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WHAT IS NEW IN ROTATOR CUFF MANAGEMENT?

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SUMMARY

Introduction

Tears of the rotator cuff are frequent. An estimated 250 000 to 500 000 repairs are performed annually in the United States. Massive rotator cuff tears (MRCTs) are a challenge, particularly in a younger population.

Aim

The aim of this study was to comment new treatment options in rotator cuff management.

Material and methods

The PubMed database was searched using the key words: "SCR, patch, LHBT, biology approach in RCR" published between 1986 and 2017.

Results

SCR theoretically improves force coupling as well as superior stability, increasing the functional outcome score. The treatment methods using biologic agents are promising, however, the relevant studies are still lacking. It is difficult to clearly assess the suitability of the patches in the reconstruction of massive rotator cuff tears.

Conclusions

A superior capsular reconstruction adds good stabilization to the glenohumeral joint. What is more, the arthroscopic SCR remains

CO NOWEGO W LECZENIU STOŻKA ROTATORÓW?

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STRESZCZENIE

Wprowadzenie

Uszkodzenia stożka rotatorów (RCR) są częste. Szacuje się, że rocznie w Stanach Zjednoczonych przeprowadza się 250 000 do 500 000 operacji. Znacząca ilość uszkodzeń stożka rotatorów (MRCT) stanowi wyzwanie lecznicze, szczególnie w populacji ludzi młodych.

Cel

Celem tej pracy było skomentowanie nowych opcji leczenia w leczeniu uszkodzeń stożka rotatorów.

Materiał i metody

Baza danych PubMed została przeszukana za pomocą słów kluczowych: „SCR, patch, LHBT, podejście biologiczne w RCR" w publikacjach w latach 1986–2017.

Wyniki

SCR teoretycznie poprawia siłę, jak również stabilność, poprawiając wynik końcowy czynnościowy. Metody leczenia za pomocą środków biologicznych są obiecujące, jednak wciąż brakuje odpowiednich potwierdzeń tych badań. Trudno jest jednoznacznie ocenić przydatność „patch" w rekonstrukcji uszkodzonych stożków rotatorów.

Wnioski

Lepsza rekonstrukcja torebki zapewnia dobrą stabilizację stawu ramiennego. Co więcej, artroskopowy SCR pozostaje techniką technically demanding. Using long head biceps tendon (LHBT) as a patch, or an element of SCR, is an option for a rotator cuff treatment. This method is effective in maintaining force coupling of the rotator cuff. However, it has high healing failure rates. Modulation of the selected matrix metalloproteases (MMPs) activity, after a rotator cuff repair, may offer a novel biological pathway to augment tendon-to-bone healing. Administration of PRP alone is insufficient to compensate the progressed tissue damage. Using marrow stem cells (MSCs) in a surgical rotator cuff repair shows great promise. Currently, there is no consensus on the optimal technique of gene therapy. Promising the functional results after using different types of patches is questioned due to a high percentage of complications.

Keywords: SCR, patch, biology, LHBT

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Introduction

Rotator cuff management is one of the most interesting and investigated problems in shoulder dysfunction treatment. Analyzing some data published recently a few new ways of its repair can be distinguished.

Aim

The aim of this study was to comment new treatment options in rotator cuff management.

Material, methods and results

The PubMed database was searched using the key words: “SCR, patch, LHBT, biology approach in RCR” published between 1986 and 2017.

wymagającą. Używanie ścięgna mięśnia dwugłowego (LHBT) do naprawy lub elementu SCR są opcjami do leczenia uszkodzonego stożka rotatorów. Ta metoda jest skuteczna w utrzymywaniu sprzężenia stożka rotatorów. Ma jednak wysokie wskaźniki niepowodzenia leczenia. Modulacja wybranych aktywności metaloproteaz (MMP), po rekonstrukcji stożka rotatorów, może oferować nową biologiczną propozycję zwiększania gojenia ścięgien. Podawanie samego PRP jest niewystarczające, aby zrekompensować postępujące uszkodzenie tkanki. Użycie komórek macierzystych szpiku (MSC) w chirurgicznej naprawie uszkodzenia stożka rotatorów jest obiecująca. Obecnie nie ma zgodności co do optymalnej techniki terapii genowej. Obiecując wyniki funkcjonalne po zastosowaniu różnych typów „patch”, kwestionuje się z powodu wysokiego odsetka powikłań.

