Research Square

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A Prospective Cohort Study: Platelet-Rich Plasma Combined with Carpal Tunnel Release Treating Carpal Tunnel Syndrome short (running) title: PRP-CTR Treating Carpal Tunnel Syndrome

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Research Article

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Abstract

Background: PRP injection was proved to promote the health condition of individuals with mild to moderate Carpal Tunnel Syndrome （CTS）. However, carpal tunnel release (CTR) was still an important treatment for individuals with moderate, as well as severe CTS.

Methods: To explore whether adjuvant PRP treatment would improve the prognosis while using CTR, we included 82 patients in this study. Preoperative and postoperative visual analog scale (VAS), Boston carpal tunnel syndrome questionnaire-symptom severity scale (BCTQ-SSS), Boston carpal tunnel syndrome questionnaire-functional status scale (BCTQ-FSS), and grip strength was used to examine the patient's symptoms and function.

Results: CTR combined with PRP treatment improved the VAS (1.9±0.5 versus 1.4±0.4, P<.05), BCTQ-SSS (1.8±0.4versus 1.5±0.3, P<.05) and BCTQ-FSS (1.8±0.5 versus 1.4±0.6, P<.05) in patients with moderate symptoms within one month after surgery. At the same time, it does not show any advantages in treating individuals with severe carpal tunnel syndrome.

Conclusions: The use of PRP does not affect long-term prognosis while increasing the surgery cost. To conclude, PRP as an adjuvant treatment of CTR has limited effect. Considering the additional financial burden on patients, CTR combined with PRP should be cautious in CTS treatment.

1. Background

Carpal tunnel syndrome (CTS) constitutes the commonest compressive neuropathy of the upper limbs, usually via the abnormal flexor retinaculum thickening [1,2]. Pain, numbness, and muscle weakness caused by CTS seriously affect patients' function and quality of life[3]. Although splinting and corticosteroid injections were proven effective, strong evidence supported that the carpal tunnel release (CTR) decompresses the median nerve by dividing the transverse carpal ligament and should have a better treatment advantage at 6 and 12 months, especially in patients with moderate or severe symptoms[3–5].

Platelet-rich plasma (PRP) has been utilized as a safe treatment form in divergent settings[6]. It is an analogous biologic agent constituting concentrated platelets, the primary component of which is believed to be products of degradation consisting of transforming growth factor (TGF), the insulin-like growth factor-1 (IGF-1), Platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF)[7]. An extensive bulk of the researches supported that PRP injection enhanced the clinical outcomes of the individuals with mild-to-moderate CTS[8]. Research-based on in vitro as well as in vivo studies supported the neurotrophic impact of PRP in peripheral nerves[9,10]. Following a PRP injection, diverse growth factors are released and activated, which leads to median nerve rejuvenation and improves the supply of neural blood via protection of the blood-nerve barrier[11]. There is limited clinical information on the utilization of PRP in peripheral neuropathies in humans[8,12]. A recent systematic review indicated that PRP is proven effective for mild to moderate carpal tunnel syndrome individuals, while PRP injection alone is not recommended for severe carpal tunnel syndrome patients [8]. No studies have pointed out whether additional PRP infusion is necessary for patients with severe symptoms who require surgical treatment.

For the lack of correlational studies, we tried to explore whether adjuvant PRP treatment could improve the prognosis of individuals with moderate to severe carpal tunnel syndrome while applying CTR. Further exploration is needed to provide robust research evidence by which surgeons should establish guidelines for utilizing this treatment in CTS patients.

2. Patients And Methods

2.1 Ethical approval

This study is a prognostic study constituting a prospective cohort. The ethics committee at Shanghai Sixth People's Hospital approved the study. In addition, this study was conducted as per the Code of Ethics of the World Medical Association (Declaration of Helsinki) for procedures involving humans.

2.2 Patients

Between 2015 and 2018, 94 patients underwent CTR for CTS treatment in our hospital. Twelve patients declined to participate in the cohort, and we included the remaining 82 patients prospectively in this cohort. Before the operation, every patient underwent a nerve conduction study for definite diagnosis and severity evaluation[13]. The demographic data consisting of age, body mass index (BMI), gender, along with preoperative evaluation by visual analog scale (VAS), Boston carpal tunnel syndrome questionnaire- symptom severity scale (BCTQ-SSS), Boston carpal tunnel syndrome questionnaire- functional status scale (BCTQ-FSS) and grip strength. Follow up was performed at one, three and six months after surgery. The CTS diagnosis was centered on the typical history constituting pain, sensory disturbances, as well as weakness entailing the median nerve distribution. All subjects included in the study were with moderate to severe symptoms or failed conservative treatment with steroid injections[14]. Patients were excluded if they aged 70 or 18, with a course of CTS is less than two months, space-occupying lesions within the carpal tunnel, pregnancy, diabetes mellitus, rheumatoid arthritis, traumatic CTS, or had previous CTS surgery.

