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Results of Shoulder Adhesive Capsulitis Treatment With the Use of Platelet Rich Plasma and Nucleotide Drugs: a Comparative Study

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Background. Intra-articular injections of autologous platelet-rich plasma (PRP), which is a natural biological stimulant and affects various parts of the regenerative process, are often used in the treatment of adhesive capsulitis. Another line of using the reparative potential of biopolymers is the application of polynucleotides (PN), which, due to their effect on fibroblasts, are able to stimulate regeneration processes during adhesive capsulitis.

Aim of study — to evaluate the clinical efficacy of intra-articular injections of autologous platelet-rich plasma and a polynucleotide-based drug in the complex therapy of shoulder adhesive capsulitis, depending on the stage of the disease.

Methods. Performed prospective cohort study included 42 patients aged 47 to 60 years with the diagnosis of adhesive capsulitis. The duration of the disease varied from 3 months to 5 years. The patients were divided into 2 groups depending on the stage of the disease at the time of the treatment: 24 patients with the first stage of the disease (group AC1) and 18 patients with the second stage (AC2). Each group was divided into 2 subgroups of patients. In subgroups either PRP or PN were administered. The results were assessed 1 week, 1 month, 3 months after the start of the treatment. Evaluation of pain management efficacy was carried out using the visual-analog scale (VAS). The change in the quality of life of patients and the function of the shoulder joint were defined using the DASH questionnaire for assessing the function of the upper limb and the Simple Shoulder Test (SST).

Results. The use of PRP made it possible to achieve pain relief regardless of the stage of the disease. Patients of the AC1 group had a progressive pain syndrome attenuation from 80 to 45 points according to the VAS scale during the first 7 days after the start of the treatment. On the contrary, patients of the AC2 group had a slight pain increase by the end of the 1st week, that was associated with growing physical activity of patients. In the group of patients treated with PN, all experienced pain regression after the first injection. 20% of patients had pain relief within 24-36 hours after the start of the treatment., Increased joint pain was registered in 2 (10%) patients, which passed spontaneously during the first day. Pain syndrome intensity decreased in patients with both stages of the disease. According to the VAS, it decreased from 90-80 to 65 points after the first injection within 4 days in the AC1 group. Patients of the AC2 group did not notice significant effect after the first injection. The second injection reduced the pain to 65-70 points.

Conclusion. The effectiveness of PN-based drugs had no statistically significant difference from that of PRP, but their effect was achieved faster.

Keywords: shoulder adhesive capsulitis, platelet-rich plasma, PRP shoulder range of motions, polynucleotides.

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Результаты лечения адгезивного капсулита плечевого сустава с применением обогащенной тромбоцитами плазмы и нуклеотидных препаратов: сравнительное исследование

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Актуальность. Внутрисуставные инъекции аутологичной обогащенной тромбоцитами плазмы (PRP — platelet rich plasma), которая является естественным биологическим стимулятором и воздействует на различные звенья регенеративного процесса, часто используются при лечении адгезивного капсулита. Другим направлением в использовании репаративного потенциала биополимеров стало применение полинуклеотидов (PN — polynucleotide), которые благодаря своему действию на фибробласты способны стимулировать процессы регенерации при адгезивном капсулите.

Целью данного исследования стала оценка клинической эффективности внутрисуставного применения аутологичной обогащенной тромбоцитами плазмы и препарата на основе полинуклеотида в комплексной терапии адгезивного капсулита плечевого сустава в зависимости от стадии заболевания.

Материал и методы. Выполнено проспективное когортное исследование, в которое было включено 42 пациента в возрасте от 47 до 60 лет с диагнозом «адгезивный капсулит». Длительность заболевания варьировала от 3 мес. до 5 лет. Пациенты были разделены на 2 группы в зависимости от стадии заболевания на момент обращения: 24 пациента с первой стадией заболевания (группа АК1) и 18 пациентов — со второй стадией (АК2). Обе группы были разделены на две подгруппы пациентов, в каждой из которой вводились PRP или PN. Результаты оценивались через 1 нед., 1 мес., 3 мес. после начала лечения. Оценку результатов купирования болевого синдрома проводили с применением визуально-аналоговой шкалы (ВАШ). Изменение качества жизни пациентов и функции плечевого сустава оценивали с помощью опросника для оценки функции верхней конечности DASH и упрощенной шкалы тестов плеча SST (Simple scale test).

