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ORTHOPEDICS | RESEARCH ARTICLE

Ultrasound-guided injections of amniotic membrane/umbilical cord particulate for painful neuropathy of the lower extremity

Ahmed Bilal Buksh^{1,2*}

Abstract: Treatment of peripheral neuropathy remains a challenge. It has been shown clinically that cryopreserved human amniotic membrane (AM) and umbilical cord (UC) reduce pain, and they may serve as a beneficial treatment option for peripheral neuropathy. Here, we report findings from a single-center, retrospective review of peripheral neuropathy patients treated with AM/UC particulate. Seventeen patients with recalcitrant diabetic ($n = 8$), idiopathic ($n = 7$), or chemotherapy-induced peripheral neuropathy ($n = 2$) were included in the study. At presentation, all 17 patients complained of pain, along with numbness ($n = 10$), paresthesia ($n = 8$), poor balance ($n = 9$), poor range of motion ($n = 5$), or weakness ($n = 7$). After an average of 2.7 injections of AM/UC particulate per extremity, symptoms improved by $30.0 \pm 24.5\%$ at 1 week, $46.6 \pm 29.9\%$ at 1 month ($P < .005$), $70.7 \pm 14.3\%$ at 2 months ($P < .001$), $72.3 \pm 16.9\%$ at 3 months ($P < .001$), and $61.0 \pm 34.4\%$ at 5–6 months ($P < .01$). No complications or adverse events related to AM/UC injection were observed. These results suggest local perineural injection of AM/UC particulate may reduce pain and alleviate symptoms in patients suffering from painful peripheral neuropathy of the lower extremities.

Subjects: Biotechnology; Health & Society; Health Conditions; Medicine

Keywords: Amniotic Membrane (AM); injection; lower extremity; pain; peripheral neuropathy; treatment outcome; Umbilical Cord (UC)



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ABOUT THE AUTHOR

Ahmed Bilal Buksh, DPM, has more than 20 years of experience in podiatric medicine and peripheral nerve surgery. Dr. Buksh is board-certified in both podiatric surgery and podiatric medicine and his research focuses on addressing chronic pain using conservative and surgical methods. This research aims to support utilization of a novel conservative treatment option (i.e. human amniotic membrane and umbilical cord particulate) for patients with chronic peripheral neuropathy.

PUBLIC INTEREST STATEMENT

Peripheral neuropathy is primarily a disorder of the peripheral nerves that can result in pain, tingling, and numbness within the extremities. Current treatment options aim to relieve the symptoms without addressing the underlying cause and often fail to completely resolve symptoms with unfavorable side effects. In this work, symptomatic improvement was noted after perineural injection of AM/UC particulate without product-related adverse events. Perineural injection of AM/UC particulate resulted in significant relief of pain and associated symptoms at 1 month, 2 months, 3 months, and 5–6 months. These results suggest that AM/UC may be a viable treatment option for refractory cases.

1. Introduction

Peripheral neuropathy is primarily a disorder of the peripheral nerves caused by (1) compression due to space-occupying lesions (osteochondromas, tumors, ganglion/synovial cysts, tenosynovitis, varicosities), (2) compression secondary to shoes, osseous spurs or deformity, (3) traumatic injury, (4) compartment syndrome, (5) tissue hypertrophy, (6) stretching of the nerve or scar traction, or (7) systemic diseases (diabetes, peripheral vascular disease). In fact, painful peripheral neuropathy occurs in 25% of patients with diabetes treated in the office setting and 20–40% of cancer patients who receive neurotoxic chemotherapy (Spallone, Lacerenza, Rossi, Sicuteri, & Marchettini, 2012; Travis et al., 2014). Symptoms in the early onset include pain, paresthesia, and numbness within the extremities that subsequently have a negative impact on sleep, functionality, and quality of life (Iqbal et al., 2018). In advanced stages of the disease, there tends to be motor nerve dysfunction with distal weakness that may result in loss of balance or falling down (Feldman, Nave, Jensen, & Bennett, 2017; Pop-Busui et al., 2017).

