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EXPERIMENTAL STUDY

Platelet concentrate vs. saline in a rat patellar tendon healing model

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Abstract
Purpose To evaluate single centrifuge platelet concentrate as additive for improved tendon healing. Platelet-rich plasma has been reported to improve tendon healing. Single centrifuge platelet concentration may increase platelet concentration enough to positively affect tendon healing. A single centrifuge process will lead to a blood product with increased platelet concentrations which, when added to a surgically created tendon injury, will improve tendon healing when compared with a saline control.
Methods Lewis rats had a surgical transection of the patellar tendon that was subsequently stabilized with a cerclage suture. Prior to skin closure, the tendon was saturated with either a concentrated platelet solution or saline. At 14 days, all animals were killed, and the extensor mechanism was isolated for testing. Biomechanical testing outputs included ultimate tensile load, stiffness, and energy absorbed.
Results Comparisons between the control group and the concentrated platelet group revealed no differences. A subgroup of the concentrated platelet group consisting of specimens in whom the concentration process was most successful showed significantly higher ultimate tensile load ($P < 0.05$) and energy absorbed to failure ($P < 0.05$) when compared to the control group.
Conclusion When successful, single centrifuge platelet concentration yields a solution that improves tendon healing when compared with a saline control. Single-spin platelet concentration may yield a biologically active additive that may improve tendon healing, but more studies must be undertaken to ensure that adequate platelet concentration is possible.

Keywords Tendon healing · Platelet · Knee · Platelet-rich plasma

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Introduction

Great interest in improving tendon healing exists in the sports medicine community [21]. Tendinopathies, traumatic tendon injuries, and degenerative tendon failures are common problems in the orthopaedic world [9, 20, 25, 30, 33]. Efforts focused on improving the healing environment for rotator cuff tendons have included the addition of growth factors, autologous platelets and ultrasound to improve the local vascularity [27, 28]. Recent basic science efforts have focused on the ability of platelets to stimulate human tenocytes [8] and change the local environment in a tendon injury model [19]. These studies have indicated that the addition of platelet-rich plasma (PRP) leads to profound changes for local cells.

Other medical disciplines, including periodontal and maxillofacial surgery and plastic surgery, have published

papers which support the theory that PRP can improve the local healing environment [1, 10, 18, 23]. Authors have also noted improved healing in anterior spinal fusion when bone graft is combined with PRP [17]. Using a porcine model, authors have noted improved healing of bone defects when PRP is combined with autologous bone grafting [15]. These positive outcomes have been attributed to the ability of platelets to recruit other important cell types and the increased release of local growth factors in the immediate healing zone. de Mos et al. [8] noted "platelets release a variety of growth factors and PRP might provide an autologous source of these growth factors". Borzini and Mazzucco [6]noted that the mechanisms of action of platelet additives are very complex and trying to explain understand tissue regeneration by evaluating single growth factors is simplistic. Despite inexact knowledge about the specific actions of platelet additives, it appears that platelets may improve the local healing environment.

Few reports of clinical platelet therapy exist in the sports medicine literature. Sanchez et al. [29] reported some clinical improvements after repair of Achilles tendon using a platelet-rich matrix additive, while Mishra et al. [24] reported improvement in patients with chronic elbow tendinosis after the injection of platelet-rich plasma in the elbow. Peerbooms et al. [26] reported that patients treated with platelet injection for lateral epicondylitis had outcomes that were superior to patients treated with corticosteroid injection. There have been multiple studies using a rat model which have supported the contention that a platelet-rich additive can improve tendon healing [2, 31].

Although no standard definition for PRP exists, the majority of research has focused on platelet preparation systems that require a double-centrifuge technique with fluid transfer to concentrate platelets [14]. While the laboratory environment allows multiple blood transfers and centrifuge steps, the clinical arena is less forgiving. If platelets could be concentrated with a single centrifuge step, this may ease the transition to clinical use. Limited studies do exist in which single-spin centrifugation technologies have been evaluated, but most are clinical in nature [3, 4, 13, 24, 29]. Recent animal studies have indicated that single-centrifugation techniques may yield a platelet mix that improves healing. Bosch et al. [7] noted improved healing in an equine tendon injury model, while Lyras et al. [22] reported that platelet concentrate seemed to accelerate the healing process in a rabbit tendon injury model.