2.3 Operative procedure

Experienced surgeons performed all Surgical procedures. Regarding the conventional method, the approach documented by Taleisnik was applied [15]. In brief, a palmar longitudinal incision starting at the ring finger axis was made passing through thenar and hypothenar eminences and proceeded proximally into the wrist proximal flexor crease. Following the exposure of the underlying transverse carpal ligament, its ulnar region was longitudinally cut. Identification of the median nerve was done for protection, and then the incision was closed in a routine way (Figure 1).

At the time of surgery, 15mL of analogous venous blood sample was drawn from every subject's contralateral (non-impacted) hand, followed by centrifugation at two successive density gradient centrifugations (800g-10min and 1100g-10min) at our hospital laboratory. In the initial centrifugation, separation of the red blood cells was achieved, whereas in the second centrifugation, separation of PRP from the platelet-poor plasma (PPP) was performed and then introduced into a sterile injector. 2 mL PRP was injected from the sutured incision, and then the incision was bandaged (Figure 1).

No brace or splint was used following the operation. Restricted wrist movement was permitted for 24 hours. We encouraged the patients to return to their daily activities. Non-steroidal inflammatory drug use was limited in both groups.

Symptom Typing[16]. 1. Low Severity (nighttime pain/sensory disturbances, and/or episodic/infrequent symptoms) 2. Moderate Severity (pain/sensory disturbances, tingling, frequent activity-related symptoms, and/or difficulty with fine motor coordination) 3. High Severity (constant sensory loss, motor clinical findings [eg, muscle weakness], and/or thenar atrophy).

2.4 Outcome measures

Postoperative follow-up visits were held by a third physician (blinded to the groups) after 3 and 6 months, during which the VAS, BCTQ and grip strength were repeated. Digital pain severity and paresthesia were determined via VAS, with 10 points designating extremely severe pain, while 0 points designated no pain. BCTQ constitutes a symptom severity scale (SSS), as well as a functional status scale (FSS). The lower scores on the BCTQ imply lesser symptom severity and better functional status of the patient[17]. Determination of strength of the grip was conducted with the flexion of elbow at 90 degrees and in neutral rotation for the forearm.

Six months after the operation, the remission was evaluated according to the clinical symptoms of the patients in the last two weeks. Remission was defined as the significant reduction of symptoms, including numbness, pain, sensory disturbance, and muscle weakness. Patients with no preoperative symptoms were defined as entirely asymptomatic.

2.5 Statistical analyses

Continuous variables were indicated as mean ± standard deviation; categorical data were shown as a number (percentage). For a continuous variable, demographic data were assessed via the independent t-test for continuous data, while X^2 test was employed for the categorical data. The repeated-measures ANOVA followed by post hoc tests was carried out for the data at various follow-ups. All statistical analysis was conducted using SPSS 22.0 in this study. All statistical evaluations were two-sided. P< .05 signified statistical significance.

3. Result

A total of 82 patients (35 males and 47 females) were enrolled for analysis. All of the study surgeons were hand surgery specialists. All subjects were followed up for more than 6 months. In our cases, 35 of the 82 cases were male, and the average age of this series was 42.1±11.7 (19 to 69). The right hand was affected in 46, and the left hand was affected in 35 cases. The mean BMI was 25.2±4.7. The mean symptom duration of the two groups was 25.6±22.8. Table 1 shows the preoperative assessment of VAS, BCTQ-SSS, BCTQ-FSS, and grip strength. The data in Table 1 statistically showed no remarkable difference in demographics between the two groups.

Table 1

Patient features.