Current treatment options are palliative, aiming to relieve the symptoms associated with neuropathy without addressing the underlying cause. Traditional therapies include over-the-counter pain relievers, opioids, anti-epileptic agents (pregabalin, topiramate, gabapentin), anti-depressants, and muscle relaxants. Non-pharmacological treatments have also been used including low-intensity laser therapy, transcutaneous electrical nerve stimulation, and more commonly steroidal perineural injections. Nonetheless, these treatments often fail to completely resolve symptoms and can be associated with unfavorable side effects (Singh, Kishore, & Kaur, 2014). Consequently, chronic pain persists and leads patients in search of alternative therapies.

Cryopreserved human umbilical cord (UC) and amniotic membrane (AM) have been used as allografts in a variety of clinical applications due to their anti-inflammatory, anti-scarring, and pro-regenerative properties. In ophthalmology, AM is applied as a sheet over the ocular surface and has been shown to alleviate pain (Espana et al., 2003; Georgiadis, Ziakas, Boboridis, Terzidou, & Mikropoulos, 2008; John et al., 2017; Pires et al., 1999) and promote restoration of nerve density in patients suffering from neuropathic corneal pain (Morkin & Hamrah, 2017). In orthopedics, AM/UC has successfully been used as a conduit or wrap to promote neural regeneration (Gaspar et al., 2016; Hasturk et al., 2018; Henry et al., 2009; Meng, Li, You, Du, & Luo, 2011; Mohammad, Shenaq, Rabinovsky, & Shenaq, 2000; Nurru Mligiliche, Okamoto, Fujimoto, & Ide, 2002; O'Neill et al., 2009; Zhang, Zhang, Liu, & Wang, 2013). In those studies, AM/UC was shown to decrease pain, improve functional outcomes, and improve nerve histomorphometry (Gaspar et al., 2016; Hasturk et al., 2018; Henry et al., 2009; Meng et al., 2011; Mohammad et al., 2000; Nurru Mligiliche et al., 2002; O'Neill et al., 2009; Zhang et al., 2013). In addition to being used as a sheet, micronized AM/UC can also be injected in-office to deliver similar therapeutic benefits due to the tissues' rich concentration of growth factors, cytokines, and other extracellular matrix components including neurotransmitters and neurotrophic factors (Duru, Williams, & Jones, 2018; Garras & Scott, 2016; Hanselman, Tidwell, & Santrock, 2015; III LOV). Given its potential in reducing pain and promoting nerve regeneration, we retrospectively assessed the safety and effectiveness of AM/UC particulate injection in relieving pain in patients with peripheral neuropathy.

2. Materials and methods

After approval from the Institutional Review Board and waiver of informed consent, a retrospective medical chart review was conducted on patients (aged >18 years) that were diagnosed with peripheral neuropathy and received AM/UC particulate injection between June 2017 and July 2018 in accordance with the Declaration of Helsinki. All patients were treated by a single physician at a private practice. Patients were diagnosed with peripheral neuropathy if they were symptomatic, displayed decreased deep tendon reflexes, and had reduced sensation. Epicritic sensation was evaluated including sharp-dull, light touch, proprioception, pin-prick (at six points of the plantar surface), and protective threshold (10-g monofilament test). In addition, the 128 Hz tuning fork was applied for evaluation of vibration sensation, and provocative (pressure, Tinel's) tests were performed around the course of peroneal and tibial nerves. Diabetic induced

neuropathy was confirmed with elevated A1c levels ($\geq 6.5\%$). De-identified data were obtained from baseline (pre-injection) up to 1-year post-injection, including patient demographics (age, gender, ethnicity), type of neuropathy, neuropathy risk factors (glucose tolerance, pre-diabetes, diabetes mellitus, B₁₂ deficiency, hypothyroidism, immune disorder, and uremia), concurrent treatments, symptoms (e.g. pain, weakness, numbness, poor balance, reduced range of motion, and paresthesia in terms of numbness and tingling sensation), duration of symptoms, and complications.