Результаты. Применение PRP позволило добиться уменьшения болевого синдрома вне зависимости от стадии заболевания. В группе АК1 отмечалось прогрессивное снижение болевого синдрома по ВАШ с 80 до 45 баллов в течение первых 7 дней после начала лечения. У пациентов группы АК2, наоборот, отмечалось некоторое усиление боли к концу 1-й нед., что связано с нарастающей физической активностью больных. В группе пациентов, лечившихся с использованием PN, у всех отмечался регресс боли уже после первой инъекции. У 20% пациентов уменьшение боли наступало уже через 24–36 ч. после начала лечения. У 2 (10%) больных отмечалось усиление боли в суставе, которое прошло самостоятельно в течение первых суток. Болевой синдром уменьшался у пациентов с обеими стадиями заболевания. В группе АК1 болевой синдром по ВАШ снизился с 90–80 до 65 баллов после первой инъекции в течение 4 дней. У пациентов группы АК2 ощутимого эффекта после первой инъекции отмечено не было. Повторная инъекция снижала болевой синдром до 65–70 баллов.

Заключение. Препараты на основе PN показали свою эффективность, которая статистически значимо не отличалась от применения PRP, однако эффект достигался быстрее.

Ключевые слова: адгезивный капсулит плечевого сустава, обогащенная тромбоцитами плазма, амплитуда движений в плечевом суставе, PRP, полинуклеотиды.

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BACKGROUND

Shoulder pain is rather frequent nowadays, most commonly in people of working age [1]. This problem might be considered multidisciplinary as the pathology has different causes that are not always connected with trauma. That fact presents difficulties in its diagnostics and treatment. Adhesive capsulitis (AC) is one of these pathologies that leads to chronic pain in the shoulder joint and periarticular tissues. Its clinical aspects include above all the pain syndrome of various intensity and severe limitations of the shoulder joint range of motions associated with capsule adhesion and fibrosis and subsequent disorders of bursal elasticity and extensibility [1, 2, 3]. Due to this the pain increases with abduction, the muscles are contracted, the motions are carried out together with the scapula. Chronic and severe pain syndrome not only limits the daily activities, but also affects the sleep and the rest adversely. As a result, the quality of life and the work capacity of patients with adhesive capsulitis get worse [4, 5].

Nowadays the patient's platelet rich plasma (PRP) is considered rather promising and safe method that has anti-inflammatory and regenerative effect [6, 7, 8]. Containing a lot different biologically active factors (clot formation products, thrombocyte growth factors, adhesive molecules and cytokines), it stimulates reparative and anabolic processes in damaged tissues and restores metabolic processes, intensifies tissue immunity, promotes cell metabolism, and tissue respiration as well as develops anti-inflammatory effect [9].

Recent researches indicated that polynucleotides (PN) affected the pain management of musculoskeletal system, especially tendons and ligaments. They are effective with rotator cuff tendinopathies, epicondylitis and plantar fasciitis [10, 11, 12]. PN is a compound of deoxyribonucleotide polymers of different length (from 50 to 2000 base pairs) and nucleosides derived from salmon milt. The PN structure represents low molecular weight species of deoxyribonucleic acid with purine and pyrimidine base monomers. Apart from relieving the pain caused by musculoskeletal disorders or injuries, it also enables regeneration of damaged tendons and ligaments [14, 15, 16]. However, there is still no agreement on optimal PRP therapy methods of treatment of this pathology, as well as there are very few reports concerning objective results of PN use in case of adhesive capsulitis [17, 18, 19]. We consider of great clinical interest the efficacy comparison of these two methods of treating patients with shoulder joint adhesive capsulitis on different disease stages.