	Control Group N=39	PRP Group N=43	P
Gender			
Male	17(43.6%)	18(41.8%)	0.874
Female	22 (56.4%)	25(58.2%)	
Age	42.5±11.7	41.9±11.7	0.839
BMI	25.6±4.1	25.0±5.1	0.608
Affected side			
Right	20 (51.2%)	26(60.4%)	0.402
Left	19(48.8%)	17(39.6%)	
Symptom duration (month)	24.3±21.7	26.8±23.6	0.613
Grading			
Moderate	26	26	0.560
Severe	13	17	
VAS	4.51±1.27	4.58±1.36	0.817
BCTQ-SSS	2.62±0.51	2.80±0.65	0.189
BCTQ-FSS	2.70±0.68	2.86±0.58	0.250
Grip strength(g/mm^2)	16.74±5.36	16.04±5.15	0.556

PRP= platelet-rich plasma, VAS=visual analog scale

BCTQ-SSS= Boston carpal tunnel syndrome questionnaire- symptom severity scale

BCTQ-FSS= Boston carpal tunnel syndrome questionnaire- functional status scale

Table 2

Clinical outcomes in all patients

	1 month after surgery			3 months after surgery			6 months after surgery		
	Control Group N=39	PRP Group N=43	P	Control Group N=39	PRP Group N=43	P	Control Group N=39	PRP Group N=43	P
VAS	2.61±1.19	2.39±1.18	0.410	1.38±1.05	1.46±1.16	0.747	0.71±1.10	0.81±1.16	0.707
BCTQ-SSS	2.13±0.58	1.91±0.59	0.097	1.46±0.64	1.39±0.67	0.630	1.02±0.86	0.93±0.85	0.665
BCTQ-FSS	2.11±0.63	1.94±0.78	0.290	1.60±0.69	1.64±0.71	0.824	1.14±0.87	1.20±0.83	0.740
Grip strength (g/mm^2)	18.01±5.24	17.88±5.05	0.852	20.68±5.15	21.81±5.12	0.909	22.87±5.10	24.34±5.59	0.222

Table 2 shows the clinical outcomes within 6 months after surgery. The results showed that there was no remarkable difference between the two groups in VAS, BCTQ-SSS, BCTQ-FSS and grip strength in 1 month, 3 months, as well as 6 months after surgery. However, the further analysis of patients with moderate preoperative symptoms showed that the PRP patient group showed a better outcome in VAS (2.42±1.30 versus 1.69±0.66, P<.05), BCTQ-SSS (1.90±0.54 versus 1.57±0.35, P<.05) and BCTQ-FSS (1.83±0.57 versus 1.54±0.37, P<.05) in 1 month after surgery. There was no marked difference between the two groups in VAS, BCTQ-SSS, BCTQ-FSS, and grips strength in 3 months and 6 months after surgery (Table 3, Figure 2).

Table 3

Clinical outcomes in patients with moderate preoperative symptoms

	Control Group	PRP Group	P
	N=26	N=26	*significant
VAS preoperative	4.00±1.07	3.84±1.16	0.630
VAS 1 month following surgery	2.42±1.30	1.69±0.66	0.016*
VAS 3 months following surgery	1.12±0.93	1.00±0.83	0.647
VAS 6 months following surgery	0.46±0.69	0.42±0.63	0.838
BCTQ-SSS preoperative	2.36±0.41	2.41±0.43	0.701
BCTQ-SSS 1 month following surgery	1.90±0.54	1.57±0.35	0.016*
BCTQ-SSS 3 months following surgery	1.25±0.51	1.06±0.48	0.201
BCTQ-SSS 6 months following surgery	0.80±0.67	0.66±0.61	0.438
BCTQ-FSS preoperative	2.42±0.58	2.51±0.41	0.521
BCTQ-FSS 1 month following surgery	1.83±0.57	1.54±0.37	0.037*
BCTQ-FSS 3 months following surgery	1.33±0.56	1.29±0.45	0.773
BCTQ-FSS 6 months following surgery	0.95±0.73	0.87±0.53	0.659
Grip strength preoperative (g/mm^2)	19.47±3.71	18.68±4.36	0.470
Grip strength 1 month after surgery(g/mm^2)	20.86±3.53	20.44±4.41	0.710
Grip strength 3 months after surgery (g/mm^2)	23.19±4.06	23.21±4.87	0.983
Grip strength 6 months after surgery(g/mm^2)	24.79±4.04	26.25±5.79	0.303

Table 4 showed that 35 (89.7%) and 40 (93%) individuals in the control group and PRP group, respectively, revealed remission 6 months after surgery. 16 (41.0%) and 19(44.1%) individuals in the control group and PRP group, respectively were found completely asymptomatic. Nonetheless, there was no remarkable difference between the two groups.

