yFFP Joint Injections as a Promising Treatment for Osteoarthritis

Abstract

Rates of osteoarthritis are rapidly increasing in recent years, and without innovative treatments that can repair damage at the source, patients are left disabled and without any hope for long-term relief. Though lifestyle changes such as exercise and weight loss can help to improve symptoms, these treatment modalities do not eliminate the presence of the disease. Commonly used treatments such as intra-articular corticosteroid injections have recently shown the possibility to result in permanent joint damage, such as cartilage volume loss. Similarly, surgery remains the last resort for intervention, due to its invasiveness, high cost, and demanding healing process that still contains many risks for complications and possible chronic pain following the procedure. Therefore, the demand for effective and long-lasting treatment in OA continues to rise. The emerging research in using biological substances to help heal the body shows promising results for these patients, specifically in the form of young fresh frozen plasma (yFFP). Young plasma contains a superior profile of rejuvenating factors and numerous biomarkers, compared to aged plasma, which presents it as a possible ideal treatment to repair joint damage in OA with a very low possibility of adverse reactions. After learning of this research, Dr. Stanley Jones, an orthopedic spine surgeon who now runs a regenerative medicine clinic in Houston, TX, decided to implement the use of yFFP joint injections for patients with osteoarthritis. Observational data comprising a total of 41 joints treated, from 27 patients, revealed that 85% of joints experienced improvement in joint function and status after receiving yFFP injections. Additionally, no patients experienced a decline in joint status from baseline or any adverse effects, further corroborating yFFP as a potentially very low-risk treatment. The evidence of such promising results seen in the clinic use of yFFP proves the need for additional investigations in order to support these findings.

Introduction

When it comes to conditions that can severely impact one's functionality, arthritis remains a leading cause of disability around the globe [1]. Osteoarthritis (OA), a chronic condition characterized by joint degeneration, has seen a worldwide increase of 132% in total cases from 1990 to 2020 [2]. The increasing prevalence rates of osteoarthritis accompanied by its large impact on mobility demonstrates the immense need for treatment in these patients. Especially due to its high prevalence in older adults, with about 73% of osteoarthritis patients being older than 55 years old [3], osteoarthritis may be an optimal target for treatment with young fresh frozen plasma.

History of blood transfusions

Ever since the discovery of blood circulation by William Harvey in 1628, blood transfusions have been a major focus in medical research and practice for the purpose of surgery, disease, and bleeding disorders [4]. The documented use of blood transfusions goes

back several hundred years, where Professor Richard Lower performed the first successful blood transfusion in dogs in the year 1665 [5]. Since then, the use of blood transfusions in medicine has increased tremendously and with great success, mainly by preventing serious injuries or death caused by a large amount of blood loss [4]. In more recent years, though, transfusions utilizing specific components of blood have developed, as well. The first proposed usage of blood plasma in medicine occurred in March 1918, where Gordon R. Ward wrote in the British Medical Journal about using blood plasma as a substitution for whole blood and for transfusion purposes [6]. In 1960, A. Solomon and J. L. Fahey reported the first known therapeutic use of plasmapheresis, where whole blood is separated into plasma, red blood cells, and white blood cells [5]. Though these techniques were developed, it was not until the early 1980s that the era of transfusion medicine really began to flourish. Since then, blood plasma has been utilized for numerous different diseases and conditions, with its general safety and efficacy proven time and time again.

Why yFFP could be a promising treatment

The use of young fresh frozen plasma may indeed be the treatment option needed in this time. Young fresh frozen plasma (yFFP) is a novel new treatment developed by Spectrum Plasma, a specialty blood bank with full accreditation from AABB (Association for the Advancement of Blood and Biotherapies) and registered with the FDA [7]. Though blood plasma is primarily used to replace certain clotting factors and blood volume in the instance of trauma or disease, plasma naturally contains immense amounts of beneficial factors and proteins that make it an ideal candidate for medicinal treatment. As the most versatile component of human blood, plasma was found to contain 1.84 billion exosomes per mL, over 10,500 individual proteins, 5,000 peptides, 45 cytokines, and at least 50 sex specific hormones, minerals, and enzymes [8,9,10,11,12,13]. With such a rich and diverse composition, human plasma possesses the ability to possibly aid in numerous different ailments and conditions in the human body.

yFFP is a specific, trademarked therapy in which blood plasma is obtained from individuals aged 18 to 25 years old, using apheresis, and then immediately frozen to -80 ° Celsius [14]. This plasma is not exposed to any chemical treatments or filtration and remains frozen at -80 ° C before it is released for sale. In typical blood banks, whole blood is first collected before being divided into components and frozen at only -30° C, where it is then chemically treated and filtered [14]. The delayed freezing along with both filtration and chemical treatment can result in up to a 58% deterioration in proteins and essential factors when compared with yFFP protocols [14]. Therefore, the freezing protocol used for yFFP helps to preserve the beneficial components of plasma significantly more than traditional protocols used at other blood banks.

Not only does yFFP offer better preservation techniques, but the use of plasma obtained from young individuals in yFFP provides a better plasma component profile and increased beneficial effects compared to plasma obtained from older individuals. A recently published study looking at cell proliferation assay and inflammatory protein content show significant differences between plasma from old and young subjects [15]. The researchers in this study reported a higher concentration of inflammation-related proteins present in plasma from older individuals, along with a significant decrease in cell proliferation [15]. Notable proteins that were significantly elevated in the old plasma compared to young plasma include CRP (C-reactive protein) and Cystatin-C. CRP is already established as a known

biomarker of inflammation, but it also may increase with age even without the presence of disease. When comparing the levels of pro-inflammatory cytokines to people under the age of 65, researchers found that significant increases in CRP and other pro-inflammatory cytokines existed even in healthy individuals over the age of 65 [16], suggesting a possible role of CRP on the aging process. Cystatin-C sees a similar increase in response to aging and inflammatory disease [17,18], and recent research implies a relationship exists between Cystatin-C and osteoarthritis. Reports have shown that Cystatin-C levels are elevated in older individuals and individuals with osteoarthritis [17,18]. Cystatin-C also increases non-linearly with age [18], and is associated with unsuccessful aging, defined as aging with an increase in physical or cognitive impairment and the development of life-threatening chronic disease [19]. Interestingly, Cystatin-C was also found to interfere with signaling properties of other molecules, including TGF-β [20]. TGF-β, Transforming Growth Factor Beta, also plays a role in OA. In normal synovial joints, active TGF-β is only present in response to joint loading for a short period of time [21]. In OA joints, however, active TGF-β is present permanently and in high levels which leads to disrupted TGF-β signaling in the joint and alters its interaction with chondrocytes [21]. Similar to Cystatin-C, active TGF-β levels also increase with age [22]. Though the interaction between active TGF-β and Cystatin-C is not fully understood, both biomarkers increase with age and in OA joints. Therefore, the reduction of Cystatin-C levels in response to yFFP provides an example as to why joints would improve after yFFP treatment.