Aim of study – to evaluate the clinical efficacy of intra-articular injections of autologous platelet rich plasma and PN-based drugs in shoulder joint adhesive capsulitis management depending on the stage of disease.

METHODS

Study design

The performed prospective cohort study included 42 patients aged 47 to 60 years with the diagnosis of adhesive capsulitis. Among them were 38 women (90.5 %) and 4 men (9.5%). Duration of disease varied from 3 months to 5 years.

The patients were divided into 2 groups depending on the stage of disease determined at the first visit using the Neviaser's method. The first stage is marked by acute inflammation and synovitis, the second is characterized by pain relief and shoulder joint contracture [20]. Thus, all patients were divided into 2 groups, 24 of them had the first stage of disease (AC1 group) and 18 had the second stage of disease (AC2 group). Each group was divided into 2 subgroups, in which either PRP or PN were administered respectively (Fig. 1).

Inclusion criteria:

– discontinuation of non-steroid anti-inflammatory drugs (NSAID) at least 10 days prior to injection therapy;

– clinical signs of the first or the second stage of adhesive capsulitis, confirmed by ultrasound (US) and MRI;

– no shoulder joint injuries in anamnesis;

– no radiographic signs of shoulder joint osteoarthritis and/or presence of cartilage flaps in the joint cavity.

Exclusion criteria:

– local corticosteroid injections;

– continuation of NSAIDs;

– additional physiotherapy treatment and alpha-adrenergic agonists therapy;

– presence of old tendon and ligament injuries of the shoulder joint.

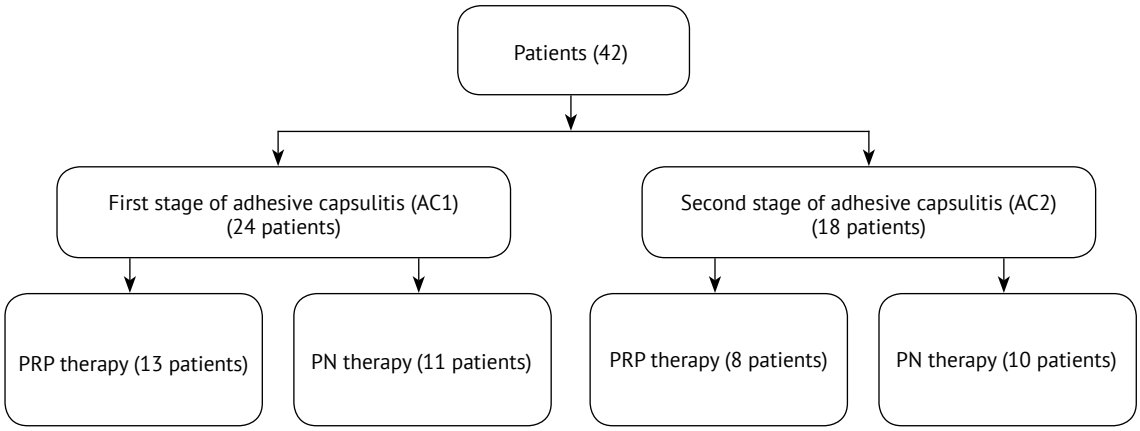

Рис. 1. Flowchart of the study

Before the start of the treatment all patients underwent standard X-ray (Siemens Multitom Rax scanner) and MRI (Hitachi Echelon Oval 1.5T scanner in T2-weighted fat-suppressed TSE PD SPAIR images) of the shoulder joint to evaluate the disease stage and severity for the following group allocation.

PRP extraction

Serum procurement and processing was performed using the unified RegenLab method (Certificate of Validation № FZN 2011/10570 dated 15.09.2011). Blue Regen BCT tubes (Rehegen Lab, Switzerland) with thixotropic separating gel without heparin were used.

Using the vacuum method, 8 ml of patient's blood were collected to a sterile tube. The tube was put into centrifuge right after the blood sampling. Centrifuge ride was carried out with the speed of 3100 rotations per minute over a period of 5 minutes. After centrifugation 4-5 ml of serum were obtained. Then the platelet rich plasma (with thrombocyte concentration of (343.28±89.37)×109/mm^3 was injected into the shoulder joint cavity via posterior approach without preliminary anesthesia under the US control. Injection protocol included 3 manipulations at an interval of 2 weeks.