Table 4

Symptom Remission

	Moderate Symptom			Severe Symptom		
	Control Group	PRP Group	P	Control Group	PRP Group	P
	N=26	N=26		N=13	N=17	
Remission	25(96.1%)	26(100.0%)	0.312	10(76.9%)	14(82.4%)	0.712
Non-remission	1(3.9%)	0(0%)		3(23.1%)	3(17.6%)	
Completely asymptomatic	12(46.2%)	13(50.0%)	0.781	4(30.8%)	6(35.2%)	0.794

As shown in Table 5, the PRP treatment increased the costs of the surgery (12363.2±901.2 versus 16206.4±1131.0, CNY, P < .001). There was no statistic difference in hospitalization between the two groups (3.56±0.59 versus 3.46±0.54 days, P =0.29).

Table 5

Economic analysis.

	Control Group	PRP Group	P
	N=39	N=43	*significant
Hospitalization (Days)	3.56±0.59	3.46±0.54	0.437
Cost (CNY)	12363.2±901.2	16206.4±1131.0	<0.001*

CNY = China Yuan.

4. Discussion

In this study, CTR combined with PRP treatment has been reported to better the health outcomes and functions of patients with moderate symptoms within one month after surgery, but it does not show an advantage in the treating individuals with severe carpal tunnel syndrome. At the same time, PRP's use does not affect long-term prognosis while increasing the surgery cost.

A large number of clinical and basic studies support PRP's role in the repair of peripheral nerve injury[18], with the continuous study of PRP treatment, different researchers have proposed that the effect of PRP in the CTS treatment is limited. A placebo-controlled clinical study indicated that a single PRP injection has positive impacts on individuals with mild to moderate CTS. However, comparing to the VAS of the placebo group, PRP showed no statistical difference in their success ratios[11]. In addition, some researchers believe that PRP injection did not add remarkably to the effects of a wrist splint. A randomized controlled trial pointed out that a single injection of PRP had no marked influence on the improvement effect of wrist splints to individuals with CTS[12]. However, in almost all PRP treatment studies for CTS, a severe form of CTS was excluded, and treatment of PRP combined with CTR was not mentioned.

CTR is still the most recommended treatment for individuals with severe carpal tunnel syndrome and some patients with no improvement after glucocorticoid injection[4]. This study came to a similar conclusion that CTR is effective in treating persons with moderate or severe carpal tunnel syndrome, which can effectively improve the symptoms and functions, and even some patients' symptoms disappear entirely. The combined treatment of PRP does not increase the long-term effect of surgery, but it can accelerate the recovery after the operation in a short time.

In this study, patients with PRP treatment were not treated blindly. However, because of the surgery, the bias could be significantly reduced. Moreover, compared with a large number of multicenter clinical studies, the number of subjects in this study is relatively small, which needs further research. Besides, lack of randomization constitutes another limitation of the present study. Subjects who were apportioned into the PRP group but declined injection treatment were allowed to participate in the control group, which elevated the risk of selection bias.

To conclude, PRP as an adjuvant treatment of CTR has limited effect. Considering the additional financial burden on patients, CTR combined with PRP should be cautious in the treatment of CTS.

Declarations

Ethics approval and consent to participate

This study was approved by Medical Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards

Consent for publication

Not applicable.

Availability of data and materials

The final dataset will be available from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yanchun Gao revising substantial contributions to research design and revising the paper critically; Qiyang Wang acquisition, analysis, interpretation of data and drafting the paper; Chenchen Wang acquisition, analysis, and interpretation of data; Hua Chen approval of the submitted and final versions. All authors have read and approved the final submitted manuscript.