Outside of these recent findings, the beneficial effects of young blood on animal models have been recorded for about the past 20 years. Based upon earlier results reporting the possible benefits of young blood, one recent study using heterochronic parabiosis in mice observed new gene sets and the reversing of established aging patterns in response to the exposure of young blood [23]. Consequently, the infusion of aged blood led to the acceleration of normal aging changes across the entire organism [23]. The organism-wide changes in response to younger, whole blood indicate that at least some markers and factors associated with aging are contained in one's blood, likely being their plasma.

In fact, numerous studies conducted within the last few years show very similar anti-aging and rejuvenating effects when using young plasma in older animals. The infusion of young plasma into older animals, mainly rats and mice, show incredible results such as inducing a protective effect on intestinal tissues, a significant decrease in the expression of key inflammatory mediators, and a biomolecular profile similar to their young counterparts in aged rats [24]. Young plasma injected into old female rats revealed a rejuvenated blood DNA methylation profile, extended mean lifespan, and healthier physical appearance [25]. A trial utilizing the transfusion of young plasma into old rats also found significantly increased levels of global DNA methylation in the old rats, while infusion of old plasma into the young rats led to a decrease in global DNA methylation levels [25]. These differences indicate a marked difference in young compared to old plasma, and hint at the possible benefits of using young plasma to improve numerous different diseases and conditions, along with helping to reverse or repair damage induced by aging. Particularly, young plasma could serve as an innovative treatment for patients with osteoarthritis, further supported by the emerging evidence from using platelet-rich plasma in this population. Likewise, IV infusions of young plasma have shown to decrease age progression, and it has proven to be very beneficial in chronic disease and anti-aging.

Plasma vs PRP

In recent years, the use of blood plasma usually revolves around isolating certain factors in plasma before reintroducing it back into the body through infusions or injections. Specifically, PRP, or platelet-rich plasma, has gained significant popularity over the last 15 years in a variety of circumstances [26]. PRP is obtained by centrifuging the patient's own blood plasma to produce a concentrated amount high in platelets [27]. The basic theory behind isolating these platelets is that they can potentially improve healing due to the cytokines, growth factors, and bioactive factors found in platelet granules [27]. Though many studies report great benefits, the results are ultimately inconclusive due the conflicting results of studies using it for different purposes. However, since PRP uses an individual's own plasma, results may vary between individuals due to the individualized makeup of one's own plasma [28]. In other words, not every person has the same amount or quality of platelets within their own plasma, so they may not possibly benefit from PRP as much as another person. Furthermore, the effect of age on PRP's healing and restorative properties has shown to be quite substantial. A comparative study looking at the effect of PRP in mice found that PRP obtained from young adults significantly improved wound healing in mice compared to PRP obtained from older adults [29]. Not only were platelet concentrations significantly higher, but levels of platelet-derived growth factor and vascular endothelial growth factor were also much higher in the young adult PRP versus the older adult PRP [29]. These findings were also supported by another study using older (aged) adult PRP and younger adult PRP on osteoarthritic chondrocytes in vitro, along with the subsequent injection of each PRP into aged male mice with osteoarthritis. In vitro, researchers found that young, but not old, PRP led to restorative properties in osteoarthritic chondrocytes by producing a young and healthy chondrogenic profile [30]. Likewise, in vivo results showed that knees in mice treated with young PRP led to significantly better outcomes in osteoarthritis than knees in mice treated with aged PRP [30]. Factors such as OARSI (Osteoarthritis Research Society International) scores and cartilage surface roughness decreased in response to young PRP, whereas the aged PRP actually induced multiple chondrocyte lacunes and increased cartilage surface disruption [30]. The knees treated with aged PRP even experienced an increase in synovial membrane thickness not seen in knees treated with young PRP or saline, suggesting a possible increase in inflammation due to the injection of aged PRP [30]. This finding may also indicate that some components of plasma in older individuals may contribute to the onset or acceleration of disease, which could be the reason behind why conditions such as osteoarthritis are more likely to develop as one ages. Overall, these findings likely indicate that PRP obtained from individuals who are older is not as effective in osteoarthritis and may even be harmful compared to PRP obtained from younger individuals, revealing a possible negative correlation in the restorative and healing properties of PRP as individuals age.

Treatment alternatives

Especially due to the lack of treatment options available for these patients, the demand for a new treatment in osteoarthritis has never been greater. Surgery usually remains as the last option for these patients, due to the invasiveness of the procedure coupled with its intense recovery and variable success rate based on joint and damage type [31]. Moreover, recent investigations into the side effects of total joint arthroplasty report a striking 15-30% of patients experience chronic postoperative pain [32], making surgery a relatively risky

treatment option for patients with OA. Besides other options like over-the-counter pain relievers or physical therapy that help to limit the impact of OA, one of the most popular treatments is intra-articular corticosteroid (IAC) injections. Since their first use in the 1950s, IAC injections have become an increasingly popular treatment for people with osteoarthritis [33]. However, more recent research reveals the possible negative effects of this treatment might outweigh the positives. One drawback revolves around its incredibly short relief duration, with each injection's relief only lasting 2 to 4 weeks on average [33]. Another more important disadvantage, though, is the possible adverse events associated that could lead to permanent damage. Several published studies currently indicate a large portion of patients with osteoarthritis experience radiographic progression of the condition after IAC injections, with one in particular finding that these injections resulted in larger cartilage volume loss compared to placebos [33]. Although, current research makes it difficult to determine the exact possibility of permanent joint damage in response to IAC injections due to the limited quality and heterogeneity of most trials. Certainly, a recent large systematic review by Jüni and colleagues concluded that there were no differences between adverse events experienced between groups [34]. Though it might seem credible on surface level, this systematic review graded the quality of evidence as low with most trials having a high or unclear risk bias [34], implying the results lack reliability and validity. Without high quality evidence to support this conclusion, the potential for worsening of the condition along with its extremely short relief duration makes IAC injections a relatively poor treatment option for patients with osteoarthritis. Thus, it is imperative that these patients are offered another viable option for treatment, and the use of young fresh frozen plasma looks to be a promising alternative.

