INTRA-ARTICULAR INJECTIONS OF EXPANDED MESENCHYMAL STEM CELLS WITH AND WITHOUT ADDITION OF PLATELET-RICH PLASMA: A RANDOMIZED, DOUBLE-BLIND AND CONTROLLED CLINICAL TRIAL

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DISCLOSURE STATEMENT

• Patients’ dislocation fares, patients’ feeding cost, hospitalization, surgical procedures related costs, cells storage, biological substances transportation and all other minor costs related with the study were sponsored by ESHO Empresa de Serviços Hospitalares S.A.
BACKGROUND AND PURPOSE

✓ Adult cartilage regeneration is still a challenge for the treatment of degenerative joint diseases owing to the sparse distribution of differentiated chondrocytes, the low supply of progenitor cells, and the lack of vascularization.

✓ MSCs and the PRP therapies displayed a promising role in the treatment of knee OA.

✓ But still show conflicting results in the literature.

Purpose: To compare the clinical and laboratory outcomes of intra-articular injection of culture-expanded MSCs with or without PRP to intra-articular corticosteroid injection for the treatment of knee OA.
METHODS

Randomized double-blind three-arm controlled clinical trial.

A total of 47 patients (mean age 53.3 years, 51% males) with radiographic symptomatic knee OA.

Randomization into 3 groups for intra-articular injections:

1. autologous bone marrow-derived, culture-expanded MSCs (n=16)
2. autologous bone marrow-derived culture-expanded MSCs enriched with PRP (n=14)
3. corticosteroid (n=17).

KOOS and ROM at baseline and 1, 2, 3, 6, 9 and 12 months follow-up.

Intra-articular cytokines at baseline, and 6 and 12 months.
MSCs HARVESTING AND CULTURE

10mL PBS + 2% Human Albumin or autologous PRP

MSCs separation

Intra-articular injection

MSCs expansion / culture

40x10^6
No more than 2 passages
PRP PREPARATION

54mL peripheral blood → 2 centrifugation steps → 10^6 platelet/µL in 10mL PBS + MSC
The sample was homogenous for the baseline sociodemographic and clinical characteristics between the three groups.
The MSCs group showed significant improvements for all KOOS domains and global score between the baseline and first month (p<0.005) and baseline and the 12-month endpoint (p<0.05).

The MSCs + PRP group showed significant improvements on the KOOS domains and global score between the baseline and first month (p<0.05) - except in KOOS-symptoms (p=0.148) and KOOS-QoL (p=0.054) domains - and from baseline to the 12-month endpoint (p<0.05) - except the KOOS-QoL domain (p=0.06).

The corticosteroid group showed significant improvement all KOOS domains from baseline and first month - except the KOOS-symptoms domain (p=0.05) - and on KOOS-pain (p=0.03) and KOOS-ADL (p=0.03) from baseline and the 12-month period.
The corticosteroid group had highest percentage for score worsening for all KOOS domains and global score, except for the KOOS-QoL domain.

The addition of PRP (MSCs + PRP group) lead to a higher percentage of expected improvement for the KOOS-pain domain.

MSCs group obtained a higher percentage of expected improvement for the KOOS-QoL domain.
RESULTS

SUBGROUP ANALYSIS

✓ When considering knee ROM, neither treatment showed significant superiority considering all subgroup analyses.

✓ For KOOS domains and global score, the gender, obesity and OA grading subgroup analyses did not show any significant differences between treatments.

✓ For the population older or equal to 60 years old the MSCs + PRP group showed significant superiority for the KOOS-pain (p=0.026) and KOOS-QoL (p=0.019) domains and global score (p=0.043) at 6 months, KOOS-pain (p=0.014) and KOOS-QoL (p=0.024) domains and global score (p=0.030) at 9 months, and KOOS-ADL domain at 12 months (p=0.026).
# RESULTS

## CYTOKINE QUANTIFICATION

- Overall decrease in inflammatory cytokines levels
- High variability among samples
- Higher decreases from baseline to 12 mo follow-up in MSC+PRP groups