Słowa kluczowe: SCR, patch, biologia, LHBT

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SCR

Tears of the rotator cuff are frequent. An estimated 250 000 to 500 000 repairs are performed annually in the United States. Massive rotator cuff tears (MRCTs) are a challenge, particularly in a younger population. With an arthroscopic approach, a repair is possible in the majority of the cases and functional outcomes are improved, particularly when a double-row repair can be achieved. The rotator cuff repairs have been successful despite fatty infiltration and atrophy of the rotator cuff muscles. There are unfortunately limitations which have come out of these factors.

However, healing of MRCTs after a repair may remain low, and failure of healing is associated with progression of arthritis. Alternatives to repair such as reverse shoulder arthroplasty (RSA) are suitable in older patients but are associated with high failure rates in young patients.

A young patient with a massive, irreparable rotator cuff tear is a challenging problem. Not only is this patient population demanding, but of the few surgical options that exist to manage this problem, each has their own unique limitations; as such, the orthopaedic community continues to search for a treatment that maximizes outcome and durability, while minimizing risk and preserving the native shoulder.

Although the emphasis in rotator cuff repair has historically focused on re-establishing the tendon attachment, there is growing interest in and understanding of the role of the superior capsule. The superior capsule is attached to the undersurface of the supraspinatus and infraspinatus muscle-tendon units and it resists superior translation of the humeral head.

The patients with irreparable rotator cuff tears have a defect of the superior capsule, which creates discontinuity of the shoulder capsule in the transverse direction (anterior-posterior direction). This effect is one of the causes underlying shoulder instability after rotator cuff tears. Herein, it is proposed that it is the defect in the superior capsule that is the "essential lesion" in a superior rotator cuff tear, as opposed to the defect in the rotator cuff itself.

In an opinion of many researchers a rotator cuff repair must restore the normal capsular anatomy to provide normal biomechanics of the joint and thus a positive clinical outcome.

SCR with side-to-side suturing, which completely restores the superior stability of the shoulder joint by establishing posterior continuity between the graft, residual infraspinatus tendon, and underlying shoulder capsule, is recommended for SCR in patients with irreparable supraspinatus tendon tears to restore superior stability after a surgery.

Over the past few years, there has been considerable interest in a new surgical technique: the superior capsule reconstruction (SCR). A Japanese surgeon, Teruhisa Mihata, originally described this technique using fascia lata autograft; however, dermal allograft has become the primary graft option in North America (Denard, Brady, Adams, Tokish, Burkhart).

Both procedures have been proposed as a joint-preserving solution for irreparable MRCTs. SCR using fascia lata technique increases the surgical time and carries donor site morbidity. In an effort to reduce donor site morbidity, Hirahara and Adams have subsequently proposed the use of dermal allograft for SCR as opposed to fascia lata. Dermal allograft limits donor-site morbidity and the time of surgery has been used previously in augmentation of rotator cuff repairs, and has been used clinically for SCR.

In the effort for joint preservation, a variety of materials have been proposed to augment or replace an irreparable rotator cuff tear. Dermal allograft, xenografts, or synthetic patches have all been reported primarily in a patch technique whereby the material is attached from the remnant rotator cuff to the humeral head or as an augment to rotator cuff repair.

The majority of medical publications in that matter concerns fascia lata and dermal allografts.

The surgical technique has previously been described in detail. First, the subscapularis was evaluated and repaired as necessary followed by biceps tenodesis or tenotomy in every case unless the tendon had previously been torn and completely retracted. Attention was then turned to the subacromial space and a limited acromioplasty was performed with preservation of the coracoacromial ligament. The posterosuperior rotator cuff was then excavated and mobilized in an attempt to repair the tendon. The decision to perform SCR was made intraoperatively based on the inability to achieve a complete repair following mobilization.