Polynucleotides used in this research belong to class III medical devices (Certificate of Validation № RZN 2019/8994 dated 09.12.2019) and are sold in pharmacies under the trade name of Chronotron (Mastelli s.r.l., Italy).

Single injection contained 2 ml of a drug product with the following composition: 20±2 mg of polynucleotides, 8.0±0.8 mg of sodium chloride, 0.30±0.03 of sodium dihydrogen phosphate dihydrate, 1.50±0.15 of sodium hydrogen phosphate dodecahydrate and water to 1 ml. Injections were introduced into the shoulder joint cavity under the US navigation via posterior approach. One treatment course included 3 injections at an interval of 4-5 days for all patients of that group. Results were evaluated 1 week, 1 month and 3 months after the start of the treatment.

Results of the first part of this research (PRP use) were described in details in our previous publication [21].

Evaluation of results

Evaluation of pain syndrome relief was performed using the 100-point VAS scale, where 0 point meant pain absence and 100 points meant unsufferable pain.

Changes in life quality and shoulder joint functions were evaluated using the DASH questionnaire for assessing the function of the upper limb [2] and the Simple Shoulder Test (SST) [22].

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 22.0. Evaluation of distribution normality was carried out with the use of Shapiro-Wilk test.

Distribution of numeric variables obtained in this research did not differ from normal, so that parametric statistical methods were applied. Continuous quantity values with normal distribution are represented as M±SD, where M stands for sample mean, SD stands for standard deviation. Student's t-test was used to compare dependent samples in the light of their normal distribution. Qualitative features were described with relative (%) and absolute frequencies. The differences were considered statistically significant at the level of $p<0.05$.

Coefficient of variation was calculated to define the difference in shoulder joint range of motions at the one and the same period or at the time of research. The higher this coefficient was, the relatively greater was the spread and the lower was the uniformity of studied values.

The following formula was used:

$$V = \frac{\sigma}{x} \times 100,$$

where σ — mean root square deviation; x — mean of studied value.

RESULTS

Patient examination results before treatment

The following pathological changes were identified during the clinical examination: shoulder is visually elevated on that side, shoulder muscles are shortened, deltoid muscle is hypotrophied.

Acute joint and periarticular muscles pain was registered in active motions and moderate pain in passive ones. Maximum pain severity was registered in extreme points of motions. According to patients, the pain persisted at night time and increased in lateral position leaning on the injured joint.

Range of active and passive motions in the joint was limited: abduction — 61±4°, flexion — 85±5° or at a deficit of 15–20°; external rotation — 32±3°, internal rotation — 37±4°.

There was a diffuse tissue swelling around the shoulder joint on palpation, as well as extended pain in the capsule area, local painful tension (trigger point) in supraspinatus, infraspinatus, trapezius and subscapularis muscles.

X-rays revealed no osteo-traumatic changes and signs of arthrosis or loose bodies. On MRI the capsule was thickened in the area of axillary pouch to 4.4±0.2 and swollen by 88±3%.

The AC2 patients showed deltoid and supraspinatus muscle hypotrophy under clinical examination. They had no pain at rest, but the pain appeared in case of full-range active and passive motions. Range of motions was severely limited: abduction — 40±7°, flexion — 50±5°, extension — 10±5°, external rotation — 20±3°, internal rotation — 5±3°. Diffuse pain in the joint appeared on palpation.

Shoulder joint MRI revealed 3.5±0.3 mm capsule thickness in the area of axillary pouch, joint capsule swelling in the same area was by 76–83%.

PRP treatment results

PRP use enabled to decrease the pain syndrome regardless of the stage of disease. AC1 patients noticed pain relief after the first injection decreasing by 20 points by the end of the treatment according to the VAS. On the contrary, AC2 patients noticed some pain increase by the end of the first week of treatment due to growing physical activity. They registered pain relief (by 40 points according to the VAS) after the second injection 14 days after the start of the treatment (Fig. 2).