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References

1. de Krom, M. C.*et al.* Carpal tunnel syndrome: prevalence in the general population. *J Clin Epidemiol* **45**, 373-376, doi:10.1016/0895-4356(92)90038-o (1992).
2. Sasaki, T.*et al.* Assessment of grip-motion characteristics in carpal tunnel syndrome patients using a novel finger grip dynamometer system. *J Orthop Surg Res* **15**, 245, doi:10.1186/s13018-020-01773-9 (2020).
3. Li, W.*et al.* Extracorporeal shock wave therapy versus local corticosteroid injection for the treatment of carpal tunnel syndrome: a meta-analysis. *J Orthop Surg Res* **15**, 556, doi:10.1186/s13018-020-02082-x (2020).
4. Graham, B.*et al.* The American Academy of Orthopaedic Surgeons Evidence-Based Clinical Practice Guideline on: Management of Carpal Tunnel Syndrome. *J Bone Joint Surg Am* **98**, 1750-1754, doi:10.2106/JBJS.16.00719 (2016).
5. Bai, J.*et al.* Carpal tunnel release with a new mini-incision approach versus a conventional approach, a retrospective cohort study. *Int J Surg* **52**, 105-109, doi:10.1016/j.ijsu.2018.02.033 (2018).
6. Laudy, A. B., Bakker, E. W., Rekers, M. & Moen, M. H. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *Br J Sports Med* **49**, 657-672, doi:10.1136/bjsports-2014-094036 (2015).
7. Sundman, E. A., Cole, B. J. & Fortier, L. A. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med* **39**, 2135-2140, doi:10.1177/0363546511417792 (2011).
8. Malahias, M. A.*et al.* Platelet-rich plasma injections for carpal tunnel syndrome: a systematic and comprehensive review. *Eur J Orthop Surg Traumatol* **29**, 1-8, doi:10.1007/s00590-018-2278-8 (2019).
9. Anjayani, S.*et al.* Sensory improvement of leprosy peripheral neuropathy in patients treated with perineural injection of platelet-rich plasma. *Int J Dermatol* **53**, 109-113, doi:10.1111/ijd.12162 (2014).
10. Malahias, M. A., Chytas, D., Babis, G. C. & Nikolaou, V. S. Platelet-rich plasma guided injections: clinical application in peripheral neuropathies. *Front Surg* **1**, 41, doi:10.3389/fsurg.2014.00041 (2014).
11. Malahias, M. A.*et al.* Platelet-rich plasma ultrasound-guided injection in the treatment of carpal tunnel syndrome: A placebo-controlled clinical study. *J Tissue Eng Regen Med* **12**, e1480-e1488, doi:10.1002/term.2566 (2018).
12. Raeissadat, S. A., Karimzadeh, A., Hashemi, M. & Bagherzadeh, L. Safety and efficacy of platelet-rich plasma in treatment of carpal tunnel syndrome; a randomized controlled trial. *BMC Musculoskelet Disord* **19**, 49, doi:10.1186/s12891-018-1963-4 (2018).
13. Stevens, J. C. AAEM minimonograph #26: the electrodiagnosis of carpal tunnel syndrome. American Association of Electrodiagnostic Medicine. *Muscle & nerve* **20**, 1477-1486 (1997).

14. Huisstede, B. M., Friden, J., Coert, J. H., Hoogvliet, P. & European, H. G. Carpal tunnel syndrome: hand surgeons, hand therapists, and physical medicine and rehabilitation physicians agree on a multidisciplinary treatment guideline-results from the European HANDGUIDE Study. *Arch Phys Med Rehabil* **95**, 2253-2263, doi:10.1016/j.apmr.2014.06.022 (2014).
15. Taleisnik, J. The palmar cutaneous branch of the median nerve and the approach to the carpal tunnel. An anatomical study. *J Bone Joint Surg Am* **55**, 1212-1217 (1973).
16. Mooar, P. A., Doherty, W. J., Murray, J. N., Pezold, R. & Sevarino, K. S. Management of carpal tunnel syndrome. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons* **26**, e128-e130 (2018).
17. Levine, D. W.*et al.* A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. *J Bone Joint Surg Am* **75**, 1585-1592, doi:10.2106/00004623-199311000-00002 (1993).
18. Wu, Y. N.*et al.* Optimization of platelet-rich plasma and its effects on the recovery of erectile function after bilateral cavernous nerve injury in a rat model. *J Tissue Eng Regen Med* **10**, E294-E304, doi:10.1002/term.1806 (2016).