The purpose of this study was to evaluate the potential of a single-centrifugation technique to adequately concentrate platelets and simultaneously evaluate the effect of the concentrated platelet mix (CP) on accelerating or improving tendon healing in the rat model. The primary hypothesis was that the addition of the concentrated platelet mix (CP) to a surgically created tendon injury would improve tendon healing when compared with a saline control.

Materials and methods

A rat tendon healing model that has been the subject of numerous prior publications was selected for testing [5, 12, 16]. Protocols were approved by the State of Bavaria, Germany and the Institutional Animal Care professionals. Lewis rats between 300 and 350 g were obtained from a commercial breeder (Charles River Laboratories Inc., Wilmington, MA, USA). Lewis rats have traditionally been utilized in transplant research because they are of the same genetic makeup. Their utilization in this study allowed allogenic blood transfer between rats without stimulating an immunologic reaction.

Plasma preparation

For plasma preparation, a single rat was anesthetized using Medetomidin (0.15 mg/kg), Midazolam (2 mg/kg), and Fentanyl (0.005 mg/kg). An abdominal incision was made and approximately 9 ml of blood was withdrawn from the descending aorta into the tested syringe, which had been preloaded with 1 ml of sterile anticoagulant citrate dextrose solution (ACDA) anticoagulant (Citra Anticoagulant Inc., Braintree, MA, USA). A novel dual chamber syringe (developed by Arthex GmbH, Karlsfeld Germany) was designed to allow blood drawing, centrifugation for platelet concentration and platelet delivery without fluid transfer.

After manual mixing of the obtained blood, approximately 0.5 ml was withdrawn for blood analysis (System 9000 Baxter International Inc., Deerfield, IL USA) to evaluate the baseline platelet number. The syringe was then centrifuged (Heraeus Sepatech Varifuge 3.0 GmbH Harz, Germany) for 10 min at a speed of 220 g (1,000 rpm on this machine). This speed was selected after a pilot study evaluating different time and speed variations. The resulting supernatant was withdrawn using the internal syringe. The resulting supernatant volume ranged from 2 to 4 ml. The inner syringe filled with supernatant was then removed. After manual mixing, approximately 0.5 ml of the supernatant was withdrawn and analyzed to verify the concentrated blood count and platelet number. Supernatant from one donor rat was then applied to two treatment rats.

Tendon injury

Following surgical anesthesia, a 10-mm longitudinal incision was made just medial to the knee. Knee side was alternated for sequential rats. The patellar tendon was

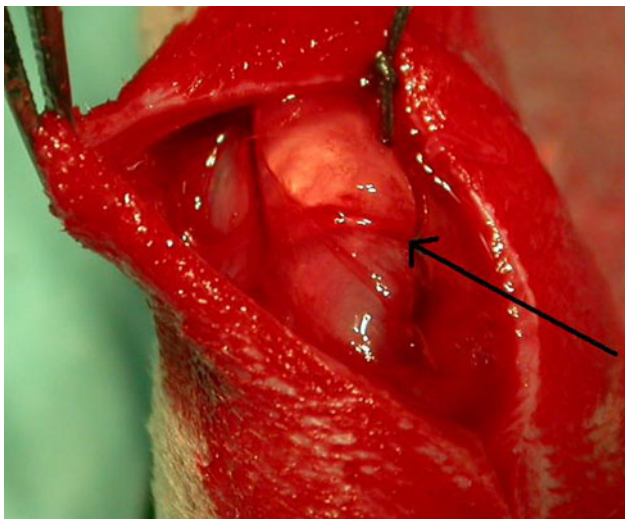

Fig. 1 Rat patellar tendon after transection and placement of cerclage. *Arrow* marks the location of tendon transection just inferior to patella

exposed, and the tendon was sharply removed from the inferior pole of the patella using a No. 11 blade scalpel. A 2–0 Ethibond suture (Ethicon Inc, Somerville, NJ, USA) was passed through the tibia and the quadriceps in a cerclage technique (Fig. 1). For treatment rats (Group P), 0.5 ml of the concentrated plasma was placed in the tendon injury site for 5 min. After 5 min, the skin was carefully re-approximated. This method of platelet application is similar to prior studies which have directly placed platelet concentrate at the site of tendon injury [22, 32]. For control rats (Group C), 0.5 ml of saline was placed in the tendon gap. After 5 min, the cerclage suture was tied in order to approximate the tendon to the patella at 120° of knee flexion. The skin was then closed with two 4.0 Vicryl (Ethicon Inc, Somerville, NJ, USA) sutures. The animals were returned to their cages and were allowed activity, food, and water ad libitum.