Methods

Due to the recent research in yFFP, Dr. Stanley Jones, orthopedic spine specialist who runs a regenerative health and wellness clinic in Houston, TX, has routinely performed yFFP injections into the joints of patients struggling with osteoarthritis. Dr. Jones evaluated each patient to determine whether yFFP injections would be an appropriate treatment. Among the patients treated with yFFP injections, a total of 27 patients responded to follow-up calls conducted by employees in Dr. Jones's clinic. Of these 27 patients, a total of 41 joint injections were performed on various joints including knees, hips, shoulders, ankles, wrists, and toes. Some patients only received injections into 1 joint while others received injections into multiple joints during one visit.

Before the procedure

Prior to receiving treatment, each patient was required to sign an informed consent form before providing a blood sample to determine blood type. Each blood type is matched by gender and A and B antigens along with Rh factor. Shortly before the scheduled injection date, the patient-matched yFFP was received in office and transferred to a temperature-controlled freezer. Patients were also given pre-treatment instructions. These instructions included a recommendation to avoid acidic foods one day before to one day after treatment for the purpose

of preventing an interaction known as citrate overload [35]. The instructions also stated that before the treatment is performed, each patient will be given an oral steroid and antihistamine medication to help alleviate any histamine release. Thus far, no significant adverse reactions have occurred in joint injections.

During procedure

When the procedure is performed, the patient lays on the examination bed in a position to expose their intended injection site. Dr. Jones then starts prepping the injection area by thoroughly scrubbing with an E-Z scrub sponge followed by a povidone-iodine prep pad. Dr. Jones continues by locating the exact source of pain and discomfort within the joint to use as a marker for where he will inject. To anesthetize the area, Dr. Jones and his nurse use ethyl chloride topical anesthetic spray to topically numb before injecting a syringe of 4 mL of Lidocaine, 1%, and 1 mL of sodium bicarbonate, 8.4%. As the area is now numbed, Dr. Jones inserts the syringe filled with yFFP and slowly injects the plasma into the joint space. Moments after the procedure is performed, Dr. Jones then manually and repetitively moves the injected joint in its intended planes of motion for the purpose of ensuring the plasma permeates throughout the entire joint space and demonstrating to the patient the joint's ability to perform regular motion.

After procedure

After the procedure is performed, patients are instructed to avoid any exercise that may stress the injected joint for at least 1 week after the procedure date. The only exercise permitted for patients during this time is walking. Immediately after the procedure, patients report feeling tightness and "fullness" within the joint, likely due to the increased amount of fluid introduced. These symptoms seem to dissipate within a few days and last no longer than one week. Beside these symptoms, not one patient has reported significant pain associated with the injection procedure.

Results

Depending on many individual factors such as joint location, severity, level of use, and others, the timeline for reported improvement varies between patients. Due to various levels of improvement experienced for varied amounts of time, the patients were split into 3 different outcome groups to best exemplify results. Long-term improvement outcomes were defined by significant improvement in a joint without reporting a subsequent recurrence of symptoms. Short-term improvement outcomes were defined as any period of improvement, mild or significant, within a joint that then experienced a recurrence of one or more symptoms. The six patients in this group reported joint improvement lasting anywhere between two and six months. No improvement outcomes were defined by a reported lack in any improvement in joint status following the procedure.

Improvement is noted to be significant from 3 to 12 months. Long-term data is not available yet due to the fact that this procedure is relatively new. No patient has had negative symptoms on a persistent basis. No infections have been reported. No patients had worsening of symptoms.

Since the data gathered from patients was an ongoing process, it is difficult to know exactly how long improvement had lasted or will last for each patient that did improve. For example, the oldest data obtained is from a patient who still has improvement 12 months after the procedure. This data exists alongside more recent data of patients who followed up from procedures occurring only 2 months prior to follow-up calls. Therefore, the two improvement outcome groups were classified by whether the joint did or did not sustain improvement without symptom recurrence to give a more realistic depiction of results.

In total, 27 patients were treated for a total of 41 joints. Out of the 41 joints, there were 23 knees, 8 shoulders, 4 hips, 3 ankles, 2 wrists, and 1 toe treated (*see Figure 1*). Patient and individual joint demographics are listed in Table 1 and Table 2.

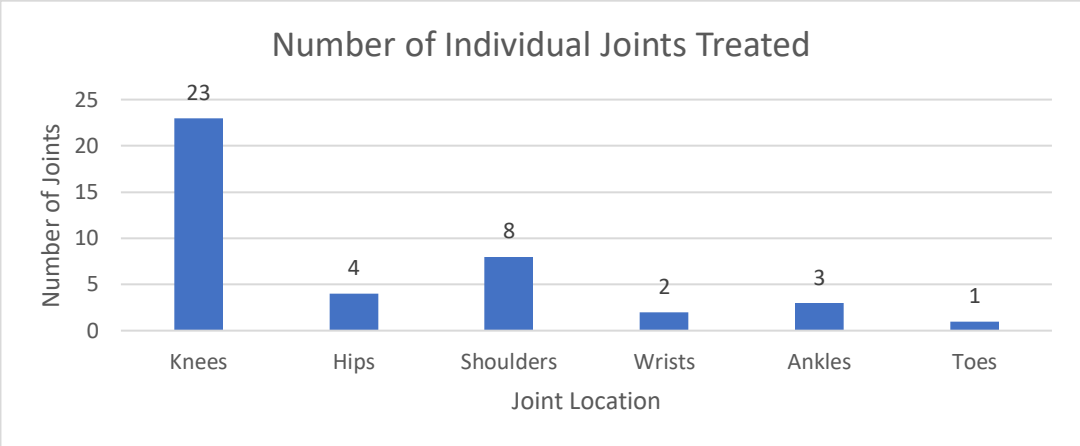

Figure 1. Classification of total joints treated per joint location.