2.1. Injection technique

All patients received ultrasound-guided injection at the common peroneal nerve at the knee, posterior tibial nerve at the ankle, and deep peroneal nerve on the dorsolateral foot. For injection of the common peroneal nerve (Figure 1), the patient was in the lateral decubitus position with the affected side up. The common peroneal nerve was found using a 7.5- to 15-Hz ultrasound probe (Sonoscape S9, Universal Medical Systems, Bedford Hills, NY) by scanning distally from the sciatic nerve in the proximal thigh and toward the proximal fibula. A diagnostic injection of 1cc of 1% lidocaine plain (Hikma Pharmaceuticals, London, United Kingdom) and 0.5cc of 8.4% sodium bicarbonate (Fresenius Kabi, Lake Zurich, IL) was performed for superficial anesthesia. Then, 25 mg of AM/UC particulate (CLARIX FLO®, Amnioc Medical, Inc., Miami, FL) pre-mixed with 1.0 cc of 0.5% Marcaine plain (Fresenius Kabi, Lake Zurich, IL) in a 25-gauge, 1.5-inch needle was inserted via out-of-plane approach. The needle tip was positioned deep to the nerve to ensure adequate circumferential and proximal perineural distribution of the injectate outside the epineurium of the nerve. Needle repositioning was performed as needed to ensure complete coverage. Injection of the posterior tibial nerve at the ankle was performed with the patient in Fowler's position with the lateral foot down to expose the medial side of the hindfoot (Figure 2). The nerve was located using the ultrasound probe placed obliquely along the malleolar-calcaneal axis, with

Figure 1. Representative case of common peroneal injection.

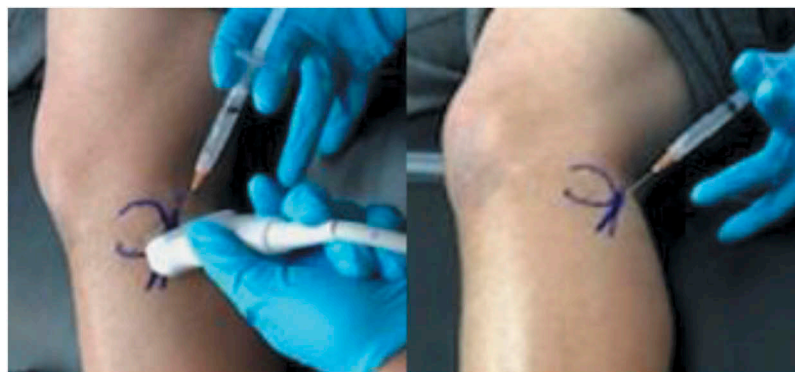


Figure 2. Posterior tibial nerve injection.



the notch toward the medial malleolus and the other end directed toward the heel. After visualization of the tibial nerve, 3cc of local anesthetic (plain 1% lidocaine and 8.4% sodium bicarbonate) was injected. Thereafter, injection of 50 mg AM/UC particulate pre-mixed with 1.5 cc of 0.5% Marcaine plain (Fresenius Kabi, Lake Zurich, IL) was performed using a 22-gauge B-beveled block needle using in-plane technique. Lastly, injection of the lateral branch of the deep peroneal nerve was performed distal to the anterolateral part of the talus head and beneath the extensor hallucis brevis (Figure 3). Local anesthetic (1cc plain 1% lidocaine and 0.5cc 8.4% sodium bicarbonate) was first provided for superficial anesthesia. Then, injection of 1.0 cc of 25 mg AM/UC particulate/Marcaine was performed to surround the nerve completely using in-plane ultrasound guidance with a 22-gauge, 50-mm-long Stimuplex needle. All patients remained in the office for 15 min after the injection to be monitored for adverse reactions. Afterwards, they were asked to avoid any strenuous activity for at least 24 h and ice the injected region as needed for post-injection pain up to 72 h. Patients were also asked to elevate the foot for 2 days and stop the use of anti-inflammatory medications for a duration of 5 days post-injection.