### Cytokine Treatment group Baseline Mean ± SD 6-month follow-up Mean ± SD p* 12-month follow-up Mean ± SD p**

**IL-17A**
- MSCs (n=12) 54.9 ± 38.4 70.6 ± 38.3 0.272 71.6 ± 38.9 0.308
- MSCs+PRP (n=10) 65.7 ± 53.0 93.7 ± 59.4 0.508 75.1 ± 37.5 0.799
- Corticosteroid (n=13) 78.9 ± 54.9 89.2 ± 63.6 0.345 41.6 ± 34.8 0.033

**IFN-GAMA**
- MSCs (n=12) 0.06 ± 0.12 0.26 ± 0.40 0.173 0.05 ± 0.16 0.715
- MSCs+PRP (n=10) 0.95 ± 1.81 0.54 ± 1.11 0.499 0.17 ± 0.54 0.173
- Corticosteroid (n=13) 0.16 ± 0.20 0.36 ± 0.59 0.313 0.14 ± 0.34 0.612

**Human-TNF**
- MSCs (n=12) 0.00 ± 0.01 0.32 ± 0.75 0.285 0.07 ± 0.25 0.655
- MSCs+PRP (n=10) 2.23 ± 4.00 1.11 ± 2.28 0.401 0.41 ± 1.00 0.128
- Corticosteroid (n=13) 0.26 ± 0.35 0.43 ± 1.07 0.674 0.30 ± 0.74 0.866

**Human-IL10**
- MSCs (n=12) 1.25 ± 1.17 0.66 ± 0.90 0.099 0.26 ± 0.51 0.023
- MSCs+PRP (n=10) 3.33 ± 3.28 1.99 ± 2.99 0.059 0.52 ± 0.99 0.013
- Corticosteroid (n=13) 1.32 ± 0.68 1.24 ± 1.37 0.583 0.64 ± 1.32 0.041

**Human-IL6**
- MSCs (n=12) 183.6 ± 243.9 194.5 ± 276.5 0.314 110.6 ± 249.4 0.060
- MSCs+PRP (n=10) 525.4 ± 1064.5 524.3 ± 819.4 0.878 121.1 ± 107.3 0.114
- Corticosteroid (n=13) 82.8 ± 89.4 123.7 ± 164.3 0.861 80.7 ± 82.2 0.972

**Human-IL4**
- MSCs (n=12) 0.21 ± 0.45 0.37 ± 0.91 1.000 0.17 ± 0.42 0.753
- MSCs+PRP (n=10) 1.38 ± 3.13 1.45 ± 2.68 0.866 0.30 ± 0.77 0.249
- Corticosteroid (n=13) 0.31 ± 0.58 0.32 ± 0.71 0.735 0.19 ± 0.48 0.446

**Human-IL2**
- MSCs (n=12) 0.21 ± 0.34 0.35 ± 0.62 0.779 0.08 ± 0.29 0.345
- MSCs+PRP (n=10) 1.38 ± 3.13 1.45 ± 2.68 0.866 0.30 ± 0.77 0.249
- Corticosteroid (n=13) 0.31 ± 0.58 0.32 ± 0.71 0.735 0.19 ± 0.48 0.446

**Intergroup sig***
- 0.534 0.688 0.057
- 0.064 0.829 0.834
- 0.149 0.769 0.899
- 0.088 0.395 0.471
- 0.077 0.895 0.938
- 0.744 0.771 0.715
Corticosteroid injections have been used for conservative treatment of OA and several local and systemic undesirable effects have been reported besides its short-term efficacy.

Despite the similarity of the three groups of treatment during the first and second months of treatment, corticosteroid group showed an inferior number of improved KOOS domains from baseline to 12 months and the highest percentage of score worsening for all KOOS domains and global score, excepting KOOS-QoL domain.

This finding reinforces the known short-term effect of corticosteroid intra-articular injections.

Conversely, the MSCs and MSCs + PRP group showed the highest percentage of improvement at 12 months in all KOOS domains and global score, in exception of MSCs + PRP group in the KOOS-sports-rec and KOOS-QoL domains.
CONCLUSION

MSC and MSC+PRP are safe.

MSC and MSC+PRP induced greater clinical benefits than corticosteroid

MSC+PRP superiority in older population

Decrease in cytokines levels