Patient Demographics		
Variables	**Total Patients**	**Percent of Total**
Gender		
Male	8	30%
Female	19	70%
Age		
40-49	3	11%
50-59	8	30%
60-69	6	22%
70+	10	37%

Table 1. Age and gender demographics of patients. Number of patients and percentage of total patients given for each variable.

Individual Joint Demographics		
Variables	**Total Joints**	**Percent of Total**
Gender		
Male	12	29%
Female	29	71%
Age		
40-49	4	10%
50-59	12	29%
60-69	10	24%
70+	15	37%

Table 2. Age and gender demographics of individual joints. Number of joints and percentage of total joints given for each variable.

Out of the total 27 patients treated, 23 experienced an improvement in joint status with only 4 having no improvement. Out of the total 41 joints treated, 35 had improvement and 6 had no improvement. Percentage of each joint outcome is displayed in Figure 2.

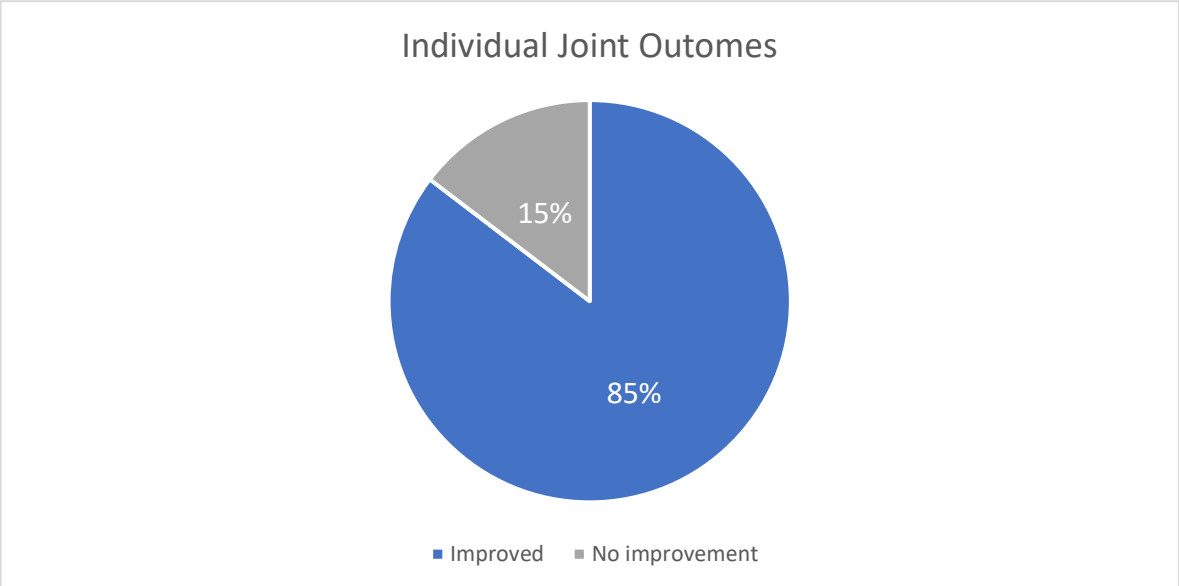

Figure 2. Pie chart illustrating the percent of total joints in each outcome group. 66% of all joints had improvement (n = 35). 15% of all joints had no improvement (n = 6).

More specifically, the results can be categorized by age and gender. More females and female joints were treated than males and male joints. However, males and male joints experienced more improvement than females and female joints, with all males reporting

improvement. Joint outcomes per gender are given in Figure 3. Joint locations treated per gender are given in Figure 4.

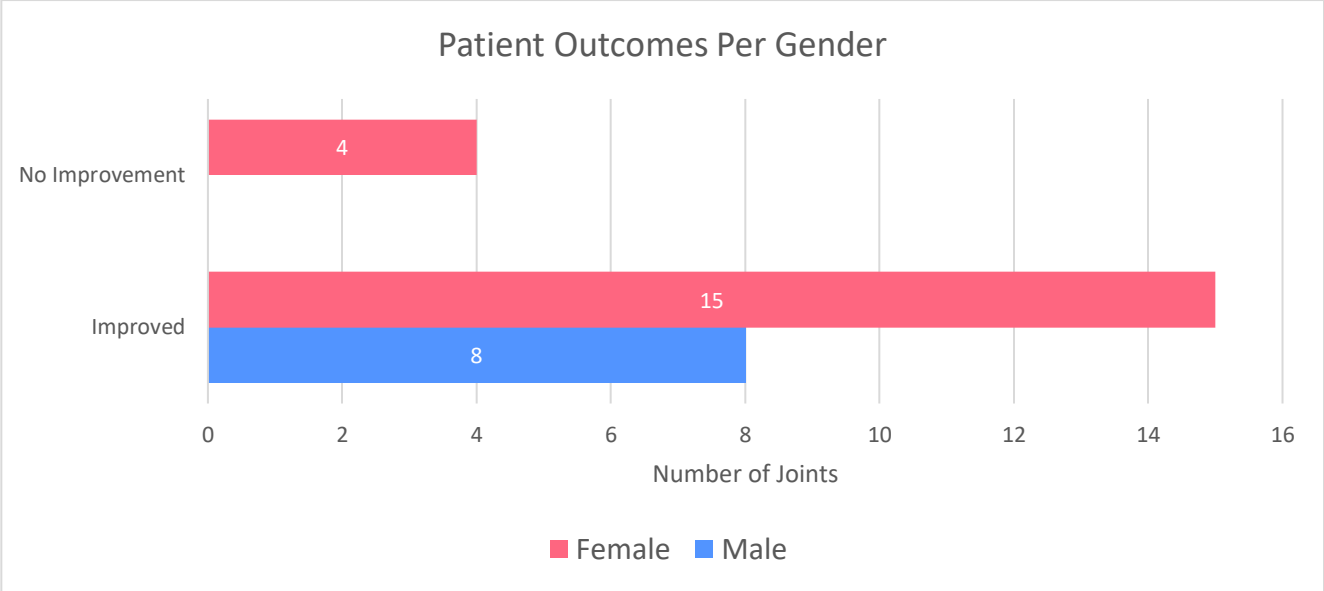

Figure 3. Bar graph showing the number of joints, separated by gender, in each outcome group. There were 19 female patients, with 29 female joints treated in total. Not as many males received treatment as females. Only 8 male patients received joint injections, with 12 male joints in total. The only joints that did not improve were female.