2.2. Outcomes

At each follow-up visit, patients were asked to report their percent improvement in pain and associated symptoms compared to baseline before AM/UC treatment. Any unfavorable and unintended signs, symptoms, or disease spontaneously reported or discovered by the investigator during follow-up visits were reported as adverse events.

2.3. Statistical analysis

All statistical analyses were carried out using IBM SPSS version 20.0. Categorical variables were described by percentages and frequencies, while continuous variables were described by means and standard deviations. The Friedman test was used to assess whether improvement of symptoms was significantly different between time points. A P value <0.05 was considered statistically significant.

3. Results

A total of 17 patients met the eligibility criteria of this retrospective study and were included in the analysis. Patients (8 male, 9 female) had an average age of 50.5 ± 10.2 years and a mean BMI of 30.7 ± 6.4 kg/m². Other baseline characteristics are summarized in Table 1. The diagnosis was diabetic ($n = 8$), idiopathic ($n = 7$), and chemotherapy-induced peripheral neuropathy ($n = 2$). The most commonly associated comorbidities included lower back pain ($n = 11$), diabetes ($n = 8$), and hypertension ($n = 5$). Autonomic nerves were damaged in two idiopathic neuropathy cases based on nerve conduction studies.

At presentation, patients complained of pain ($n = 17$), numbness ($n = 10$), and paresthesia ($n = 8$) with poor balance ($n = 9$), poor range of motion ($n = 5$), and weakness ($n = 7$) for a median of 38.5 months (range: 7–180). The average pain score ($n = 8$) at baseline was 8.8 ± 1.6 despite NSAIDs/acetaminophen ($n = 11$), opioids ($n = 8$), nerve pain/anti-depressant medication (e.g. gabapentin,

Figure 3. Injection of the lateral branch of the deep peroneal nerve.



Table 1. Baseline clinical characteristics of patients

Characteristic	N (%)	Characteristic	N (%)
Race, Caucasian	17	Medications	
Ethnicity, Hispanic	1	NSAIDs	11 (65)
Smoking status		Narcotics	8 (47)
Smoker	4 (24)	Gabapentin	11 (65)
Former smoker	6 (35)	Duloxetine	2 (12)
Non-smoker	7 (41)	Venlafaxine	1 (6)
BMI (kg/m ²), mean \pm SD	30.7 \pm 6.4	Pregabalin	2 (12)
Normal (18.5 to <25 kg/m ²)	3 (18)	SSRIs	4 (24)
Overweight (25 to <30 kg/m ²)	6 (35)	Anti-Diabetic	5 (29)
Obese (\geq 30 kg/m ²)	8 (47)	Muscle Relaxant	6 (35)
Side Affected with Symptoms			
Immunosuppressant	1 (6)		
Bilateral L = R	6 (35)	Blood pressure	9 (53)
Bilateral L > R	5 (29)	Anastrozole	1 (6)
Bilateral L < R	5 (29)	Anti-OA	2 (12)
Left	1 (6)	Prior Surgeries	
Co-morbidities		Back Surgery	2 (12)
Diabetes	8 (47)	Foot Surgery	1 (6)
Hypertension	5 (29)		
Lower Back Pain	11 (65)		
Sciatica	4 (24)		
Arthritis	3 (18)		
Hypercholesterolemia	4 (24)		
Hyperlipidemia	2 (12)		
Thyroid Issues	4 (24)		
Anemia	3 (18)		
Fibromyalgia	2 (12)		
Pancreatitis	1 (6)		

duloxetine, venlafaxine, pregabalin; n = 15), and injections of Dexamethasone (n = 9) or Cyanocobalamin (n = 7) within 2 years.