Specimen preparation

All animals were euthanized at 14 days post-surgery using pentobarbital as a euthanasia agent. Hind limbs were disarticulated at the hip, placed in saline-soaked gauze and stored at −20°C until the day of mechanical testing or placed in neutral buffered formalin after dissection for histological testing. On the day of testing, the limbs were allowed to thaw at room temperature. Dissection was carried out to isolate the quadriceps, patella, patellar tendon, and the tibia (Fig. 2).

Biomechanical testing

The tibia was secured in a custom-designed grip. The quadriceps was placed in a custom-designed cryoclamp

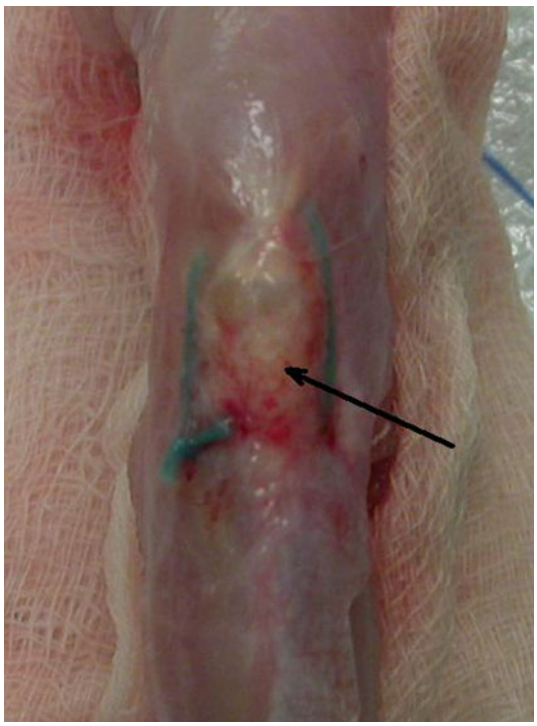

Fig. 2 Specimen after explantation. The cerclage suture passes through the proximal tibia and the quadriceps tendon. The healed tendon–patellar interface is marked by the *arrow*

(Fig. 3). The cerclage suture was removed prior to biomechanical testing. A Zwick 1120 (Zwick GmbH & Co. Ulm, Germany) materials testing machine was utilized. The tendon was preloaded to 0.5 N, then the construct was pulled to failure at a rate of 0.1 mm/s. A single operator performed all biomechanical testing. The load–deformation curve was recorded. The structural properties of linear stiffness, energy absorbed, and ultimate tensile load (UTL) were calculated using data acquisition and analysis software included on the materials testing machine. The ultimate failure load was defined as the peak force of the load–elongation curve. Stiffness was calculated using the most linear portion of the failure curve. Energy absorbed was calculated by defining the area under the curve until the peak failure load. Data analysis was carried out using the Zwick internal software and Excel Spreadsheet (Microsoft Redmond, WA, USA).

Histology

Two specimens from each group, consisting of the origin of the patellar ligament at the tibial tuberosity, the patellar ligament and the patella itself were harvested for histological evaluation. Specimens were placed into 6% neutral buffered formalin before processing for 24 h at 4°. Following, the specimens were decalcified using 5% EDTA and embedded in paraffin. Longitudinal sections (each

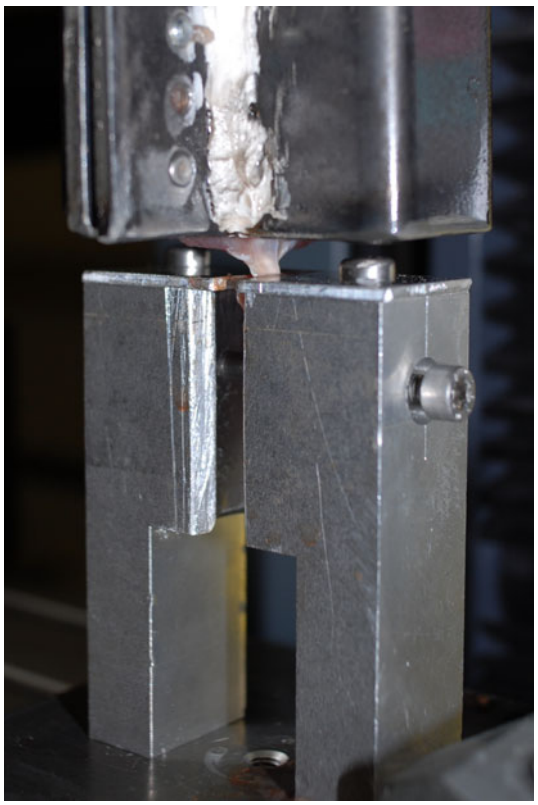

Fig. 3 Specialized Cryoclamp developed to grasp and position tendon for biomechanical testing

