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Cryopreserved Amniotic Membrane and Umbilical Cord Particulate with Manipulation 2 for Arthrofibrosis after Total Knee Arthroplasty: A Retrospective Study

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Abstract

Background: Arthrofibrosis develops in ~7-10% of patients who undergo total knee arthroplasty (TKA), leading to patient pain, loss of knee motion, and disability. In these cases, manipulation under anesthesia (MUA) is commonly performed to increase range of motion and reduce knee stiffness. **Aims and Objectives:** In this study, we evaluate the effectiveness of MUA with adjunctive cryopreserved amniotic membrane umbilical cord particulate matrix (AMUC) due to its known anti-scarring and anti-inflammatory properties. **Study Design:** Retrospective cohort study. **Setting:** Private practice. **Materials and Methods:** A retrospective study of patients that developed joint stiffness (≤ 90° flexion) 6-weeks after primary TKA and received MUA with adjunctive AMUC. The patient's range of knee motion, level of pain, and pain medication consumption were evaluated before and 4 weeks after MUA. **Results:** A total of 46 cases (45 patients) were included in the study. Prior to MUA, the average initial ROM was 80.2° ± 10.3° and patients experienced discomfort with an average pain score of 5.3 ± 1.8. In addition, a total of 25 (55.6%) patients were taking narcotic medication. Four weeks after MUA with AMUC, the average ROM was 93.8° ± 12.1° ($p < 0.01$), which represented a 16.9% increase. Patient's pain decreased 28.6% to 3.8 ± 2.0 ($p < 0.01$) and only eight (17.8%) patients were still taking narcotic medication for their pain. **Conclusions:** This data suggests MUA with adjunctive AMUC 29 may reduce pain and improve patient's ROM in patients suffering arthrofibrosis post-TKA. Further studies are warranted.

Keywords: Total Knee Arthroplasty, Manipulation under anesthesia, MUA, Amniotic tissue.

INTRODUCTION

Total knee arthroplasty (TKA) aims to repair degenerative knee joints in order to effectively relieve pain and restore normal function, natural alignment, and balance [1, 2]. Although it is considered a highly effective treatment option, TKA often leads to post-operative pain and inflammation that can result in stiffness in the joint. This then may lead to decreased mobility, inability to perform daily life activities, and reduced overall standard of living [1-3]. If not properly mitigated, these complications could lead to much more deleterious impediments down the road and work against the initial intention of the procedure.

Arthrofibrosis is the most common cause of post-TKA stiffness and is characterized by abnormal scarring of the joint that restricts normal range of motion (ROM) [4]. Arthrofibrosis develops in about 7-10% of patients who undergo TKA, leading to patient pain, loss of ROM, and disability [5,6]. Although the exact cause of arthrofibrosis is unknown, elevated inflammation has been implicated to lead to excessive fibroblast proliferation and sustain the arthrofibrotic response [7]. The primary method utilized to facilitate healing for these patients is the non-invasive procedure of manipulation under anesthesia (MUA) [2,8,9]. Patients who undergo MUA have a reasonable prognosis, however it has been observed that the procedure becomes less effective as time progresses between the time of surgery and MUA [1]. Patients who undergo MUA by the 12 week mark after TKA have shown to have better outcomes than those who undergo MUA later on, especially for those with very severe arthrofibrosis [10,11].

Cryopreserved amniotic membrane (AM) and umbilical cord (UC) tissues are fetal tissues that have been processed to retain the key biological and structural components of the innate tissue [12]. These tissue have been demonstrated to have both anti-scarring and anti inflammatory properties *in vitro* and *in vivo* which has led to their use in many clinical orthopedic procedures [13-17]. Due to their ability to reduce inflammation and prevent further scarring, we evaluated the adjunctive use of cryopreserved AMUC during MUA to improve post op ROM and reduce patient's discomfort.

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MATERIALS AND METHODS

Patients

After approval by the Institutional Review Board (Western IRB, Puyallup, WA), a retrospective review was performed on consecutive patients that developed arthrofibrosis (≤ 90° flexion) 6-weeks after primary TKA and received manipulation under anesthesia (MUA) with adjunctive AMUC. All patients underwent primary TKA by the same surgeon (S.B) between May 2015 through December 2016. Patients between 18 and 80 years old were eligible for the study. Exclusion criteria included patients without post-surgical outcome measurements and patients that underwent revision TKA.