The superior glenoid was prepared preserving the superior labrum. At least 2 anchors were preplaced in the superior glenoid, about 5 mm medial to the superior labrum. Next, 2 anchors were placed in the greater tuberosity adjacent to the articular margin in order to cover the span of the defect. The anteromedial anchor was placed 5 mm posterior to the bicipital groove. The posteromedial anchor was placed just anterior to the intact rotator cuff. The graft size was measured and extended 5 mm medially, anteriorly, and posteriorly to provide a margin and 10 mm laterally to cover the greater tuberosity. The sutures from each anchor were retrieved out of a lateral portal and passed through an auto- or allograft. The sutures were then used to shuttle the graft into the subacromial space. The graft was first secured medially to the glenoid. Finally, the graft was secured laterally to the greater tuberosity. In all cases the margin convergence sutures were placed between the graft and the remaining infraspinatus or teres minor posteriorly.

Postoperatively, patients were immobilized in a sling for 6 weeks without dedicated physical therapy. At 6 weeks, postoperatively, the sling was discontinued and passive forward flexion and passive external rotation were allowed. At 3 to 4 months postoperatively, active forward flexion and passive internal rotation were allowed and strengthening was initiated. Return to full activity was allowed in 6 to 12 months, including all sports activities without restriction.

Graft thickness may be important for optimizing the outcome of SCR. Anatomically the normal thickness of the superior capsule ranges from 4.4 to 9.1 mm.

Based on biomechanical analysis Mihata *et al.* (2013) have argued for using a thick graft for SCR. They compared 4 mm and 8 mm thick fascia lata grafts and noted that while both grafts decreased subacromial contact pressure, the 8-mm graft was better at reducing superior translation. However, 3 mm is the maximal thickness that dermal allograft has currently commercially available. Furthermore, while it is more expensive compared with fascia lata autograft, dermal allograft carries the advantage that it is less morbid and reduces the operative time.

Based on Mihata study superior capsule reconstruction normalized the superior stability of the shoulder joint when the graft was attached at 10° or 30° of glenohumeral abduction. An 8-mm-thick graft of fascia lata had greater stability than a 4-mm-thick graft had.

Grafts 8-mm thick and attached at 15° to 45° of shoulder abduction (equal to 10° to 30° of glenohumeral abduction) biomechanically restore shoulder stability during superior capsule reconstruction using fascia lata.

Technical Pearls and pitfalls for Superior Capsule Reconstruction include:

Indications:

- Best results are with Hamada 1 or 2; avoid Hamada 3 or 4.

(*Discussion: Mihata states that using fascia lata SCR can improve shoulder function even in Hamada grade 3 or 4 tears*)

Technical remarks:

- Biceps tenodesis or tenotomy with SCR in every case, unless the tendon had previously been torn and had been completely retracted.

(*Discussion: Mihata's experience is the biceps does not need to be treated in SCR; in most of the cases if the SCR heals, the biceps symptoms disappear, even without biceps tenodesis or tenotomy*).

- SCR theoretically improves force coupling as well as superior stability, increasing functional outcome score. If a patient has an irreparable subscapularis tear, then the force coupling cannot be restored by SCR. Repair the subscapularis to balance force couples, but avoid SCR with an irreparable subscapularis tear.

(*Discussion: in Mihata's experience, shoulder function improves after fascia lata SCR, even in patients with both irreparable subscapularis tears and irreparable posterior-superior* (*supraspinatus and infraspinatus*) *tears, suggesting that SCR can be used even in irreparable subscapularis tears*).

- Use at least a 3 mm thick graft (*Discussion: maximum thickness for dermal allograft, Mihata suggests thicker graft; see text*).
- A flexible cannula is used to push the graft into the joint after all sutures are checked for tangles. The graft can be pulled into the joint through a superior portal (Neviaser portal) to avoid pulling excessively on the medial glenoid anchors.
- The majority of failures occur on the tuberosity; strong fixation is encouraged.

Postoperative protocol:

- Strengthening is delayed until 12 to 16 weeks postoperatively.

The findings of the Japanese and American studies confirm the hypothesis that SCR with autograft and dermal allograft leads to an improvement in the functional outcome in the majority of cases. Overall, approximately 70% of the cases were considered successful based on our criteria of successful treatment. While the rate of secondary procedures was nearly 19%, the overall findings provide several insights into the indications and factors associated with success.