By the end of the first month all patients had significant increase in range of motions regardless of the stage of disease. This increase was higher in patients with earlier disease stage, as far as the pain relief effect was more accentuated and the tissue changes were less discernible (Fig. 3).

Improvement of range of motions in shoulder joint persisted over a period of 3 months.

Being the most affected adhesive capsulitis dynamic parameters, shoulder external rotation and abduction improved significantly nearly by fifty percent, that may provide evidence of medication efficacy.

Patients of both groups had statistically significant function increase according to the scales applied comparing with that in the beginning of the treatment.

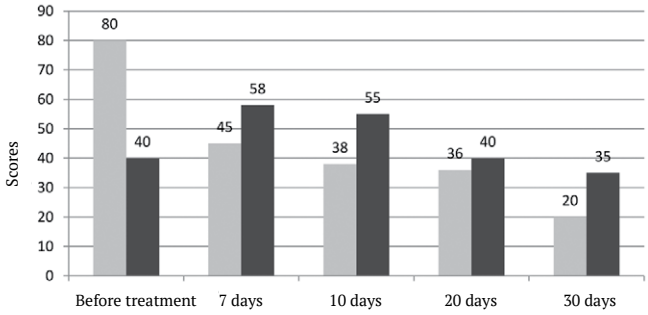

Fig. 2. The intensity of pain syndrome according to VAS during PRP therapy

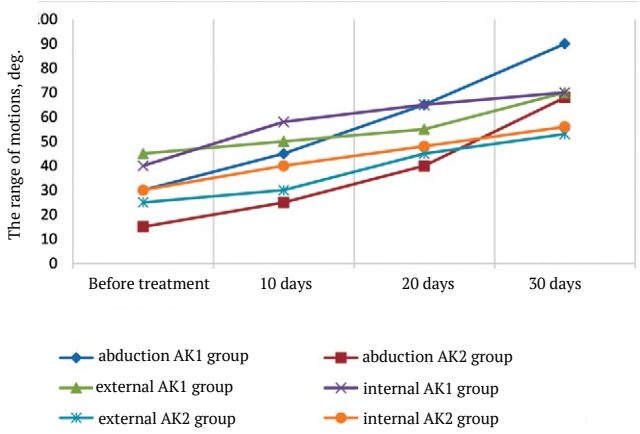

Fig. 3. The range of motions in the shoulder after PRP therapy

Medical effect grew over a period of 3 months of examination. This may indicate that this treatment method has stable and not temporary effect and is focused on pathogenetic aspects of disease. Experiencing pain relief, the patients could mobilize shoulder joint more actively that led to range of motions increase.

PN treatment results

All patients had pain regress after the first PN injection. 20% of patients experienced pain decrease 24-36 hours after the start of the treatment. Two patients (10%) noticed joint pain increase that spontaneously passed within 24 hours. Pain syndrome decreased in patients with both disease stages. According to the VAS, pain intensity in AC1 group diminished from 80-90 points to 65 points within 4 days after the first injection. AC2 patients experienced no significant effect after the first injection. The second injection decreased pain syndrome level to 65–70 points. The third injection was given 15-21 days after the start of the treatment; 3-4 days later the patients noticed pain relief to 20-30 points (Fig. 4).

Four patients of the AC1 group increased the range of motions by more than 50% right after the first injection. The second and the third ones been introduced, the range of motions grew insignificantly. Ten patients (91%) of the AC1 group completely recovered active range of motions by the end of the treatment, 1 patient preserved 15° internal rotation deficit. Range of motions recovery in the AC2 group was harder. Coefficient of variation for this group of patients equaled 47%, that indicates great variability in population. Shoulder joint range of motions increased on average by 12% after the first injection, while the linear progression was noticed after

the second and the third injections. At the end of the treatment 7 patients (70%) were able to recover active range of motions completely. Two patients (20%) preserved near 10° abduction deficit and 1 patient (10%) suffered external rotation that was limited to 20°.