All manipulations were performed under general anesthesia to the point of maximal muscle relaxation and where the ipsilateral hip was flexed to 90 degrees. The knee was then slowly flexed with the middle tibia held until audible separation of the adhesions was heard. The surgeon continued slow and gentle flexion until no audible and palpable adhesions occurred. All patients received adjunctive cryopreserved AMUC product (CLARIX® FLO, Amniox Medical Inc., Atlanta, GA) immediately following MUA. A total of 200 mg AMUC in saline was injected using a 25-gauge needle into the affected knee using ultrasound. Post-manipulation rehabilitation protocol for all patients was started the next day after the procedure under the supervision of a physiotherapist, who emphasized early fully weight-bearing, range of motion exercises. The study was conducted in accordance with the Declaration of Helsinki.

Data Collection and Statistical Analysis

Data was gathered from baseline (before MUA) and at 4 weeks post-MUA to include patient demographics, knee range of motion (ROM), level of pain, and pain medication consumption. For measurement of ROM, a goniometer 84 was used to measure the angle of extension and flexion with the patient lying in supine. Pain was subjectively assessed by the patient using a 11-point numerical pain rating scale (0 to 10), where 10 represented the most severe pain and 0 represented no pain. The occurrence of complications was also assessed by reviewing physical exams and post-operative assessments. Cases were also reviewed to determine if the patients received revision TKA during the post-operative period.

STATISTICAL ANALYSIS

Descriptive statistics were used to characterize the study endpoints and are reported as mean ± standard deviation. All data were recorded using an Excel spreadsheet (Microsoft Corporation, Redmond, Washington). Continuous outcome measures were evaluated using a standard t-test. A p value of less than 0.05 was considered statistically significant.

RESULTS

In this study, a total of 45 patients (15 male, 30 female) with 46 knees (26 left, 20 right) underwent MUA with AMUC (Table 1). The average age of the patients was 63.0 ± 11.6 years old and their ethnicities included African American (18/45), Caucasian (23/45), Hispanic (3/45), and unknown (1/45). Forty-two of the patients did not use nicotine products (including cigarettes, cigars, electronic cigarettes, gum, smokeless tobacco, pipe tobacco) whereas 3 patients were cigarette smokers.

Prior to MUA, the patient's average flexion and extension was 82.2° ± 9.8° and 2.0° ± 4.4°, respectively, for a total range of motion of 80.2°. A total of 19 patients were not using any assistive walking devices, 10 patients were using only a walking cane, 11 patients were using only a walker, 4 patients were using a walker and cane, and 1 patient was using crutches for assistive mobility. The patient's average pain score was 5.3 ± 1.8 and 25 (55.6%) patients were taking narcotics for their pain.

During the MUA procedure, the average intra-operative flexion was 105.4° ± 9.7° and the average extension was 1.1° ± 2.1°. Patients were then administered 200 mg of AMUC and prescribed pain medication for the immediate post-operative period.

Four weeks after the MUA, the patient's pain had decreased by 1.5 ± 1.7 ($p < 0.01$) and only 8 (17.8%) patients were taking narcotics for their pain (Table 2). The average flexion was 95.9° ± 11.4° and the average extension was 2.1° ± 3.6°, which represented a 16.9% increase in ROM ($p < 0.01$). Forty-one (89.1%) of the 46 cases achieved increased knee flexion following manipulation. Only five cases (10.9%) did not reach functional flexion of ≥ 90 degrees. The distribution of patients based on their change of flexion was: 117 15 cases with < 5° flexion, 10 cases with > 5 to 10° flexion, 7 cases with > 10 to < 20° flexion, and 15 cases with > 20° flexion. During this follow up period, two patients underwent TKA revision where one experienced peri prosthetic knee inflammation unrelated to the product that required antibiotics. Two other patients experienced flexion contracture (5° and 10°) one to two months after MUA.

Table 1: Patient Demographics

Characteristic	Value
No. of cases (patients)	46 (45)
Gender	
Male	15
Famale	30
Age (years)	63.0 ± 11.6
Operation Site	
Right	20
Left	26

Table 2: Outcome Measures

Characteristic	Pre-MUA	Intraop-MUA	4 Weeks Post-MUA
Flexion (deg)	82.2 ± 9.8	105.4 ± 9.7	95.9 ± 11.9*
Extension (deg)	2.0 ± 4.4	1.1 ± 2.1	2.1 ± 3.6
Pain	5.3 ± 1.8	N/A	3.8 ± 2.0*

* represents $p<0.05$ from baseline

DISCUSSION

Knee stiffness, reduced ROM, and increased pain are well recognized challenges after TKA. Knee stiffness can be a particularly debilitating condition which impacts day-to-day activities. It has been reported at least 83 degrees of flexion is needed to climb stairs, 90 degrees to descend stairs, at least 105 degrees to easily rise from a low chair, and 65 to 70 degrees for walking [18,19]. To treat patients with post-op stiffness or arthrofibrosis, MUA is commonly performed to increase the patient's ROM and this is further confirmed in this study. In addition, our results show for the first time MUA with AMUC significantly improves ROM and decreases pain post-operatively.