$n = 3$) were cut. Additionally, control tendons of the untreated side were processed. Specimens were stained with hematoxylin and eosin as well as alcian blue staining to test for chondrogenic differentiation. Specimens were then examined and reviewed by a single observer experienced with histopathology of the musculoskeletal system.

Statistical analysis

Biomechanical data were evaluated using the Students' *t* test function in Excel Spreadsheet (Microsoft Redmond, WA, USA) for equal and unequal groups where applicable. A value of $P < 0.05$ was set to denote significance.

Results

The final count of operated rats included 22 for the control group (Group C) and 25 for the plasma group (Group P). After a laboratory failure led to loss of results for two of the plasma rats, the number of rats entered into the plasma group was increased. For the control group, there was one death unrelated to the surgery, two rats which were utilized for histological testing and three rats in whom the cerclage was not intact at the time of killing rendering the limb unsuitable for biomechanical testing. This left a total of 16 rats for biomechanical testing. For the plasma group, there was one death unrelated to the surgery, two rats in whom platelet numbers could not be verified due to laboratory error, two rats used for histological testing, two rats for whom the plasma platelet concentrate was less than the whole blood and two rats in whom the cerclage was not intact at the time of killing. This left a total of 16 rats available for biomechanical testing. There was a natural division within Group P into two groups of 8 rats: Group A (platelet concentration increase 0–50%: avg. 34%) and Group B (platelet concentration increase >51%: avg. 80%) each had 8 rats. After comparing the results of Group C vs. Group P, it was decided to undertake an additional statistical analysis which compared Group C vs. Group A and Group C vs. Group B.

Platelet concentration results

See Table 1

Biomechanical results

Ultimate load to failure

All specimens ruptured at the site of the former tendon dissection (inferior patella pole–tendon interface). For the control group (Group C), the average UTL was 23.4 N (SD ± 6.8). For the plasma group (Group P), the average UTL was 26.8 N (SD ± 8.3). The difference between them

Table 1 Platelet concentration per rats (thousand/mm^3) utilized for biomechanical testing

Group/rat #	Whole blood	Platelet concentrate	% change
A	416	445	7
A	450	620	38
A	450	620	38
A	371	520	40
A	371	520	40
A	427	602	41
A	427	602	41
A	419	606	45
B	380	608	60
B	380	638	68
B	380	638	68
B	391	687	76
B	391	687	76
B	350	664	90
B	415	862	106
B	415	862	106

Table 2 Summary of ultimate tensile load results

	Ultimate tensile load (N)	Group C comparison *P* value
Group C	23.4 ± 6.8	
Group P	26.8 ± 8.3	(n.s.)
Group A	21.7 ± 5.5	(n.s.)
Group B	31.8 ± 7.7	0.02

was not significant ($P = 0.12$). Comparing Group C with Group A (21.7 N SD ± 5.5), the difference was not significant ($P = 0.29$). However, comparing Group C with Group B (31.8 N SD ± 7.7) the difference was significant ($P = 0.02$) (see Table 2).

Stiffness

For the control group (Group C), the average stiffness was 10.5 (SD ± 4.6). For the plasma group (Group P), the average stiffness was 11.3 (SD ± 5.1). The difference between them was not significant ($P = 0.32$). Comparing Group C with Group A (10.4 SD ± 3.9), the difference was not significant ($P = 0.48$). Comparing Group C with Group B (12.3 SD ± 6.3), the difference was not significant ($P = 0.20$) (see Table 3).

Energy absorbed

For the control group (Group C), the average energy absorbed was 50.7 mJ (SD ± 28.1). For the plasma group (Group P), the average UTL was 64.4 mJ (SD ± 47.9). The difference between them was not significant ($P = 0.20$). Comparing Group C with Group A (41.0 mJ SD ± 15.4), the difference was not significant ($P = 0.19$). Comparing Group C with Group B (87.8 mJ SD ± 56.8), the difference was significant ($P = 0.02$) (see Table 4).