In most cases the first PN injection had no significant clinical effect, that resulted in slight SST increase (just 2,5 for patients with the second stage of adhesive capsulitis). However, it increased sharply after the second injection (more than twofold) and remained unchanged after the third injection (Table 1).

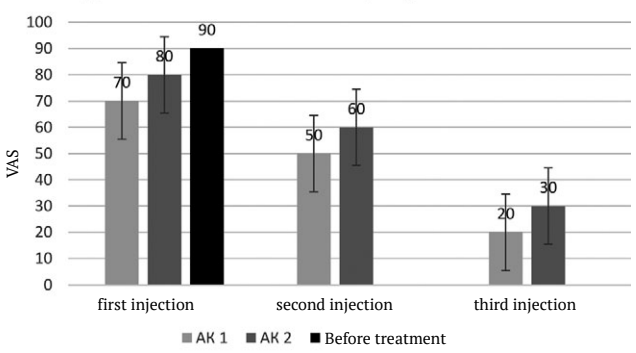

Fig. 4. Dynamics of pain changes in your after administration of a polynucleotide-based drug

Patients that underwent PN therapy as well as PRP treated patients had statistically significant improvements according to applied shoulder joint functional scales in comparison with pre-treatment levels (Table 2).

Being slight after the first injection, further improvements appeared rather dramatic after re-injections. According to the SST scale, significant shoulder function improvement was noticed after the second injection. We also observed upper limb functional improvement according to the DASH scale, that is demonstrated in the Table 3.

Table 1

Dependence of PN treatment results on number of injections

Group of patients	1st injection	2nd injection	3rd injection
SST			
AC1	4.3	6.7	9.8
AC2	2.5	6.6	8.8
DASH			
AC1	38	24	9
AC2	39	28	12

Table 2

Comparison of functional outcoms after PRP and PN treatment (M±m)

Period	Flexion		Extension		Abduction		External rotation		Internal rotation	
	PN	PRP	PN	PRP	PN	PRP	PN	PRP	PN	PRP
Before treatment	110.5±5.9	112.9±7.1	25.1±4.1	24.8±8.7	62.2±5.9	60.0±7.1	32.1±6.1	33.2±3.6	21.7±5.1	23.6±3.1
In 1 month	158.7±8.7	161.2±4.9	39.8±6.2	40.3±7.9	144.3±10.1	141.2±12.3	50.8±13.2	52.0±12.8	38.9±7.1	40.5±9.8
In 3 months	169.1±6.2	170.9±11.1	46.1±9.9	44.7±9.9	170.1±14.7	166.2±13.5	64.6±11.9	62.7±12.1	55.1±6.4	58.5±7.7

$p<0.05$.

Table 3

Comparative assessment of treatment (M±m)

Scale	Before treatment		In 1 month		In 3 months	
	PN	PRP	PN	PRP	PN	PRP
SST	2.7±0.8	2.8±1.1	6.4±2.7	6.5±1.1	9.1±2.3	9.2±1.4
DASH	42.2±5.8	43.1±8.1	22.5±3.1	21.0±2.4	9.9±3.1	10.7±2.7

$p<0.05$.

By the end of the treatment PN-based drugs were comparable to PRP in efficacy that reflected in almost complete upper limb functional recovery.

DISCUSSION

The main aim of adhesive capsulitis treatment is to reverse inflammatory process in the joint capsule, decrease pain syndrome and improve function of muscular strength and shoulder joint range of motions that all in all enhances the quality of life. [17, 18, 23]. In most cases (up to 90%) conservative therapy is efficiently applied all over the world to achieve that aim. If it has no effect, the surgical treatment is carried out [20, 24]. Shoulder pain treatment is usually combined and indispensably includes both pharmaceutical (NSAID, glucocorticoids) and non-pharmaceutical methods (passive mechanotherapy, kinesiotaping, physical therapy) [1, 3, 16, 25, 26]. Other authors prefer using anaesthetic blocks before passive joint mobilization [27].