Patients received 2.7 ± 1.8 injections of AM/UC particulate per extremity. The average time between injections was 25.2 days for each extremity. No complications (including foot drop) or adverse events related to AM/UC were observed. However, one patient experienced vomiting 5-days post-injection and another patient fell in a parking lot the same day of injection.

Following AM/UC injection(s), symptoms improved by $30.0 \pm 24.5\%$ at 1 week, $46.6 \pm 29.9\%$ at 1 month ($P < .005$), $70.7 \pm 14.3\%$ at 2 months ($P < .001$), $72.3 \pm 16.9\%$ at 3 months ($P < .001$), and $61.0 \pm 34.4\%$ at 5–6 months ($P < .01$) (Table 2). Patients with idiopathic (n = 7) neuropathy improved 44.2% at 1 month, 65% at 2 months, and 70% at 3 months with 2.6 injections on average. Patients with diabetic neuropathy (n = 8) improved 50% at 1 month, 73% at 2 months, and 75% at 3 months with 2.75 injections on average.

Table 2. Patient clinical outcomes

#	Neuropathy type	Baseline symptoms	Duration of symptoms (mos)	Leg	Txs per Leg	Days between Tx's	Percent improvement in symptoms				
							1 week	1 month	2 months	3 months	5-6 months
1	Idiopathic	Pain, Numb	180	L	1	-	-	-	-	-	0
2	Idiopathic	Pain, Numb	24	L, R	7	25	-	0	70	70	70
3	Idiopathic	Pain, Numb, Pare, Weak, ROM	-	R	2	26	-	20	-	50	-
4	Diabetic	Pain, Amb, Weak	7	L	1	-	-	95	100	-	-
5	Idiopathic	Pain, Amb, ROM	120	L, R	3	37	-	70	50	50	-
6	Idiopathic	Pain, Numb, ROM	-	L, R	1	-	-	50	80	80	-
7	Diabetic	Pain, Numb, Pare	108	L, R	5	45	0	35	80	80	80
8	Chemo	Pain, Numb, Pare, Amb, Weak	18	L, R	1	-	-	80	80	-	-
9	Diabetic	Pain, Pare, Amb, ROM	12	L, R	2	18	-	80	80	85	-
10	Chemo	Pain, Numb, Pare, Amb	12	L, R	7	20	0	0	75	70	80
11	Diabetic	Pain, Numb, Amb, Weak	180	L, R	4	30	-	30	60	50	75
12	Diabetic	Pain, Numb, Amb, ROM, Weak	126	L, R	3	28	50	70	70	90	-
13	Idiopathic	Pain, Pare	47	L, R	2	16	-	75	75	100	-
14	Diabetic	Pain, Pare, Amb, Weak	24	L, R	3	21	-	10	70	70	-
15	Idiopathic	Pain	54	L, R	2	12	50	50	50	-	-
16	Diabetic	Pain	-	L, R	2	28	50	40	50	-	-
17	Diabetic	Pain, Numb, Pare, Amb, Weak	30	L, R	2	21	30	40	-	-	-

Abbreviations: Pare, paresthesia; Amb, poor ambulation or balance; Numb, numbness; ROM, range of motion; Tx's, treatments; Weak, weakness.