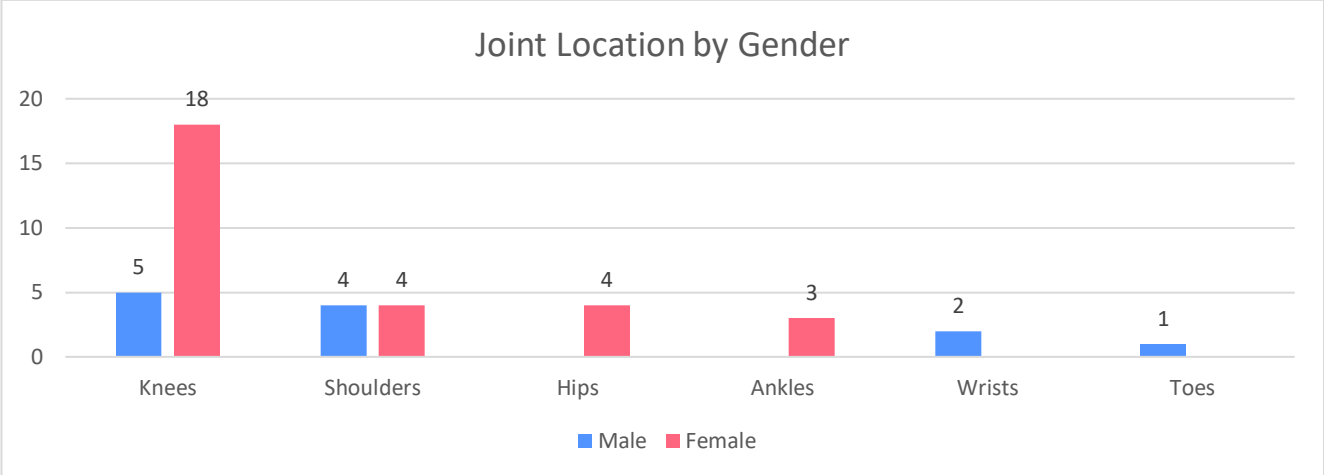

Figure 4. Bar graph with number of joints treated per gender, in each location. Female knees comprised the majority of all joints treated.

Within each gender, joint outcomes were also separated by joint location to examine whether the injected joint locations significantly correlated to certain outcomes. No significant correlation was observed in either gender. Joint outcomes per location for males is shown in Figure 5. Joint outcomes per location for females is shown in Figure 6

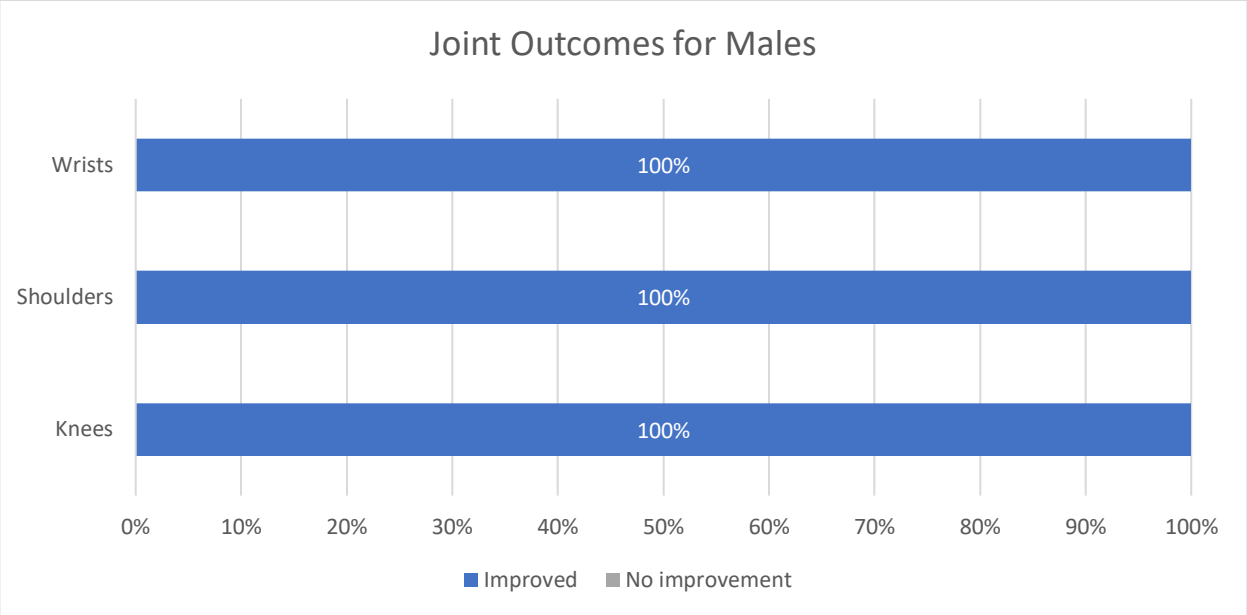

Figure 5. Male joint outcomes classified by percent of each outcome group in each joint location. There were 12 male joints total, with 5 knees, 4 shoulders, 2 wrists, and 1 toe treated. Only 2 shoulders improved short-term, out of all male joints, while all other joints improved long-term.