The differences can be observed in the rates of allograft healing (45% healing rate among the 20 patients who had underwent magnetic resonance imaging at 1-year follow-up in the Denard's study vs. Mihata's landmark paper that reported an autograft healing rate of 83.3%).

Perhaps the answer is in a graft selection and this would not be the first time that allografts were inferior graft choices for patients undergoing orthopaedic procedures.

Despite the theories that SCR improves the biomechanical function of the shoulder by depressing and re-centering the humeral head, the Denard's study did not find any improvement in the acromiohumeral interval (AHI) at 1-year follow-up. Again, this is contrary to the findings of Dr. Mihata's original study, where at a mean follow-up of almost 3 years (34 months) the authors reported a significant improvement in the AHI of w 4 mm. This discrepancy may be explained by the differences in graft thickness and type (a 6- to 8-mm fascia lata autograft in the original procedure popularized in Japan vs. a 3-mm dermal allograft in the variation of the procedure common in North America), a theory that is supported by a recent publication demonstrating that SCR with a thicker (w 8 mm) fascia lata allograft has superior biomechanical properties to SCR with a thinner (w 3 mm) dermal allograft, but further study is certainly warranted to better understand how various graft properties impact clinical outcomes.

Finally, this commentary would not be complete without a discussion pertaining to cost and a potential for the performance bias. First, it is not debatable that the SCR with dermal allograft is a very expensive procedure. As such, it is likely that in the current health care system, where the finances of a surgical practice are increasingly scrutinized, it will (if not already) be asked to demonstrate the value of this procedure to justify its cost and continued use.

Superior capsular reconstruction (SCR) of the shoulder has recently gained popularity as an option for joint-preserving shoulder surgery for patients with an irreparable rotator cuff tear. In the absence of glenohumeral arthritis, rotator cuff tear irreparability should only be diagnosed for most patients after a careful diagnostic arthroscopy. Superior capsular reconstruction adds biological, passive, superior constraint to the glenohumeral joint, thereby optimizing the rotator cuff force couples and improving joint kinematics. At short-term follow-up, SCR has been shown to be effective for pain relief and restoration of active shoulder motion, even in the worst cases of shoulder dysfunction (true shoulder pseudoparalysis). The rapid, early adoption and expansion of SCR is justified by its excellent anatomical, biomechanical, and short-term clinical results. The techniques for arthroscopic SCR continue to improve, however, the operation remains technically demanding. The patients with risk factors for irreparability and who might benefit from a reconstruction of the superior capsule should be counseled about the operation as an additional, joint-preserving procedure that can be done in conjunction with an arthroscopic, partial rotator cuff repair.

All results suggest that this reconstruction technique is a reliable and useful alternative treatment for irreparable rotator cuff tears. Nevertheless, it also needs further studies.

LHBT – autopatch for RCR and autograft for SCR

Long head of biceps tendon (LHBT) is one of the most investigated structures in the human shoulder. Its role has been described many times and numerous procedures have been created and applied. LHBT tenotomy or tenodesis are usually done during a rotator cuff repair, but recently many studies dedicated to using LHBT as a patch or an element of SCR have been published.

Few comparative studies have reported on the use of biologic grafts for irreparable massive rotator cuff tears. With good postsurgical results using current techniques, one can build upon this with new techniques using biologic agents to, hopefully, improve healing rates. The advantages of using a biceps tendon autograft to augment rotator cuff repairs include the use of truly biologic material that may enhance healing and scar formation. An autograft source that would otherwise be discarded after biceps tenodesis is being used. These techniques are also adaptable to the use of other types of autograft or allograft to augment the rotator cuff repair. The limitations to these techniques include longer operating time, tedious graft preparation, and the lack of a long-term follow-up.

Considering results, it can be assumed that bridging grafts are effective in maintaining force coupling of the rotator cuff. However, the compared groups (LHBT and other patches) showed high healing failure rates.

The new option of using LHBT is a procedure known as the SCR. On the basis of the principles of SCR, the purpose of the new described methods is to propose a technical modification of the original reconstruction using the long head of the biceps tendon (LHBT). The tendon's insertion into the glenoid is left intact, whereas laterally, it is tenotomized and sutured with anchors onto the greater tuberosity, preventing possible superior head migration.

