Editorial Commentary: The Acellular Osteochondral Allograft, the Emperor Has New Clothes

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Abstract: For larger lesions (>2.5-cm^2), clinical evidence and practice have shown that fresh osteochondral allograft have good durability, with 88% return to sport and greater than 75% 10-year survival rates for treatment of large femoral condyle lesions. That said, the use of fresh osteochondral allografts in clinical practice is limited by the availability of acceptable donor tissues for eligible patients in a timely fashion. Significant diminution of chondrocyte viability and density occurs during the preservation and storage period. All osteochondral allografts are not equal in performance and outcome. Chondrocyte density and viability are critical for successful transplantation and outcome in the short and long term. This commentary highlights the high failure rates of tissue when it is acellular.

See related article on page 2219

"The Emperor's New Clothes" is a short tale written by Danish author Hans Christian Andersen that challenges the status quo. Two fake weavers convince an Emperor that they can make cloth so fine that the foolish cannot see it, and he parades in his kingdom without clothes espousing that his suit is magnificent but no one dares to say that they don't see a suit of clothes out of fear that they will be seen as stupid, incorrect, or incompetent. Finally, a child cries out, "but he isn't wearing anything at all!" As a clinical, and scientific, community, it is critical that we evaluate techniques, procedures, and processes in a systematic, deliberate, and accurate manner. Contemporary surgical management of chondral and osteochondral lesions in patients includes microfracture or marrow stimulation, biological augmentation of marrow stimulation, autologous chondrocyte implantation, and osteochondral autograft transplantation, with the last being the most commonly used.[1]

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For larger lesions (>2.5-cm^2), clinical evidence and practice have shown that fresh osteochondral allograft have good durability, with 88% return to sport and greater than 75% 10-year survival rates for treatment of large femoral condyle lesions.[2-7] That said, the use of fresh osteochondral allografts in clinical practice is limited by the availability of acceptable donor tissues for eligible patients in a timely fashion. Significant diminution of chondrocyte viability and density occurs during the preservation and storage period. Clinical practice and consensus has determined essential chondrocyte viability and density to be at least 70% of time zero.[8,9] Now here is the leap of faith for the Emperor's wardrobe, assuming that transplantation with and without healthy and viable chondrocytes is equivalent or has equipoise. This term was first used by Benjamin Freedman in 1987 to assume there is genuine uncertainty in the expert medical community over which treatment is ideal. In this situation, there are clear and substantial differences in comparing these similar interventions.

In the study by Johnson, Garica, Wang, Pais, Degen, Burge, Williams, and Johnson, "High Short-Term Failure Rate Associated with Decellularized Osteochondral Allograft for Treatment of Knee Cartilage Lesions,"[10] the authors have attempted to extrapolate from the paradigm of fresh osteochondral autografts and allografts with viable chondrocytes to report the short-term clinical radiologic and magnetic resonance imaging outcomes following the use of decellularized

osteochondral allograft plugs (Chondrofix; Zimmer-Biomet, Warsaw, IN) in the treatment of distal femoral osteochondral lesions. This retrospective study within a prospective registry identifies 34 patients who were identified with a mean age of 45 years. This is, therefore, an older population as most cartilage resurfacing or repair studies have an average age of approximately 35 years.[11] This comprehensive study does not address the percentage of patients not included in this study or the compliance of the patients treated similarly with these plugs. There are several conclusions regarding osteochondral repair that we can glean from this important study:

1. The knee joint is a complex organ where the meniscus, alignment, and ligament issues are critical, but age, defect size, and gender must be considered in the algorithmic decision making.
2. Estrogen is an important hormone in the female patient population, and deficiency in and of itself results in progression of osteoarthritis and may limit success in cartilage repair.
3. In cartilage repair algorithms, we always must consider the lesion size, the severity of preexisting chondropenia, or osteoarthritis. It is these stratifications that are the most challenging situations and may be associated with potentially compromised results.
4. All osteochondral allografts are not equal in performance and outcome. Chondrocyte density and viability are critical for successful transplantation and outcome for the short and long term. This study and the Farr[12] study highlights the high failure rates of tissue when it is acellular.
5. As surgeons, it is imperative to understand all aspects of the allograft paradigm such as the age of the graft, location of harvest, the media and temperature during preservation, and the time period prior to implantation.

The selection of patients for these plugs was not specifically addressed by the authors but it "was based on a decision to proceed with these implants by the patient after a comprehensive discussion of the other options." In addition, as the authors state, there was "no control group and with a short follow-up period." Rather than waiting to publish these results with longer follow-up, the authors felt compelled to make the surgical community aware of these untoward results. It is here that the author team, captained by the senior author Dr. Riley Williams, should be commended. The lesions were large, with a mean defect size of 4 cm^2, and the median number of allografts per knee was 2. The mean follow-up duration was 15.5 months, which is short in relation to other studies. Furthermore, one would expect to observe a higher failure rate with longer follow-up, and thus, the data in the present study likely underestimate the true failure rate. The primary outcome of interest was failure of the procedure, which was defined as any reoperation resulting in removal of the implant, such as revision to fresh osteochondral allograft transplantation or arthroplasty. This is another problem of potential underreporting because failure can also be defined as low patient-reported outcome scores, and/or structural lack of incorporation or reoperation. Based on these limitations, 10 patients (29%) required revision surgery with removal of the implant, and the survivorship was 61% at 2 years. Female gender was independently predictive of failure, with a hazard ratio of 9.4 ($P = .005$). This is exceptionally high, but expected in a population of women of mean age 45 with potentially low estradiol levels and approaching menopause.[13] The defect size was also independently predictive of failure, with a hazard ratio of 1.9 per 1-cm^2 increase. In essence, an inverse relationship exists as the larger the cartilage deficiency and burden, the lesser the outcome.

Although this is a flawed scientific study with problems of compliance, lack of a control group, and poor and biased selection, Johnson et al. have attempted to extrapolate from the paradigm of fresh osteochondral autografts and allografts with viable chondrocytes to report the short-term clinical radiologic and magnetic resonance imaging outcomes following the use of decellularized osteochondral allograft plugs. This study and the Farr study highlights the high failure rates of tissue when it is acellular.[12] As surgeons, it is imperative to understand all aspects of the allograft paradigm such as the age of the graft, location of harvest, the media and temperature during preservation, and the time period prior to implantation. In this paradigm, we are only as strong as our weakest link.

In conclusion, in clinical science our moral authority always must trump expedience and the conventional wisdom of the mainstream. In this spirit, the authors should be congratulated for the diligence and detail of this scientific study. After all, we always learn that bad experiences facilitate and ensure that we make subsequent good judgments. Thank you for pointing out that the Emperor had no clothes after all!

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