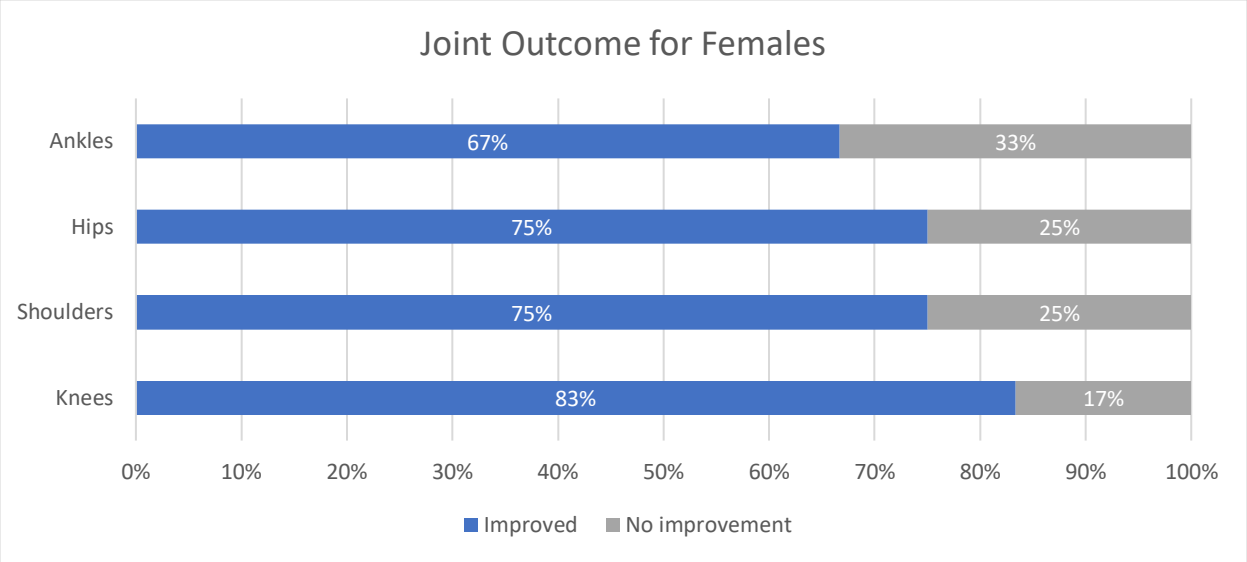

Figure 6. Female joint outcomes classified by percent of each outcome group in each joint location. There were 29 female joints total, with 18 knees, 4 shoulders, 4 hips, and 3 ankles treated. While some joints did not improve, most female joints responded positively to treatment. Female knees had the highest percent of improvement.

Joint outcomes can also be separated by the age groups of patients. All 27 patients were in between the ages of 42 and 80 at the time the procedure was performed. The joint outcomes were classified into 4 age groups, 40-49 years old, 50-59 years old, 60-69 years old, and 70 or above (*see Figure 7*). Total number of each joint outcome within each age range given in Figure 8. Overall, there was no significant difference or correlation in age response.

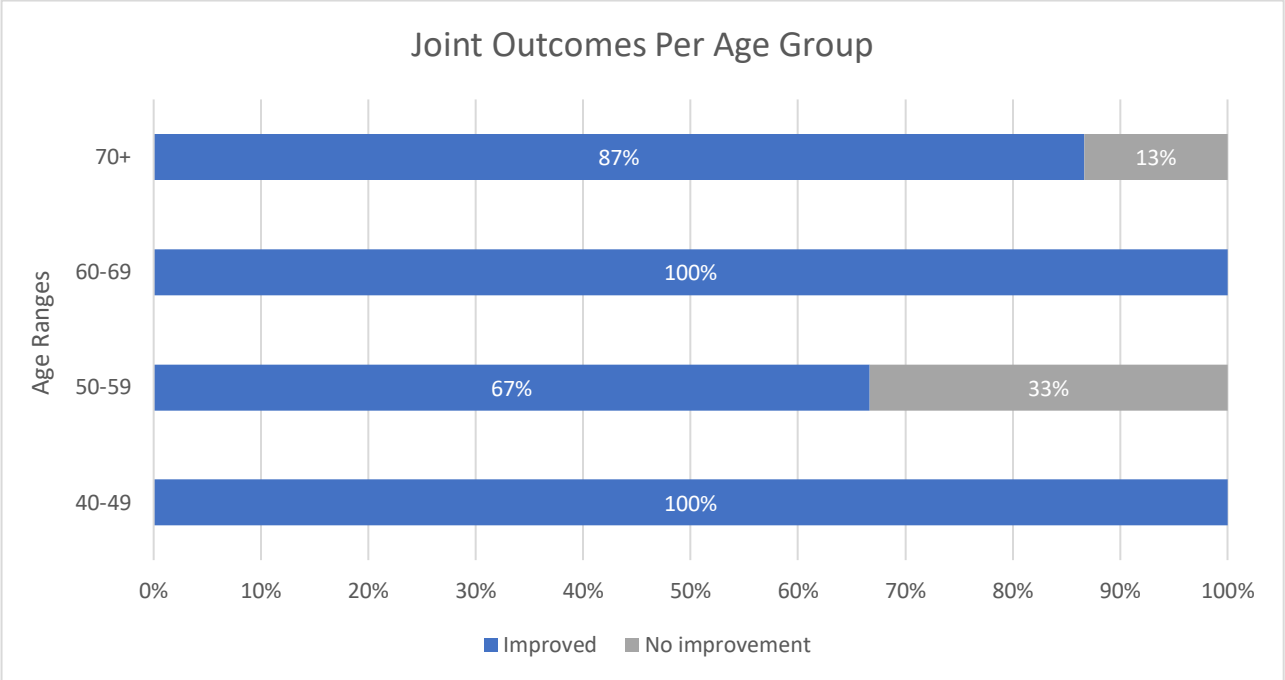

Figure 7. Bar graph illustrating percent of each outcome group within age ranges. All joints from patients in age groups 40-49 (n = 4) and 60-69 (n = 10) reported experiencing improvement, with 0 patients reporting no improvement. Joints in age group 50-59 (n = 12) reported 4 out of the 12 joints had no improvement. Joints in age group 70 and above reported 2 out of 15 joints had no improvement (n = 15).