4. Discussion

Patients with peripheral neuropathy often experience debilitating pain that significantly impacts their jobs, limits their social interactions, and impairs their day-to-day functionality. To alleviate the pain, these patients must weigh the benefits with the side effects of taking multiple pharmacological medication. Although patients might note a modest reduction in pain that allows a level of functionality that they would not have had otherwise, they might also experience a variety of cognitive side effects including drowsiness, difficulty focusing, and short-term memory loss. In the present study, patients presented with chronic symptoms that had been present for a median of 38.5 months, with 59% of patients experiencing motor weakness suggestive of chronic neuropathy progression. In addition, 94% of patients were refractory to prior perineural injections, and of those, many were not operative candidates due to various comorbidities. Nonetheless, patients showed symptomatic improvement after perineural injection of AM/UC particulate without product-related adverse events, suggesting that AM/UC may be a viable treatment option for refractory cases. Perineural injection of AM/UC particulate resulted in significant relief of pain and associated symptoms at 1 month, 2 months, 3 months, and 5–6 months in patients with diabetic ($n = 8$), idiopathic ($n = 7$), and chemotherapy-induced peripheral neuropathy ($n = 2$). In particular, the 8 patients with diabetic neuropathy in this study improved 50% at 1 month, 73% at 2 months, and 75% at 3 months with 2.75 treatments on average, which is promising as these patients are especially hampered in treatment options as steroids are known to cause hyperglycemia (Choudhry, Malik, & Charalambous, 2016).

Despite the favorable results, several limitations should be considered when interpreting the findings. First, the retrospective design only allowed analysis of data from prior medical records and not all data were consistently captured. Pain was not compared among individuals, rather measured before and after AM/UC for each individual. Patients were not followed up at exact specified timepoints and not routinely tracked for concomitant medication and compliance. Many of the patients were on nerve pain medications that may have influenced pain score. Future studies should track medication usage and laboratory values of vitamin B₁₂ and A1c that could confound symptoms. The AM/UC treatment was also not administered at consistent timepoints which introduces variability without a proper control group. With these limitations in mind, future studies could be designed with longer follow-up visits in order to study the duration of symptomatic relief.

If the aforementioned efficacy was verified in larger randomized studies, the underlying mechanism may be related to suppression of inflammation. AM/UC and its major biochemical component, i.e., HC-HA/PTX3, have been shown to significantly promote apoptosis of activated neutrophils (He et al., 2008; He, Zhang, Tighe, Son, & Tseng, 2013), promote phagocytosis by macrophages (He et al., 2013), and promote M2 macrophage polarization (He et al., 2009; He et al., 2013). These action mechanisms are advantageous in this particular application as nerve injury has been shown to activate inflammatory mediators and produce spontaneous neural activity (Moalem & Tracey, 2006). Hence, an analgesic effect is experienced after alleviating inflammatory response. Aside from this effect, AM/UC has also been shown to promote regeneration and normal neural regeneration which may also aid in pain alleviation (Morkin & Hamrah, 2017; Tseng, 2016). This action differentiates AM/UC from steroids, which are commonly used for perineural injections, but only provide an anti-inflammatory effect. Overall, perineural injection of AM/UC particulate may provide a differentiated alternative treatment option that aims to address the underlying pathologies.

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Competing Interests

The author reports no conflict of interest.

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References

Choudhry, M. N., Malik, R. A., & Charalambous, C. P. (2016). Blood glucose levels following intra-articular steroid injections in patients with diabetes: A systematic review. *JBJS Reviews*, 4, 1. doi:[10.2106/JBJS.RVW.0.00029](https://doi.org/10.2106/JBJS.RVW.0.00029)

