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Comparison of monosodium iodoacetate model of osteoarthritis between in-vivo and ex-vivo osteochondral unit in rabbits

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Dear Editor,

Treatment of articular cartilage defects and osteoarthritis using cell-based therapy requires evaluation and validation using animal models. Osteoarthritis (OA) in animal model is created by ligament transection, enzymatic digestion (collagenase and chymopapain) or intra-articular injection of monosodium iodoacetate (MIA).[2] Inducing OA with MIA has the advantage of having a mechanically stable joint and also the ability to control the grade of OA, depending on the dose injected.[4] However, these models need to be optimized. Recently, in view of optimizing and reducing animal studies, ex vivo osteochondral plug model was developed[1,5]; Osteochondral plug culture provides a platform more representative than cell culture and less invasive than animal models with greater scope for standardization. It also offers an environment to test a number of biomimetic factors hence providing a pre-clinical assessment platform. In our study, following approval from the Institutional Review Board (Christian Medical College, Vellore) and the Institutional Animal Ethics Committee, four adult male New Zealand white rabbits with normal weight bearing function were procured. Using sterile aseptic precautions, 2.5mg of MIA reconstituted in 250μl of normal saline was injected as a single dose intra-articularly (hind limbs-*in-vivo;* n = 3) whereas the control joints (n = 3) were not intervened with. After 28 days, rabbits were euthanized, and the knee joints were harvested for histopathological examination (Fig. 1A). For creation of the *ex-vivo* model, normal knee joints were fashioned using a microtome blade to create osteochondral units (1.5mm^2), that were maintained in culture plates, with exposed chondral surface and the remaining unit gelled in 2% agarose (Fig. 1D). 2.5mg of MIA was added to the culture supernatant (n = 3) (Glutamax-DMEM containing 10% fetal bovine serum plus antibiotics) at day 0 and control units (no MIA; n = 3) were also cultured. The units were maintained under standard culture conditions with a medium change every 3 days for a period of 28 days, following which histological analysis was done. Osteoarthritis Research Society international (OARSI) scoring was performed by three blinded investigators.[3] The average scores showed that the grade of OA created was comparable in both the in-vivo [score: normal = 0 (Fig. 1B), 2.5mg = 5.1 (Fig. 1C)]and ex-vivo [score: normal = 0 (Fig. 1E), 2.5mg = 4.99 (Fig. 1F)] preparations. The OA changes included surface discontinuity and changes in matrix like variable, cationic staining, rarefication and condensation of collagen fibres and edema. Cellular changes like empty lacunae due to chondrocytes death, disorientation of chondron columns extending into the mid-zone have also been noted. This is the first report to show creation of OA *ex-vivo* using MIA. Although this demonstrable comparability is promising, studying the effects at various doses will provide better knowledge. Future direction would be to create a MIA pharmacological profile for controlled experimentation in the ex-vivo setting. This model would offer the ability to obtain multiple units/samples from the same joint and studying various interventions concurrently. Thus, it will not only reduce animal experiments but also allow studies using human samples which are otherwise discarded.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jcot.2018.08.023.

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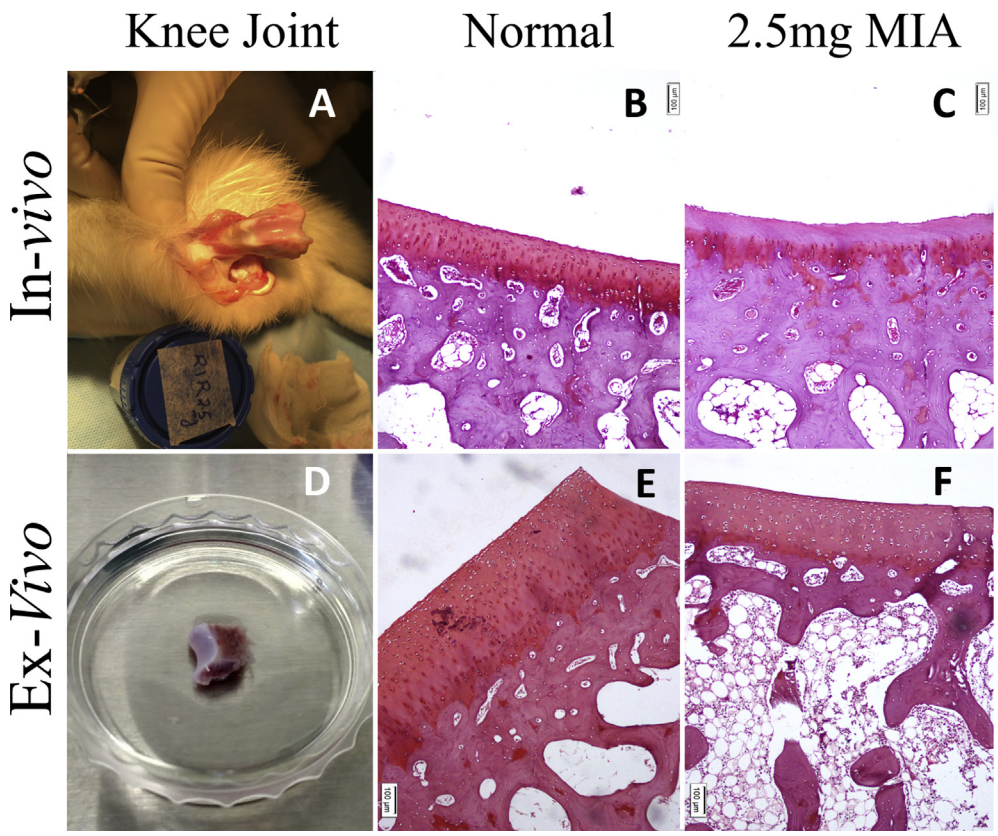


Fig. 1. Creation of osteoarthritis using mono sodium iodoacetate (MIA-28days). A) Osteoarthritic knee joint prior to harvestation, D) Ex-vivo osteochondral unit used for culture, Histological analysis: Representative images of Safranin O staining of articular cartilage of B) *in-vivo* normal joint, C) *in-vivo* 2.5mg MIA E) *ex-vivo* normal joint, C) *ex-vivo* 2.5mg MIA (magnification 10x).

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