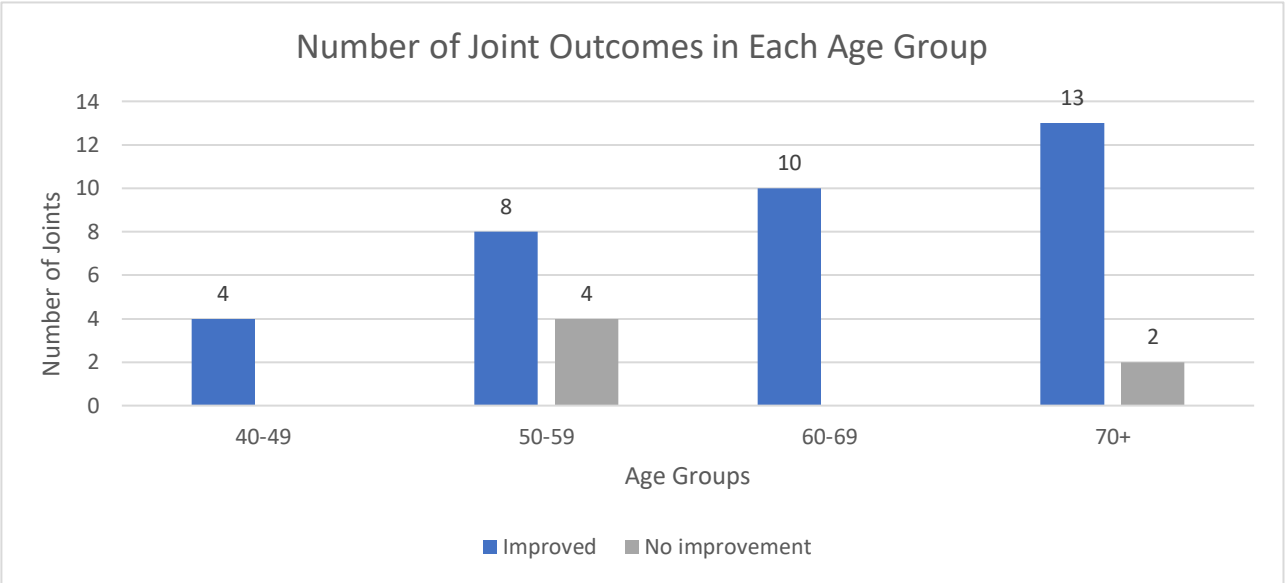

Figure 8. Bar graph showing the number of joint outcomes per age group.

The data for each outcome per joint location seems to significantly vary between each location, most likely due to the varied number of joints treated per location. Joint outcomes for knees, hips, shoulders, ankles, wrists, and toes are given in Figure 9.

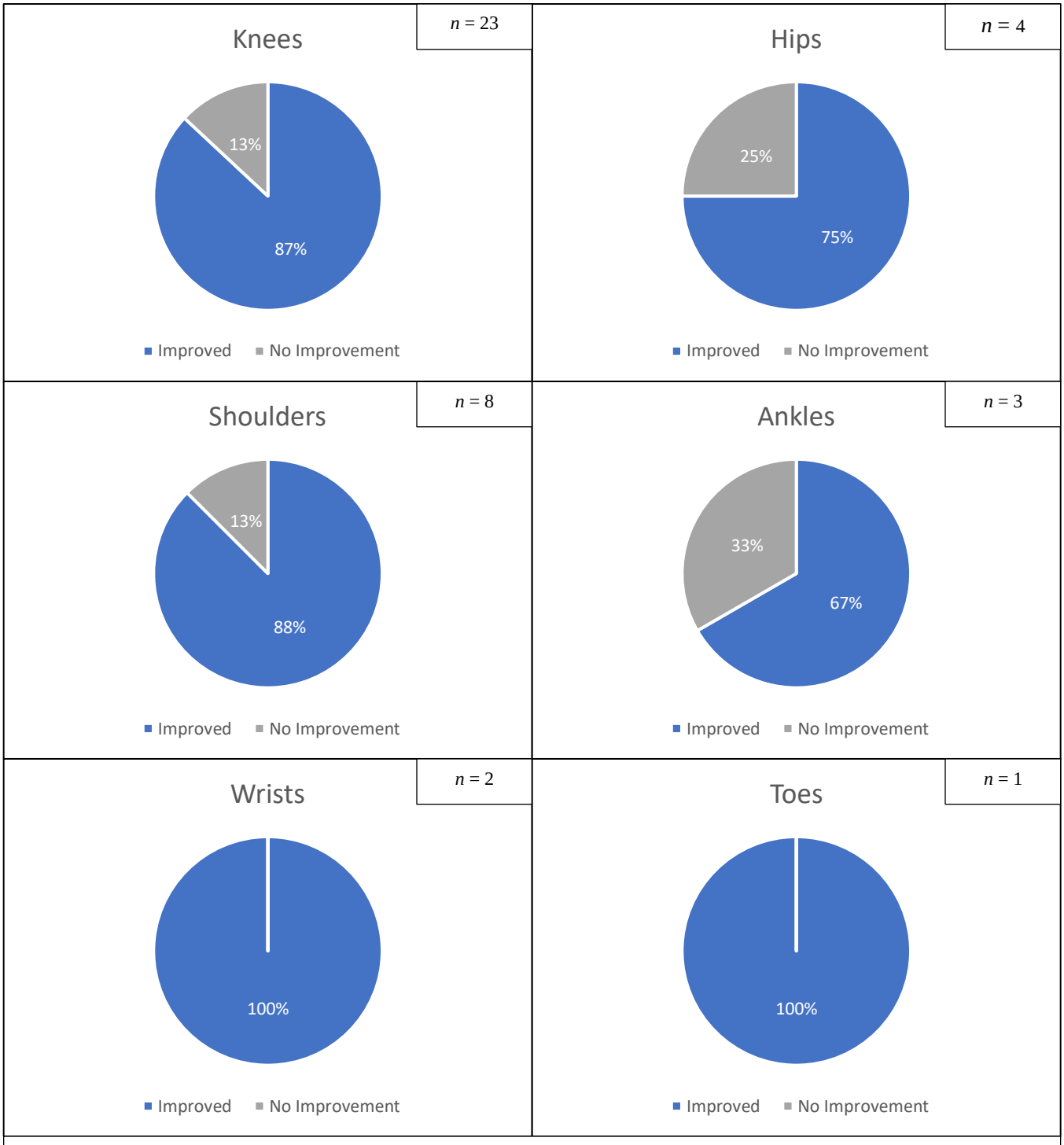

Figure 9. Pie charts illustrating percent of each outcome in each individual joint location. Knees and shoulders saw somewhat similar outcomes, with both resulting in 13% of joints that did not improve. Ankles saw the most varied response, with each ankle treated resulting in a different outcome. Both wrists and toes had improvement, although each location had a very small sample size.

