes of intra-articular bleeding cause damage to the joint, leading to deformity and crippling<sup>1</sup>. This condition is called hemophilic arthropathy (HA). It causes pain, stiffness, loss of motion, and functional disability<sup>2</sup>. Finally result is a fibrotic and destroyed joint. The joints most frequently involved are the knees<sup>3</sup>. Currently the HA is the most serious and invalidating complication in hemophilia. There are advances in the study and application of adult stem cells showing remarkable advantages compared to the embryonic ones<sup>4</sup>, since its handling is more simple, economic and they are obtained from the own subject to be treated and have great potential for healing articular cartilage defects all this has, become markedly evident during the last years<sup>5</sup>. The **purpose of this report** is to present the long term follow-up of two patients who received an intraarticular percutaneous implant, into a knee with HA, of autologous mononuclear cells (AMNC) derived from bone marrow (BM) and mobilized to peripheral blood (PB) by granulocyte colony-stimulating factor (G-CSF). It is well known that among these cells are different types of stem cells including hematopoietic and mesenchymal stem cells.

## METHODS

Two men with severe hemophilia A had had recurrent bleeding into their left knee since many years. The patients had experienced progressively worsening pain and stiffness, occasional locking, and reduced mobility. Patients' informed consent was obtained. Routine blood tests, X-ray and ultrasonography studies were performed. Follow-up included: the pain by visual analog scale (VAS) of joint involvement, motility, requirements of antihemophilic factors, corticoids, or analgesics. Both patients were stimulated with G-CSF (Hebervital, Heber Biotec INC; Havana, Cuba) to mobilize AMNC from BM into PB, with a total dose of 40 mg/kg divided in 4 independent doses that were subcutaneously administered every 12 hours. Blood was extracted from a peripheral vein of the arm in the same way as is done for a blood donation. The concentrate of AMNC was obtained by a sedimentation method<sup>6</sup>. Twenty-four hours later the patients were infiltrated in the intra-joint space of the left knee. A volume of 5 mL, containing  $110 \times 10^6$  cells ( $1.63 \times 10^6$  CD34+) (viability 99%) was injected into affected joint of the first patient and  $910 \times 10^6$  cells ( $13.5 \times 10^6$  CD34+) (viability 97%) in the second patient. The whole process was carried out with patients hospitalized F VIII replacement therapy was used at a dose of 40u/Kg up to 24 hours after the implants. Relative rest for two weeks followed the procedures.



## RESULTS

These case reports showed clinical evidence of pain reduction, by the VAS scores and increased range of motion (Table 1-2). The radiologic study showed improvement of the degenerative changes in both cases, and showed some capability of bone regeneration of a knee subchondral cyst (Fig 1-2).

Table 1. Follow-up the intensity of pain by visual analog scalee (ranging from 0 to 10, with 0 indicating no pain and 10 indicating severe pain).

Patients	Pre.Therapy	6 months	12 months
1	7/10	2/10	1/10
2	6/10	1/10	1/10

Table 2. Follow-up of joint motility (range flexion-extension)

Patients	Pre.Therapy	6 months	12 months
1	110° - 20°	105° - 0°	90° - 0°
2	115° - 10°	90° - 10°	85° - 0°



Fig 1: AP and lateral X-ray in patient one (A, B) before implants, (C, D) after implants.



Fig 2: AP and lateral X-ray in patient two (A,B) before implants, (C,D) after implants.

The BM derived cells implanted into degenerated joints have shown some promises for joint repair<sup>7</sup>. According to our research in this area, a percutaneous intraarticular implant of AMNC mobilized to PB by G-CSF obtained a fast clinical and radiological improvement<sup>8</sup>.

## CONCLUSIONS

- ✓ These are the first cases reported in Cuba which has been carried out this new therapy and up to our knowledge the first ones reported in the world at moment of the writing of this paper.
- ✓ The application of adult hematopoietic stem cells in the treatment of AH, is an advanced technique in this field.
- ✓ The application of AMNC derived from BM and mobilized to PB by G-CSF in the treatment of HA improves the quality of life and the incorporation of these patients to their normal activities.
- ✓ This option is a low-cost, relatively simple and easy to perform procedure that opens new ways for the treatment of HA.

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