- Duru, N., Williams, G. K., & Jones, D. (2018). A comparative, controlled, retrospective study of patient reported outcomes after meniscectomy with adjunctive use of platelet-rich plasma or amniotic membrane/Umbilical cord particulate. Paper presented at 106th Annual Meeting of the Clinical Orthopaedic Society; September 26-29, 2018. Austin, TX.
- Espana, E. M., Grueterich, M., Sandoval, H., Solomon, A., Alfonso, E., Karp, C. L., Fantes, F., & Tseng, S. C. (2003). Amniotic membrane transplantation for bullous keratopathy in eyes with poor visual potential. *Journal of Cataract & Refractive Surgery*, 29, 279-284.
- Feldman, E. L., Nave, K. A., Jensen, T. S., & Bennett, D. L. H. (2017). New horizons in diabetic neuropathy: Mechanisms, bioenergetics, and pain. *Neuron*, 93, 1296-1313. doi:10.1016/j.neuron.2017.02.005
- Garras, D., & Scott, R. (2016). Plantar fasciitis treatment with particulated human amniotic membrane. *Foot & Ankle Orthopaedics*, 1, 1. doi: 10.1177/2473011416S00245
- Gaspar, M. P., Abdelfattah, H. M., Welch, I. W., Vosbikian, M. M., Kane, P. M., & Rekan, M. S. (2016). Recurrent cubital tunnel syndrome treated with revision neurolysis and amniotic membrane nerve wrapping. *Journal of Shoulder and Elbow Surgery*, 25, 2057-2065. doi:10.1016/j.jse.2016.09.013
- Georgiadis, N. S., Ziakas, N. G., Boboridis, K. G., Terzidou, C., & Mikropoulos, D. G. (2008). Cryopreserved amniotic membrane transplantation for the management of symptomatic bullous keratopathy. *ClinExperimentOphthalmol*, 36, 130-135.
- Hanselman, A. E., Tidwell, J. E., & Santrock, R. D. (2015). Cryopreserved human amniotic membrane injection for plantar fasciitis: A randomized, controlled, double-blind pilot study. *Foot & Ankle International*, 36, 151-158. doi:10.1177/1071100714552824
- Hasturk, A. E., Yilmaz, E. R., Hayirli, N., Kayalar, A. E., Akyildiz, S., Gökce, E. C., ... Bakir, A. (2018). Stereologic and ultrastructural comparison of human and rat amniotic membrane wrapping for rat sciatic nerve repair. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia*, 57, 157-161. doi:10.1016/j.jocn.2018.08.007
- He, H., Li, W., Chen, S. Y., Zhang, S., Chen, Y.-T., Hayashida, Y., ... Tseng, S. C. G. (2008). Suppression of activation and induction of apoptosis in RAW264.7 cells by amniotic membrane extract. *Investigative Ophthalmology & Visual Science*, 49, 4468-4475. doi:10.1167/iov.08-1781
- He, H., Li, W., Tseng, D. Y., Zhang, S., Chen, S., Day, A., & Tseng, S. C. (2009). Biochemical characterization and function of complexes formed by Hyaluronan and the Heavy Chains of Inter- α -inhibitor (HC \cdot HA) purified from extracts of human amniotic membrane. *Journal of Biological Chemistry*, 284, 20136-20146.
- He, H., Zhang, S., Tighe, S., Son, J., & Tseng, S. C. (2013). Immobilized heavy chain-hyaluronic acid polarizes lipopolysaccharide-activated macrophages toward M2 phenotype. *Journal of Biological Chemistry*, 288, 25792-25803.
- Henry, F. P., Goyal, N. A., David, W. S., Wes, D., Bujold, K. E., Randolph, M. A., & Redmond, R. W. (2009). Improving electrophysiologic and histologic outcomes by photochemically sealing amnion to the peripheral nerve repair site. *Surgery*, 145, 313-321. doi:10.1016/j.surg.2008.11.005
- Iqbal, Z., Azmi, S., Yadav, R., Ferdousi, M., Kumar, M., Cuthbertson, D. J., ... Alam, U. (2018). Diabetic peripheral neuropathy: Epidemiology, diagnosis, and pharmacotherapy. *Clinical Therapeutics*, 40, 828-849. doi:10.1016/j.clinthera.2018.04.001