Histology

The saline (Group C) and plasma (Group P) groups showed no gross differences concerning cellularity or tissue organization (Fig. 4). Repair tissue consisted of unorganized fibrous tissue with abundant cells and small vessels. No longitudinal orientation of fibers was seen in both groups after 2 weeks. However, slightly more elongated cells were seen in plasma group. Alcian blue staining showed no cartilaginous differentiation in the repair tissue; however, glycosaminoglycan content appeared slightly increased (pictures not shown).

Table 3 Summary of stiffness results

	Stiffness	Group C comparison *P* value
Group C	10.5 ± 4.6	
Group P	11.3 ± 5.1	(n.s.)
Group A	10.4 ± 3.9	(n.s.)
Group B	12.3 ± 6.3	(n.s.)

Table 4 Summary of energy absorbed results

	Energy absorbed (mJ)	Group C comparison *P* value
Group C	50.7 ± 28.1	
Group P	64.4 ± 47.9	(n.s.)
Group A	41.0 ± 15.4	(n.s.)
Group B	87.8 ± 56.8	0.02

Discussion

The most important finding of the present study was improved tendon healing in those rat tendons exposed to significant increase in local platelet concentration. Previously, the majority of published research on the potential for platelets to improve healing has investigated the use of so-called platelet-rich plasma (PRP) which has traditionally been defined as a platelet preparation that requires two centrifugations and laboratory manipulations [2, 8, 11, 29]. As single-spin centrifugation technologies have advanced one step, preparation of platelet concentrate has become possible and more research into this area is ongoing.

One clinical study with implications for tendon healing was reported by Mishra and Pavelko [24] appears to have used a single-spin technique although the authors identified their additive as PRP. Other authors have now reported clinical improvements in patients treated for chronic lateral epicondylitis with a CP mix [26]. Both authors reported excellent clinical results with their treatment method and attributed those results to the higher percentage of platelets and accompanying growth factors presumed to be in the platelet concentrate.

Little basic science work exists which focuses on single centrifugation platelet concentration. This study was an attempt to evaluate the idea that single-spin centrifugation/platelet concentration may yield a biological additive of platelets in sufficient numbers to improve tendon healing using a laboratory model. The primary hypothesis was partially supported as that group in which platelets were successfully concentrated (Group B) had superior biomechanical results when compared with saline controls. This is a positive finding indicating that single-spin platelet concentration methods may yield a biologically active concentrate useful in supporting tendon healing. The