One of them is called, by the authors, "The Chinese way", in which the biceps tendon is dissected and tenotomized approximately in the middle of the bicipital groove without tenodesis of the distal part of the LHBT.

To restore the stabilizing force couple in the transverse plane, a surgeon should always attempt to repair the subscapularis tendon by also preserving the portion of thesuperior glenohumerale coracohumeral ligament complex ("comma sign"). Depending on the retraction and in elasticity of the remaining infraspinatus tendon, its partial repair is attempted.

Other way is called by Yang-Soo Kim's team "Arthroscopic In Situ Superior Capsular Reconstruction Using the Long Head of the Biceps Tendon". A lack of biceps tenotomy with two point of fixation on the greater tuberosity makes a difference between these two procedures. The weak point of this procedure may be stretching and increasing the biceps tension associated with the prolongation of its course.

The expectations are the same and the mentioned way seems to be an effective procedure for patients to avoid progression to cuff tear arthropathy. Further clinical trials are needed to investigate the long-term benefits of this technique, as well as to determine the best indications for this procedure.

Patch in rotator cuff repair

One of the treatment methods of massive rotator cuff tears is the use of patches. The first article on the use of a patch in the reconstruction of the rotator cuff was published by Ozaki *et al.* in 1986. The authors presented promising results after use of a Teflon patch.

The patches have a twofold effect. First of all, they create scaffolding or a bridge for the healing tendon. On the other hand, bioinductive materials with stimulating properties and accelerating healing of the tendon are still being sought.

At the beginning only synthetic patches were in use. Their main advantage is very high mechanical strength (tensile strength of 2500N, cut resistance trough surgical sutures of 550N), accessibility (ethical considerations), the ability to modify the structure and chemical composition and the lack of autoimmune reaction. First synthetic patches were not bio-absorbable so they were increasing the risk of an infection and chemical reactions with the adjacent tissues. A new generation of biodegradable patches is about to facilitate the integration with human tissue.

Biological patches from the intercellular matrix are bioabsorbable and better induce tissue regeneration.

Currently the following types of patches in rotator cuff repair are used:
Synthetic:
- polyurethane (SportMesh™ Soft Tissue Reinforsement),
- poly-L lactides (X-Repair),
- polycarbon (Biometrix RCR),
- Gore-Tex®.

Biologic (intercellular matrix of human, swine or bovine skin/ mucous membrane of the small intestine):
- allografts (GraftJacket™, AthroFLEX®), and
- xenografts (Conexa®, Tissue Mend®).

The rotator cuff can be augmented with the patch in the „onlay" technique (the patch is placed on the repaired cuff) or by bridging („intercalary") the ruptured tendon and the humerus (large, hypomobile retraction).

The surgeries that previously were performed, mainly in the open method, are more frequent arthroscopic nowadays. An indication for the patch is massive rotator cuff lesion with large retraction (stage II/III according to Patte) that cannot be properly mobilized and repositioned to the its footprint on the humerus. Contraindications for the use of a patch are: active inflammation, arthrosis, autoimmune diseases, paresis of the shoulder girdle [1], rheumatoid arthritis, insulin-dependent diabetes [2], "frozen shoulder" (3 studies), revision after rotator cuff repair (2 studies), previous muscle transfers in the operated shoulder, but also smoking. The use of the patches in stage 3–4 of fatty degeneration of cuff muscles (that is >50%) according to Goutallier's classification seems controversial. Some authors find indications for a patch during revision after the first failure [4]. The age limit was not specified in any publication (the biological status of tissues is assessed by radiological parameters and arthroscopic examination). Most often the patch is used in the superior capsule reconstruction, much less frequently in additional damage to the subscapularis muscle tendon:
- SST and IST 72.3%,
- SST, IST and SSCAP 15.9%
- SST and SSCAP 6.1%
- SST 5.7%

The analysis of 24 studies published between 1986 and 2012 by Steinhaus *et al.* (2016) presents in details the functional results of patch-augmented rotator cuff repair. In the augmentation and bridging reconstruction of the rotator cuff, an improvement in mobility was observed in all studied directions. The best results were achieved in abduction (58° of improvement) and forward flexion (66°). The worst were observed in internal rotation (16°). The best range of motion was recorded after use of synthetic patches, slightly worse in the allograft group, the worst – among xenografts. There was no significant improvement in muscular strength during abduction and forward flexion of the shoulder in the patch group whereas weakening of external rotation was noticed in this group. The use of patches led to a significant reduction in pain compared to the condition prior to the procedure (on average about 5 points on the VAS scale).