Nowadays the main classification criterion of different PRP medications is their thrombocyte and leucocyte concentration. However, this problem remains under discussion, as there is no precise information on the correlation between PRP thrombocyte concentration and obtained results [28, 29, 30]. That is due to the fact that growth factors may affect cell receptors in different ways. Low PRP thrombocyte concentration has no stimulant effect, while in case of concentration increase to 1000×109/l and more the regeneration may on the contrary inhibit [25, 31]. The second criterion is the leucocyte concentration in the medication obtained. High leucocyte count increases the number of proinflammatory mediators that stimulate inflammation. However, some fractions including lymphocytes and monocytes have positive effect on growth factors due to their interaction with many bioactive molecules. Patients in our study were injected with PRP with thrombocyte concentration of (343.28±89.37)×109/ml^3 and partially reduced leucocytes. This blood cell count may probably be optimal, as we observed no inflammation after injections. Choosing PRP, we should take into account that high concentration of externally introduced coagulation factors may lead to local thrombosis [18]. That is why we should use PRP with extra care in elderly patients.

Many clinical studies showed that PN-based drugs are leveraged to manage multiple diseases associated with inflammation such as bursitis, fasciitis, mucositis and tendinopathy [14, 15, 24].

Therapeutic effect of PN injections into subacromial bursa under the US control for chronic supraspinal tendinopathy treatment was acknowledged [10]. Moreover, PN-based drugs administration contributed to pain decrease in case of rotator cuff tendinopathy [11]. Assessment of treatment efficiency in both publications was based on evaluation of shoulder pain index according to the VAS. Thirty-two patients with chronic rotator cuff disease (aged from 30 to 75 years) had significant shoulder pain decrease due to weekly PN injections (max 5 times). Thus, our study do follow the world practice in the application of such medications regarding to nosology and evaluation methods of therapeutical effect.

Comparing the efficiency of both treatment methods (PRP and PN), it is worth mentioning that they are truly alike in their mechanism of action as they both affect the inflammation process locally at the cellular level. However, L. Hwang's et al. recent study results showed deeper PN's mechanism of action. Authors noticed that PN-based drugs inhibited inflammatory response by stimulating A2AR adenosine receptors under inflammation and thereby suppressing IL-1β and IL-6 inflammatory cytokines expression. Moreover, 100 mcg/ml of PN inhibited secretion of nitrogen oxide (NO) and IL-12 and TNF-α proinflammatory cytokines, as well as stimulated IL-10 anti-inflammatory cytokine secretion [13].

Results of our study elicited different PRP and PN levels of impact. Longer-term period was needed to reach positive dynamics in case of PRP treatment (3 injections at an interval of 2 weeks), while PN-based drugs in most cases showed significant effect right after the second injection with the interval of 4-5 days between them. Such treatment regimens limit the reliability of methods' comparison but still demonstrate faster therapeutic effect of PN-based drugs. As for the persistence of therapeutic efficacy and final outcomes, both methods turned out to be similar. It is worth noticing that patients especially with the second stage of adhesive capsulitis experienced insignificant improvement after the first PN injection, that sharply grew after the last injections.

This fact corresponds to L. Hwang's et al. experimental study results. Apparently PN-based drugs need some time to produce anti-inflammatory effect by blocking inflammatory mediators [13]. That is why we consider reasonable to administer more than 3 injections. What is more, no cases of side effects were registered. One of the most evident advantages of PN-based drugs is their ease of use, as the medication is contained in a sterile syringe and is ready to be injected. PRP medications must be prepared in aseptic conditions and are more traumatic due to necessity of additional patient's vein sampling.

CONCLUSION

Local administration of PRP and PN-based drugs in patients with the first and the second stage of adhesive capsulitis decreases the pain syndrome and affects indirectly the range of motions restoration. PRP and PN therapy are comparable in their efficacy, but the first one requires longer treatment especially in patients with the second stage of adhesive capsulitis.

DISCLAIMERS

Author contribution

Lychagin A.V. — study concept and design.

Bogatov V.B. — evaluation and interpretation of the data, text writting and editing.

Tselishcheva E.Yu. — collection and processing of data.

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