Discussion

As the prevalence of OA continues to increase over time, the demand for effective and low-risk treatment surely follows. Existing as one of the leading causes for disability worldwide, OA patients not only suffer from the condition itself but also the limited function and mobility imposed upon them as a result of the disease. With the emerging evidence of potential permanent damage caused by IAC injections, patients living with OA are left with very few effective treatment options unless willing to undergo invasive and time-intensive surgery that cannot promise significant results. After evaluating the results of OA patients treated with yFFP in Dr. Jones's clinic, the use of young fresh frozen plasma shows promising results, possibly emerging as the optimal treatment method for these patients.

Overall, the data obtained from clinic patients who underwent yFFP joint injections seems to support the theory that yFFP injections could serve as a beneficial alternative therapy for patients with osteoarthritis. Out of the 41 joints treated, 85% resulted in some level of improvement, with only 15% of all joints reporting no improvement. More importantly, no significant adverse events associated with the injection were reported. Though the duration of relief seemed to vary, in some part due to the ongoing data collection process, the minimum relief duration reported by patients who improved was 2 months. Female patients comprised the majority of patients seen, likely due to the higher prevalence of osteoarthritis in women, comprising 60% of people living with OA [2]. Similarly, the majority of joint locations injected were knees, likely due to knees being the most frequently affected joint in OA [2].

Comparing results between each sex, it appears that male joints strongly respond to yFFP injections, while female joints were the only joints that did not experience improvement. The reason behind this difference could be that males are more likely to improve, however it is difficult to hypothesize due to the small sample size of total patients and males treated. A recent systematic review investigating the relationship between gender/sex and OA did find some differences between OA factors in men and women [36]; however, it is difficult to simply categorize these differences as one gender responding better than another. Therefore, the significant difference in improvement seen in men as a result to yFFP injections may not be reliable, as larger sample sizes and further investigation is needed.

Response rates between age groups also did not seem to significantly differ in response to yFFP. Again, the small sample size of patients treated leads to difficulty when interpreting these results. Still, there was no large difference or significance in relation to how patients of each age group responded to treatment. Although the only patients who did not see improvement were in the 50-59 age group category and 70 and above age group category, this does not imply any relationship between aging and the response to yFFP injections.

Likewise, there does not seem to be a strong correlation or relationship between joint outcome and joint location. The outcomes seen in shoulders and knees present more reliable data due to the increased number of those joint locations treated. The similarity between the percent of joints that did not improve in knees and shoulders, 13% each, suggests that data from these locations is more reliable, likely due to their larger sample sizes. Conversely, the data from hips, ankles, wrists, and toes are likely the least reliable as they only contain data from 4 joints or less. Still, the results show that each location had at least 67% improvement, with the highest being 87%, insinuating that the outcomes could be somewhat consistent across joint locations if a larger number of each joint location is treated.

Though most people in this cohort did experience improvement from the yFFP injections, 6 joints in 4 different patients did not see any improvement. However, the lack of improvement in these joints does not necessarily mean the injections were completely ineffective. Without conducting a proper trial to account for confounding variables, the reason for the lack of improvement in these joints cannot be definitively determined. It is likely possible that the lack of improvement in the 6 joints could be due to severely advanced disease progression or permanently damaged joint tissue. Nevertheless, additional research for yFFP in osteoarthritis is needed to determine the reliability and validity of these results.

Besides the overall favorable outcomes seen in response to yFFP injections, this new treatment also shows promise to surpass results of other OA treatment modalities. Even with 2 months of relief being the shortest duration reported, this duration already surpasses the average relief duration for IAC injections, which is 2 to 4 weeks [33]. The percentage of patients who improved with yFFP also surpasses most if not all estimations of improvement from IAC injections. A systematic review of IAC injections in the knee concluded a response rate of only 10% in patients given IAC injections compared to placebos [34]. IAC injections also pose a risk of permanent damage to the joint, whereas no adverse effects or decline in joint status were observed with yFFP injections. Though the risk of adverse events cannot be fully determined from the data presented in this article, as larger trials are needed, the safety of young plasma, other plasma-derived therapies, and blood transfusions has already been proven. In regard to fatalities, the FDA concluded that no fatalities occurred as a result of plasma transfusions [37,38]. More importantly, yFFP, specifically, was proven to be safe and well tolerated during a randomized control trial for patients with mild to moderate Alzheimer disease dementia [39]. While the trial only included Alzheimer patients, meaning the safety and tolerability has only been proven in this disease, blood and plasma transfusions have occurred for decades with relatively low risk. Even then, the risks associated with plasma transfusion have significantly decreased in recent years due to improved donor testing and preservation protocols [40]. Moreover, yFFP is obtained by the Spectrum Plasma blood bank, in which donors are required to undergo the most comprehensive testing before they are even allowed to donate. Unlike normal blood bank or source plasma procedures, yFFP screenings contain the largest list of tests and conditions that are contraindicated for plasma donation [14]. The comprehensive testing of each donor helps to further eliminate the risk of any adverse reactions in relation to yFFP treatment, making it a relatively low risk therapy.

The preliminary results of this observed cohort serve to support the theory that yFFP injections are an effective and low-risk option for OA treatment. While the need for further research is acknowledged, the patient responses seen in clinic prove the beneficial effect of yFFP injections for OA joints exists. The ability of yFFP therapy to improve biomarkers like Cystatin-C indicates the possible use of yFFP in the treatment of other conditions, especially in relation to aging. A clinical trial utilizing yFFP infusions for Parkinson's Disease found that the infusions significantly improved multiple outcome measures for patients compared to placebo [41]. With so many benefits in relation to aging and disease, yFFP therapy could become an optimal therapy that could effectively change the current approach to treatment, especially in patients with OA and autoimmune diseases.

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