A functional assessment in ASES score, UCLA scale and Constant Shoulder score showed improvement in all types of the used patches. The best results were achieved in synthetic rather than in allograft group. The worst – in xenograft group. Better functional results were observed after augmentation than in "bridging". Observations exceeding two years indicate that in 1/4 of patients secondary, total rotator cuff rupture is likely to occur (most often – xenografts, the least – allografts). Interestingly, secondary damage of the rotator cuff occurs in 33% patients after augmentation and only in 7% of patients after „bridging" techniques. Flury *et al.* reported no significant difference in the clinical outcomes after a patch reconstruction of the rotator cuff (allografts and synthetic) and the simple reconstruction itself. 27% of secondary damage (of which 50% are xenografts) indicates the need for particular caution when using this technique [2]. On the basis of previously published studies, it is difficult to clearly assess the suitability of the patches in the reconstruction of massive rotator cuff tears. Promising functional results, improvement in the range of motion and reduced pain is questioned mainly in long-term studies. It should be noted that patches are used mainly in massive lesions, with a large retraction of damaged tendons and a progressive fatty degeneration. Despite of no age limits, patches are used mainly in patients older than 65 years. A relatively high percentage of complications and secondary lesions (mainly after using xenografts) indicate that this method requires technological modifications, searching for new materials and further research. Moreover, the availability of this method (not only in Poland) is limited by the high prices of the implants (1200–2000 euros).

Biological approach to rotator cuff tears

Rotator cuff tears are common. Although surgical implants, instrumentations, and techniques have improved, postoperative rotator cuff retears occur in as little as 11% to as many as 94% of repair surgeries. Considering the relatively high percentage of repair failures occurring with current surgical techniques, it is important to explore techniques of biologic augmentation of a rotator cuff repair to reduce the retear rates and improve long-term shoulder function. Biologic adjuvants have great potential to improve rotator cuff healing and reduce rates of reinjury.

Biological options:

Growth factors

These factors function primarily to promote the inflammatory response/angiogenesis (vascular endothelial growth factor [VEGF], basic fibroblasts (TGFβ); promote bony incorporation of tendon (bone morphogentic protein [BMP]) and remodel extracellular matrix (matrix metalloproteinase [MMP]).

VEGF describes a family of signalling proteins that stimulate vasculogenesis through tyrosine kinase receptor – mediated signalling cascades. The TGFβ superfamily of cytokines includes 3 isoforms (TGFβ1, TGFβ2, and TGFβ3) that have diverse physiologic effects, including cellular proliferation, differentiation, and matrix synthesis within the tendon.

Certain BMPs, namely BMP1, BMP12, BMP13, and BMP14 are expressed in the acute phase of healing after rotator cuff tears. Number of BMPs (including BMP2 and BMP7) has been reported to induce collagen production when added to cultured tenocyte-like cells derived from samples of human rotator cuff.

Matrix metalloproteases (MMPs) are a large family of proteolytic enzymes degrading all components of the extracellular tendon matrix. Their activities are antagonized by the interaction with the tissue inhibitors of metalloproteases (TIMPs). The balance between MMPs and TIMPs plays a critical role in tendon degeneration and healing. The interaction between MMPs and TIMPs (tissue inhibitors are a complex process since TIMPs are not only inhibitors of MMPs), but are also able to regulate the activation of MMPs. Modulation of the selected MMPs activity, after rotator cuff repair, may offer a novel biological pathway to augment tendon-to-bone healing.