- John, T., Tighe, S., Sheha, H., Hamrah, P., Salem, Z. M., Cheng, A. M. S., & Rock, N. D. (2017). Corneal nerve regeneration after self-retained cryopreserved amniotic membrane in dry eye disease. *Journal of Ophthalmology*, 2017, 10. doi:10.1155/2017/6404918
- Meng, H., Li, M., You, F., Du, J., & Luo, Z. (2011). Assessment of processed human amniotic membrane as a protective barrier in rat model of sciatic nerve injury. *Neuroscience Letters*, 496, 48-53.
- Moalem, G., & Tracey, D. J. (2006). Immune and inflammatory mechanisms in neuropathic pain. *Brain Research Reviews*, 51, 240-264. doi:10.1016/j.brainresrev.2005.11.004
- Mohammad, J., Shenaq, J., Rabinovsky, E., & Shenaq, S. (2000). Modulation of peripheral nerve regeneration: A tissue-engineering approach. The role of amnion tube nerve conduit across a 1-centimeter nerve gap. *Plastic and Reconstructive Surgery*, 105, 660-666.
- Morkin, M. I., & Hamrah, P. (2017). Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain. *The Ocular Surface*, 16, 132-138.
- Nurru Mligiliche, K. E., Okamoto, K., Fujimoto, E., & Ide, C. (2002). Extracellular matrix of human amnion manufactured into tubes as conduits for peripheral nerve regeneration. *Biomed Mater Res (Appl Biomater)*, 591-600. doi:10.1002/jbm.10349
- O'Neill, A. C., Randolph, M. A., Bujold, K. E., Kochevar, I. E., Redmond, R. W., & Winograd, J. M. (2009). Preparation and integration of human amnion nerve conduits using a light-activated technique. *Plastic and Reconstructive Surgery*, 124, 428-437.
- Pires, R. T. F., Tseng, S. C. G., Prabhasawat, P., Puangsricharem, V., Maskin, S. L., Kim, J. C., Tan, D. T. (1999). Amniotic membrane transplantation for symptomatic bullous keratopathy. *Archives of Ophthalmology*, 117, 1291-1297. doi:10.1001/archophth.117.10.1291
- Pop-Busui, R., Boulton, A. J., Feldman, E. L., Bril, V., Freeman, R., Malik, R. A., ... Ziegler, D. (2017). Diabetic neuropathy: A position statement by the American Diabetes Association. *Diabetes Care*, 40, 136-154. doi:10.2337/dc16-2042
- Singh, R., Kishore, L., & Kaur, N. (2014). Diabetic peripheral neuropathy: Current perspective and future directions. *Pharmacological Research*, 80, 21-35. doi:10.1016/j.phrs.2013.12.005
- Spallone, V., Lacerenza, M., Rossi, A., Sicuteri, R., & Marchettini, P. (2012). Painful diabetic polyneuropathy: Approach to diagnosis and management. *The Clinical Journal of Pain*, 28, 726-743. doi:10.1097/AJP.0b013e318243075c
- Travis, L. B., Fossa, S. D., Sesso, H. D., Frisina, R. D., Herrmann, D. N., Beard, C. J., & Dolan, M. E. (2014). Chemotherapy-induced peripheral neurotoxicity and ototoxicity: New paradigms for translational genomics. *Journal of the National Cancer Institute*, 106. doi:10.1093/jnci/dju044
- Tseng, S. C. (2016). HC-HA/PTX3 purified from amniotic membrane as novel regenerative matrix: Insight into relationship between inflammation and regeneration. *Investigative Ophthalmology & Visual Science*, 57, ORSFH1-8. doi:10.1167/iov.15-17637
- Vaughan, L., & Sisco-Wise, L. (2018). Outcomes of Revision Carpal Tunnel Release with Umbilical Cord Allograft. Paper presented at 106th Annual Meeting of the Clinical Orthopaedic Society, September 26-29, 2018. Austin, TX.
- Zhang, Y.-R., Zhang, G.-C., Liu, Q.-H., & Wang, Y.-S. (2013). Effect of amnion-wrapped allogenic nerve bridging on peripheral nerve injury. *International Journal of Morphology*, 31, 980-985. doi:10.4067/S0717-95022013000300034



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