Figures

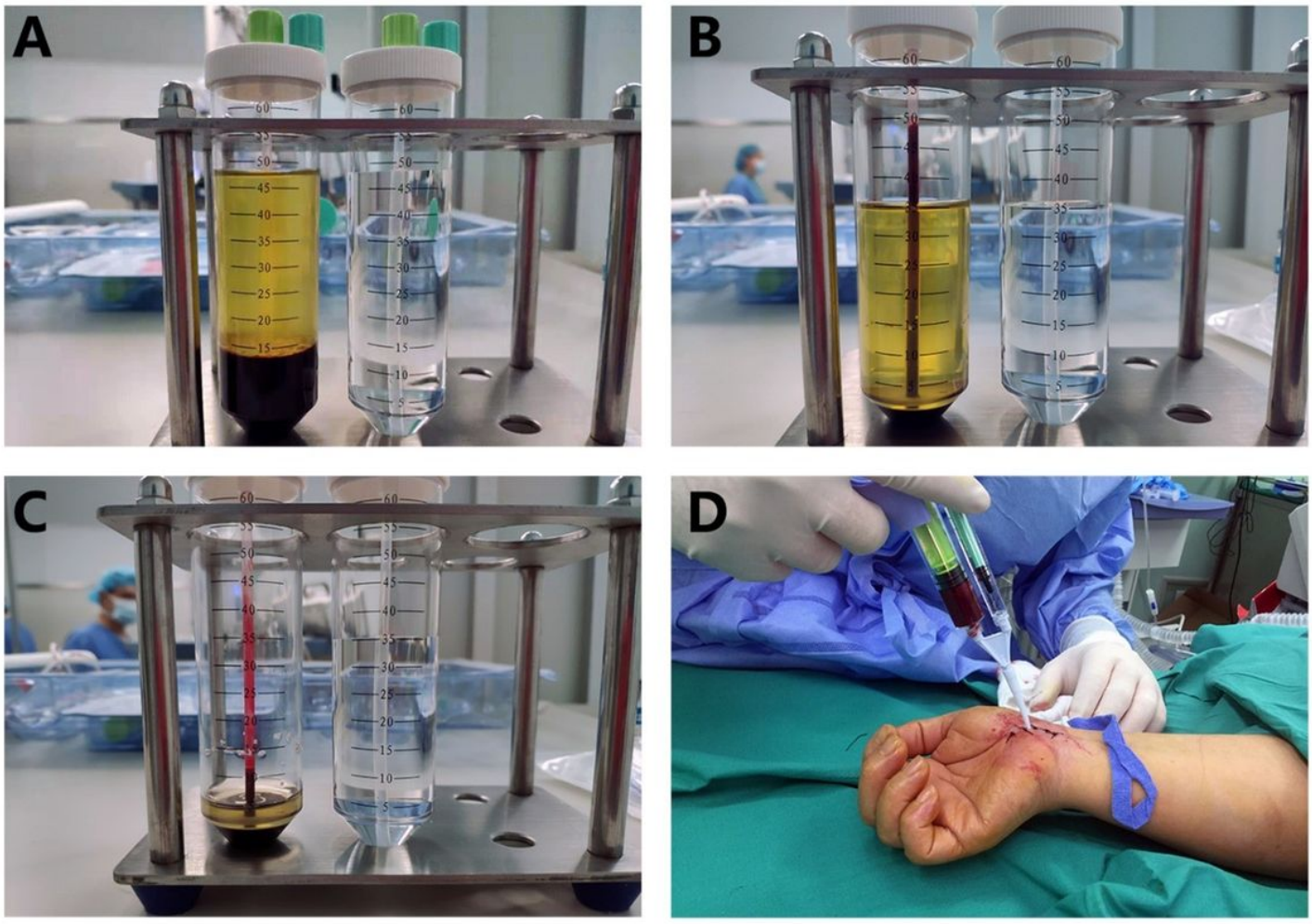

Figure 1

Preparation and injection of PRP

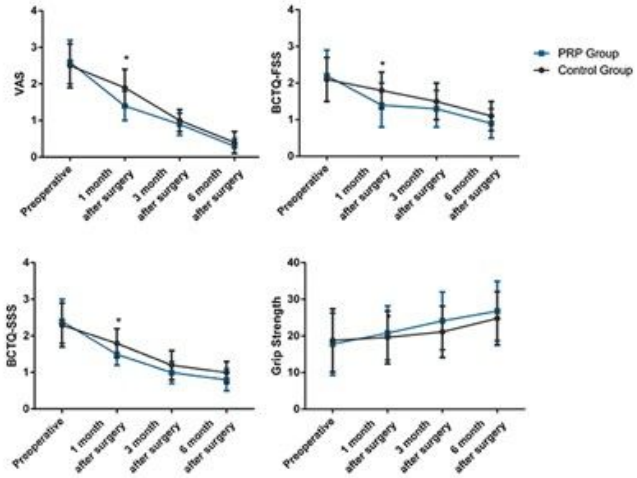

Figure 2

VAS BCTQ-FSS, BCTQ-SSS and grips strength after surgery