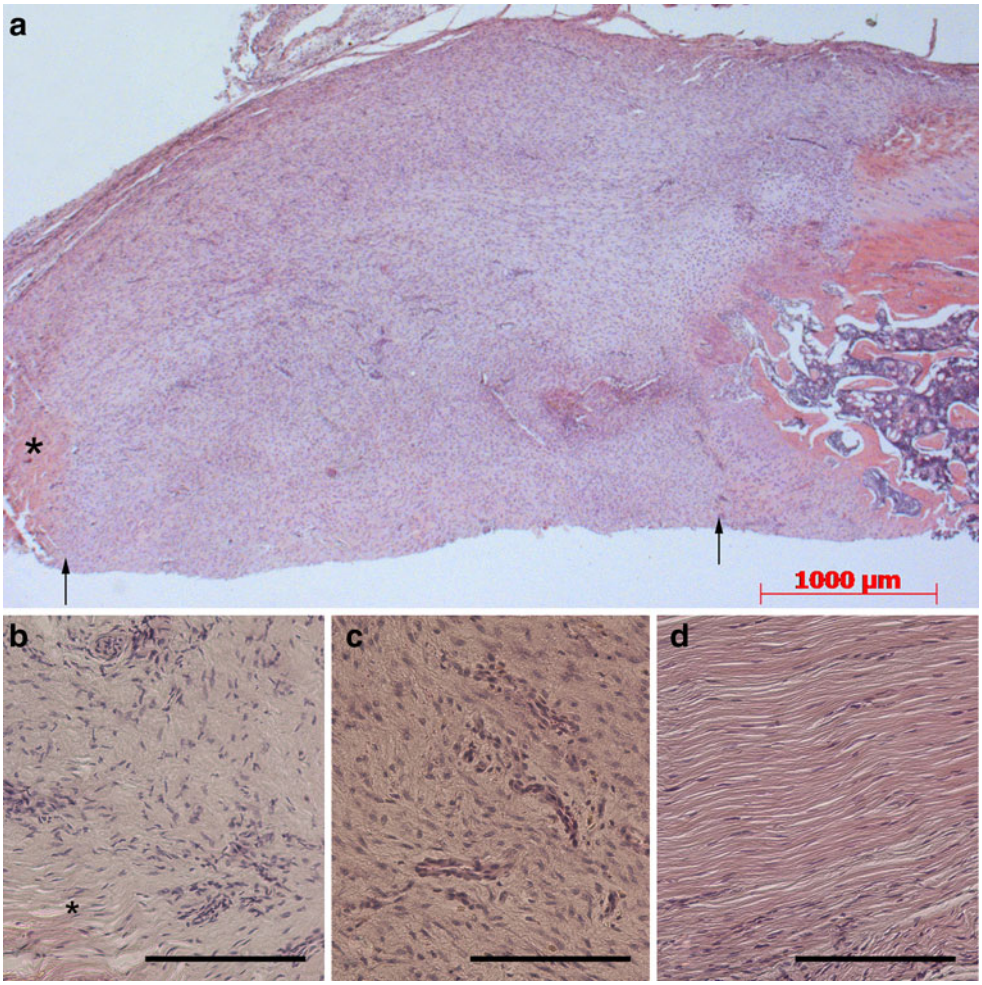

Fig. 4 **a** Overview of the defect in plasma group. The patella can be seen on the *right side,* and on the *left side,* part of the normal tendon is visualized. In between (regenerate zone, marked by two *arrows*), highly cellular, disorganized fibrous repair tissue fills the defect. Multiple blood small blood vessels can be seen especially in the centre. High-power view (×200, *bar* size = 100 µm) of plasma (**b**) and saline (**c**) and healthy tendon (**d**) specimens shows the regenerate tissue more clearly. No marked differences can be noted between both groups. Cells appear more spindle shaped in plasma vs saline group. In b, the normal tendon reaching the defect can be seen (*asterisk*). All stainings HE

results are consistent with prior rat studies in which platelet additives have been able to show improved healing and biomechanical properties after an induced tendon injury [2, 31, 32]. Research on the cellular level has also recently supported the contention that platelet interaction can directly influence tenocytes on a cellular level [8]. Recent work by other authors in animal/tendon injury models using single-spin centrifugation for platelet concentration also noted improved healing with the addition of a CP mix [7, 22]. The improved biomechanical results noted in Group B (the high platelet concentrate group) indicate that single-spin centrifugation and concentration of platelets are worthy of further study.

In reviewing this research, there were some weaknesses which merit review. The primary weakness in this work was the inability to reliably increase the platelet concentration with single-spin technology when compared with whole blood. The testing group (Group P) had wide variability with respect to the amount of platelet concentration achieved. Whether this represents weaknesses in the testing, problems with concentration rat platelets in a device designed to concentrate human platelets or individual variation in blood behavior during processing is unknown. Further research on concentrating human blood using single-spin technology must be published in the peer-reviewed literature. A secondary weakness of the research is the small groups that were ultimately created by the split data analysis. While the split of the plasma group into two groups (Group A and Group B) for further statistical evaluation decreased the number of specimens available for comparison between groups, we believe the notable differences between Group A and Group B were worth further

examination. Another weakness was the decision to evaluate the rats at a single post-surgery time point. The longer-term effects of the intervention are not known.

Questions about the reliability and validity of single-spin methods remain. If possible, human trials should be undertaken to accurately and completely document the potential for single-spin centrifugation to concentrate platelets while establishing clear instructions on how to achieve the best results. Basic science findings seem to support the idea that single-spin centrifugation can create a biological product that improves the local healing environment in a tendon injury model. Clinical applications might include tendon injuries (flexor tendons or Achilles tendons) and tendon-bone repairs (rotator cuff repair and anterior cruciate ligament grafts). Future research should strive to develop other animal models which more closely mirror clinical scenarios, particularly rotator-cuff repair models.

Conclusion

The addition of platelet concentrate created using single-spin centrifugation improved healing in a rat patellar tendon healing model when compared with saline controls. In some animals, platelet concentration was not successful and improved healing was not noted. If single-spin centrifugation can reliably improve platelet concentration of human blood in clinical trials, then future research can focus on clinical applications for a potentially potent additive which may improve tendon healing.

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