It remains unclear why stiffness develops after TKA, although the pathogenesis is considered multifaceted. Risk factors may include decreased pre-operative ROM, age, genetic predisposition, increased inflammation, previous knee surgery, Diabetes, and patient lack of compliance [3,7,20-22]. In addition, prolonged lack of knee motion leads to fibrosis, adhesions between tissues, and shortening of ROM. In this study, our results show 89.1% of patients achieved improvement of knee flexion following manipulation with AMUC, comparable to 90% previously reported [23]. Functional flexion of ≥ 90 degrees was achieved in 89.1% of patients which was greater than previously reported [24]. The average ROM was shown to increase by 14 degrees

which are also comparable to other studies [18,25-29] whom showed an average increase of 10 to 20 degrees in ROM at one week to 3 months post-MUA. Further long-term analysis is warranted as patients typically gain ROM between week 2 and week 6 [30] and on average have 30 degrees of flexion at 1 year (reviewed in 8, 31). However the patient's pre-MUA flexion in prior studies is typically 65 degrees (compared to 82 degrees in the current study) [8,31].

The adjunctive use of AMUC during the MUA procedure may increase the overall clinical benefit due to AMUC's known anti-inflammatory and anti-scarring actions [32]. Cryopreserved AMUC have been shown to induce apoptosis of activated neutrophils and macrophages, increase the expression of anti-inflammatory cytokines, and decrease the expression of pro-inflammatory cytokines [14,33]. In addition, it has been shown to decrease fibroblast proliferation and limit their differentiation to myofibroblasts through the downregulation of TGF-β signaling which is a known critical regulator of scar formation [14,33]. Hence the AMUC matrix may allow for resolution of inflammation and prevent further scar adhesions leading to better post-MUA outcomes.

Controlling post-operative inflammation and pain is an important issue. Increased pain prevents knee flexion and leads to further adhesions. In addition, proper pain management has received increased attention recently due to the opioid epidemic and opioid-related adverse events [34]. In particular, orthopedic surgeons are the third highest prescribers of opioid prescriptions which puts these patients at an increased risk for chronic opioid use and abuse [35]. Our study demonstrated significant improvements in post-operative pain scores and reduced opioid consumption after MUA with AMUC. More specifically, 25 (55.6%) patients were taking narcotics before MUA and only 8 (17.8%) patients were still taking them 4 weeks afterwards. Therefore, these data suggest the potential to facilitate an opioid-sparing post-operative period and potential to reduce healthcare costs.

We acknowledge there are limitations of the current study including being a retrospective design, lack of control group, and use of a limited sample size. However, all MUAs were performed and all ROMs were measured by the authors for data consistency. Furthermore, our 4- week post-MUA flexion ROM and pain were shown to be significantly different ($p<0.05$) from baseline, which was not demonstrated in other studies [21,36,37]. A longer term of study is warranted to determine if the ROM improves, declines or stays constant. Previous studies have shown increased flexion after MUA, regardless of the timing it was performed after TKA, can be maintained over a long term [23,38]. Although there is no consensus on the optimal timing, it has been shown significantly better outcomes are expected when MUA is performed within 12 weeks of TKA compared to later treatment, since scar tissue may mature as time progresses [11,31]. In our study, MUA performed at 6 weeks with cryopreserved AMUC reduced pain and improved patient's ROM in patients suffering arthrofibrosis post-TKA. As our patient population does not reflect the most severe cases of arthrofibrosis (i.e., post-TKA flexion < 70 degrees), prospective studies could focus on the potential added benefit of using AMUC in conjunction with MUA, as MUA alone is less effective with a flexion of less than 70 degrees [21]. Further prospective studies could also be performed to evaluate the use of MUA with and without AMUC at a later time point, which may have better outcomes compared to standard of care due to AMUC's known anti-scarring properties.

CONCLUSION

This data suggests MUA with adjunctive AMUC may reduce pain and improve patient's ROM in patients suffering arthrofibrosis post-TKA. Further studies are warranted.

Conflicts of Interest

No disclosures to declare.

Authors' Contribution

Both authors contributed equally.

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