Raising the Osmolarity of Arthroscopic Irrigating Solutions May Be Chondroprotective

Editorial Commentary: Raising the Osmolarity of Arthroscopic Irrigating Solutions May Be Chondroprotective: We Must Be Kind to Joints During Arthroscopy!

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Abstract:

The irrigation of joints during arthroscopic procedures typically uses a non-physiological solution. This replaces the natural synovial fluid and rapidly subjects the connective tissues to an alien hypo-osmotic environment in which cartilage cells are far more sensitive to iatrogenic injury. Raising the osmolarity of the irrigating solution may be a simple, safe and effective chondroprotective strategy.

The osmolarity of human synovial fluid is approximately 400mOsm and during arthroscopic surgery is replaced by continuous irrigation with saline (0.9% w/v), or lactated Ringer's (both approx. 270mOsm). This reduced osmolarity will immediately expose tissues to a hypo-osmotic challenge causing the *in situ* cells to swell rendering them far more sensitive to the iatrogenic mechanical injury caused by the arthroscope or surgical instruments. Such unintended iatrogenic injuries may be under-reported[1-3] but damage or death of chondrocytes may be a serious long-term complication of an apparently benign procedure as cartilage repair generates weak fibrocartilage[4] whereas dead chondrocytes are not replaced leaving areas of cartilage more vulnerable to mechanical stress[5].

Previous *in vitro* studies have demonstrated that raising the osmolarity of normal saline to levels (600mOsm) above those of synovial fluid using sugar (sucrose) or NaCl is chondroprotective against various forms of cartilage injury including impact loading, cartilage drilling and scalpel cutting[6]. It is therefore quite remarkable and perhaps intolerable that the osmolarity (at least) of the solution routinely used is considerably less than that normally experienced by cartilage. Intuitively during arthroscopy everything possible should be done to protect the cartilage and the chondrocytes therein, minimise iatrogenic injury and *primum non nocere* ('first, do no harm').

While the protective effects of hyper-osmolarity protecting chondrocyte viability during mechanical trauma have been demonstrated, their influence on other key elements of connective tissue biology, notably release of inflammatory mediators, degradative enzymes (matrix metalloproteinases; MMPs) and extracellular matrix glycosaminoglycan (GAG) and collagen metabolism have received less attention. The present work[7] by Oladeji, Stoker, Stannard and Cook *'Use of a hyperosmolar saline solution to mitigate pro-inflammatory and degradative responses of articular cartilage and meniscus for application to arthroscopic surgery'* is therefore a welcome step in this direction. While it was demonstrated that for articular cartilage hyperosmolar (600mOsm/L) saline applied for 3hrs and then cultured for 3 days significantly decreased levels of some (2/9) biomarkers, for meniscal explants the effect was more potent with 6/9 biomarkers showing a reduction compared to normal isotonic saline (300mOsm/L) with other biomarkers showing no change. Experimental design is obviously crucial here and the exact conditions of the incubation period during the osmotic challenge which one imagines would attempt to simulate the *in vivo* irrigation period, should be clearly described. Similarly, the specific details of the incubation period after this are important and whether culture should be in standard (hypo-osmotic) tissue culture medium (as in the Oladeji *et al* study[7]) and for only 3 days should be considered carefully. In addition, while the responses to the osmotic challenge might be modest, these results are just a 'snapshot' of the response following the osmotic challenge as the release pattern may differ between the biomarkers investigated over time. The longer-term consequences of saline irrigation and whether there is permanent injury to the mechanical properties of the tissue remain to be explored. Furthermore, the effects of simulated iatrogenic injury could exacerbate the damaging changes seen during saline irrigation and this could be a fruitful area for future study. The differential chondroprotective response between hyaline articular cartilage and fibro-cartilage (meniscus) is particularly interesting and illustrates our lack of knowledge about why these connective tissues should demonstrate apparently different responses. As stated by the authors, differences in cell phenotypes (chondrocytes of hyaline cartilage *vs* fibroblasts of fibro-cartilage) and their extracellular matrices (primarily collagen type II and aggrecan *vs* collagen type I and small proteoglycans respectively) could account for the different responses. However, there is no obvious reason to assume that the time course of biomarker release should be the same. Further benefits and apparent safety of increasing intra-articular osmolarity have already been reported[8] where hyper-osmotic irrigation reduced peri-articular fluid retention during arthroscopic rotator cuff surgery without any undesirable long-term effects.

The present study highlights the problem many researchers in connective tissue encounter, that of obtaining appropriate tissue for testing the hypotheses and hence its clinical applicability. Thus, while it would be expected that healthy joints would normally be subjected to arthroscopy, the majority of samples investigated in the Oladeji *et al* study

were classified Outerbridge grade 2-3 i.e. demonstrating significant osteoarthritis. It is possible that the responses of healthy (grade 0) cartilage/meniscus are different but protection of *in situ* human and *in vivo* animal chondrocytes against mechanical injury using hyper-osmotic saline (supplemented with sucrose rather than NaCl to limit changes in electrolyte concentrations) is already firmly established[9,10]. Clearly protecting the existing healthy cartilage by any means possible must be a 'prime directive' during arthroscopy. It is notable that the osmolarity of synovial fluid from OA joints at 300mOsm is markedly less than that of normal joints (400mOsm)[11] meaning that any mechanical trauma (whether during *in vivo* loading or with arthroscopy) is potentially more damaging as the chondrocytes will be swollen[12].

Perhaps an obvious question is why should we just modify the osmolarity of the saline? If we are trying to mimic the basic components of synovial fluid then should we not also consider the pO_2, pH, temperature and electrolyte constituents? However, one element that it may be advisable to avoid is Ca^{2+}. Its removal from an irrigation fluid would be recommended because even at the levels present in lactated Ringer's solution (1.5mM), chondrocyte viability is significantly reduced during mechanical injury[13]. This is probably because of the activation of membrane-bound stretch-sensitive ion channels in response to mechanical trauma.

A key question remains however, why have we not yet developed an optimised irrigation solution specifically for arthroscopy? Part of the reason could be that the clinical benefits might not be immediately obvious and the various patient reported outcome scores (PROMS) now widely utilised to quantify clinical outcomes are not appropriate tools for measuring the long-term deleterious effects of non-physiological arthroscopic irrigation solutions. Consequently, it becomes very difficult to design large multi-centre randomised clinical trials that are able to demonstrate meaningful differences in patient outcome using simple, cheap, laboratory proven chondroprotective innovations such as increasing joint osmolarity. Without such evidence, wider adoption among the end-users, the arthroscopists, becomes very challenging. The results from the basic science on strategies for chondroprotection are, in our opinion, becoming compelling, and hopefully this will drive interest in developing more appropriate irrigation 'solutions' tailor-made for arthroscopic procedures.

The Oladeji *et al* study adds to the growing body of recent evidence that normal saline/lactated Ringer's is potentially harmful as an irrigating fluid for arthroscopy especially if iatrogenic injury occurs. No negative effects of raised osmolarity appear to have been reported and there are potential benefits beyond chondroprotection to include the suppression of the inflammatory response and reduced extravasation into the peri-articular tissues. Everything possible should be done to protect these connective tissues during arthroscopy by keeping the joints 'sweet'.

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