PRP

The use of PRP as a biological adjuvant to improve rotator cuff tendon healing has recently gained popularity. PRP is a term used to describe preparations of the whole blood enriched for platelets that, once activated, release a host of growth factors that may contribute to tissue repair. A number of these growth factors have been shown to increase rotator cuff-derived tenocyte proliferation and promote the production of key extracellular matrix proteins including collagen types I, II, and X; decorin; aggrecan; and biglycan. Unfortunately, the use of PRP in a number of recent randomized controlled trials of surgical rotator cuff repair has not met the expectations raised by the in vitro studies. Clinical trials using different autologous PRP formulations to augment rotator cuff tear repairs have yielded controversial results. The recent analysis have revealed that PRP use at the time of arthroscopic rotator cuff repair does not universally improve retear rates or affect the clinical outcome scores. There was no significant difference in the rate of persistent tears between a PRP and control group. However, an analysis of small or medium lesions showed a significantly lower persistent tear rate in the PRP group.

Furthermore, another study revealed that in large tears, even with a double-row repair, the beneficial effects of PRP alone are insufficient to compensate the progressed tissue damage. Administration of PRP, despite the substantial biological effect, at the current cost, the use of PRP is not cost-effective in arthroscopic repair of small- and medium-sized tears. There are still many aspects of using PRP to resolve such as: the most effective method of PRP activation for rotator cuff healing, optimal timing of delivery, optimal dosing (including repeated dosing) and the most effective platelet and leukocyte counts, the tear location (tendon substance/avulsion) influences PRP preparation or timing of delivery, potential for PRP used in a combination with GFs and MSCs.

Stem cells

Around the 1960's a unique group of bone marrow cells was discovered with the capability to differentiate into various other cells. It is now known that several types of SCs exist, each with different characteristics. The MSC-based therapies may facilitate rotator cuff healing by differentiating into tenocytes or osteoblasts, by recruiting and stimulating progenitors, and by reducing inflammation.

Bone marrow and fat remain the most popular source of MSCs in the studies evaluating rotator cuff regeneration. However, a number of studies have explored the sources of MSCs within the shoulder in an attempt to avoid the requirement for a distant surgical procedure (e.g. pelvic bone marrow aspirate or lipoaspirate). Utsunomiya *et al.* isolated and characterized MSCs from 4 shoulder tissues during arthroscopic rotator cuff repair: synovium of glenohumeral joint, subacromial bursa, rotator cuff tendon, and enthesis at greater tuberosity.

The use of MSCs to enhance tendon regeneration has been examined in several animal models of a tendon injury, only two studies have evaluated the application of MSCs in a rotator cuff surgery. Ellera Gomes *et al.* (2012) investigated the effects of bone marrow mononuclear cells (BMMCs) on rotator cuff healing in 14 patients with the complete tears. Although no control group was used in this study, the authors concluded that delivery of BMMCs was safe and had potential to enhance rotator cuff regeneration. In a case-control study of 45 patients, Hernigou *et al.* (2014) reported a significant improvement in the healing outcomes at

10 years in patients receiving MSCs as an adjunct therapy in standard of care rotator cuff repair. In this study, injection of MSC as an adjunctive therapy enhanced the healing rate and improved the quality of the repaired surface as determined by ultrasound and magnetic resonance imaging (MRI).

Clinical studies evaluating the use of MSCs in a surgical rotator cuff repair show great promise, but randomized clinical trials are lacking and considerable work is required to establish the true mechanism by which these cells contribute to rotator cuff regeneration.

Gene therapy

Gene therapy involves the insertion of genetic material into a target cell so as to manipulate the behaviour of that cell. Understanding the expression profile of the growth factors central to the development of the normal enthesis in development might reveal candidate cytokines that could be used to augment the tendon repair site. Gene therapy approaches in a rotator cuff repair have been used to manipulate expression of scleraxis, BMP13, and platelet-derived growth factor receptor – ß (PDGFRß).

Conclusions

An increased morbidity of rotator cuff tears led to an increased interest in the potential effect of biologic factors to improve cuff tendon healing. Despite many efforts, currently there exists a lack of consensus on the optimal preparation, source, delivery method, and dosing of biologics for orthopaedic. Continued research with animals and human subjects is mandatory to evaluate the safety, efficacy, and applicability of biological options in treatment of shoulder disorders, especially rotator cuff tears.

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