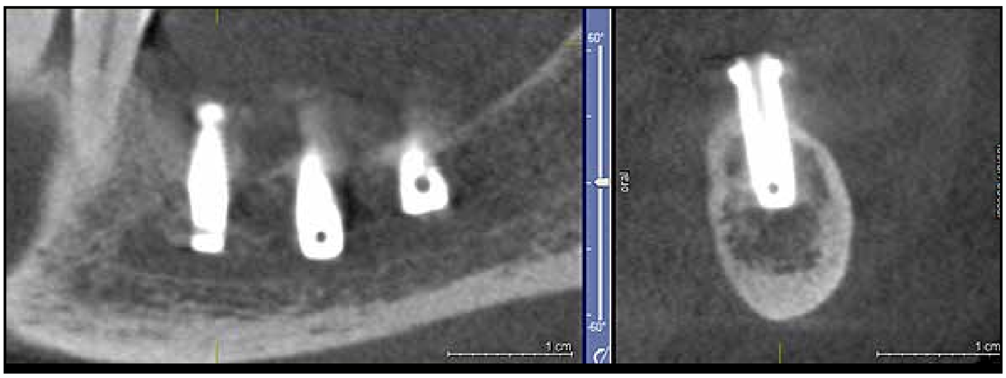
Repair of Dental Implant Induced Inferior Alveolar Nerve Injuries with Dehydrated Human Amnion-Chorion Membranes: A Case Series

Dan Holtzclaw, DDS, MS[1] • Roger Telles, MBA[2]

Abstract



Dental implant treatment has become a common treatment modality for the replacement of missing teeth. As the number of implants placed annually continues to increase, so too has the incidence of iatrogenic nerve damage secondary to implant placement. Over the past decade, a handful of conservative protocols have been proposed for the treatment of neural maladies following the placement of dental implants with varying degrees of success. Recent advances in biologic growth factor technology have introduced products that may serve as adjuncts in the treatment of neural injury. Medical literature has documented a variety of cases in which placentally derived amnion-chorion membranes were used for the treatment of neural issues with promising results. The aim of the current paper is to document a treatment protocol used by the author for the treatment of iatrogenic neural maladies secondary to the placement of dental implants. A series of 5 cases are presented in which the author utilized amnion-chorion membranes as an adjunct for treatment of damaged inferior alveolar nerves. In all cases, significant improvement was documented. While these results are encouraging, case controlled studies with larger patient populations are needed to verify these results.

KEY WORDS: Dental implants, nerve injury, amnion, chorion, iatrogenic

1. Private practice. Austin, Texas. San Antonio, Texas.
2. San Antonio, Texas.

INTRODUCTION

As more dental implants are placed by an ever-increasing number of practitioners with varying degrees of skill and experience, it is inevitable that the number of complications associated with implant treatment will rise. This is just as true today as it was more than 20 years ago when Worthington predicted the same.[1] One of the most common and serious complications of dental implant treatment is iatrogenic damage to the mandibular branch of the trigeminal nerve. The incidence of nerve injury following dental implant treatment is extremely variable with reports ranging anywhere from 0-44%.[2-5] Furthermore, the degree of nerve injury following dental implant treatment is likewise highly variable.[2-5] Treatment of neural injury following dental implant placement remains a challenge, evidenced by the fact that few published studies have defined standardized treatment protocols for the majority of dentists that do no specialize in nerve repair.[6-12]

Over the past decade, a plethora of published articles have documented the efficacy of various growth factors in surgical dentistry.[13-16] Some of these growth factors, such as placental allografts, have been utilized in medical studies for nerve repairs and adjuncts to reduce the incidence of neural injury following various surgical procedures.[17-26] To date, no known dental studies have documented the use of growth factors for the treatment of nerve injuries sustained during the course of dental implant treatment. Accordingly, the purpose of the current case series is to document cases in which placental growth factors were incorporated into a systematic protocol for the treatment of iatrogenic neural injuries following the placement of dental implants.

METHODS

Based on studies documenting the use of placental derived growth factors for the treatment of non-dental, medically based neural maladies, a protocol was initiated in the private practice of the author for the treatment of iatrogenic nerve injuries related to the placement of dental implants. Upon presentation of such injuries, the following treatment was enacted (Table 1): 1) mapping of neural deficits with commonly used subjective methods[27] including pin prick test[28] and direction of movement test[9,28] 2) removal of the suspected offending item if possible (ie. Dental implant penetrating or in close proximity to the mandibular canal)[29] 3) irrigation of the implant osteotomy with 4mg/ml Dexamethasone solution[9,10,21] 4) placental derived amnion-chorion membrane (BioXclude, Snoasis Medical, Denver, Colorado, USA) soaked in 4mg/ml Dexamethasone solution[21] for 2 minutes and placed into the implant osteotomy directly upon the site of the suspected neural injury[17-26] 5) collagen tape soaked in 4mg/ml Dexamethasone solution placed on top of the amnion-chorion membrane 6) bone allograft (Maxxeus, Community Tissue Services, Dayton, Ohio, USA) hydrated with normal saline placed on top of the collagen tape 7) dry amnion-chorion membrane placed on top of the bone allograft and left exposed to the oral environment. The external layer of amnion-chorion allograft is then hydrated with blood or saline and tucked under the adjacent gingival tissue in a fashion similar to previously published studies in which this material was used for extraction site preservation[30] 8) post-operative narcotics as needed; 9) post-operative large dose non-steroidal anti-inflammatory drug (NSAID) (800mg Ibuprofen, three times orally per day for 10

Table 1: Amnion-Chorion Protocol
1. Pre-surgical subjective nerve mapping of affected sites.
2. Repositioning or removal of any irritant in close approximation to the neurovascular bundle.
3. Rinse osteotomy and affected nerve with 4mg/ml dexamethasone solution.
4. Place dexamethasone hydrated amnion-chorion membrane into osteotomy down to the level of the affected nerve.
5. Place collagen tape soaked in dexamethasone over amnion-chorion membrane.
6. Place bone allograft hydrated with saline into osteotomy over collagen tape.
7. Place dry amnion-chorion membrane over bone allograft.
8. Place patient on post-surgical systemic antibiotics (Medrol dose pack).
9. Place patient on post-surgical NSAIDs (800mg ibuprofen, TID).
10. Place patient on post-surgical narcotics as needed.
11. Place patient on post-surgical antibiotics.
12. Cryotherapy ice applied to surgical site.
13. Post-surgical subjective nerve mapping of affected sites.

days)[9,11] 10) post-operative tapering Medrol systemic corticosteroid dose pack[9,11] 11) post-operative systemic antibiotics taken orally 12) ice pack application to the surgical site intensely for the first 24 hours after surgery and then episodically for the next 3 days[9] 13) follow-up visits performed at 10 days, 30 days, 60 days, 90 days, 180 days, and yearly. At each follow-up visit, the aforementioned neurosensory tests and mapping were repeated and recorded. When applicable, dental implants were replaced at the sites of the prior neural injury or in other sites as indicated by the patients' treatment plans.

RESULTS

From 2011 to 2015, a total of 5 patients presented to the private office of the author with chief complaints of iatrogenic nerve injury following the placement of dental implants at other offices. The average length of time from injury to treatment was 6.25 years (range 1 – 16 years). Cumulatively, a total of 9 iatrogenically placed dental implants were removed and their corresponding osteotomy sites treated with the amnion-chorion protocol. Nine of the ten dental implants partially penetrated or compressed the mandibular canal while one of the dental implants penetrated the

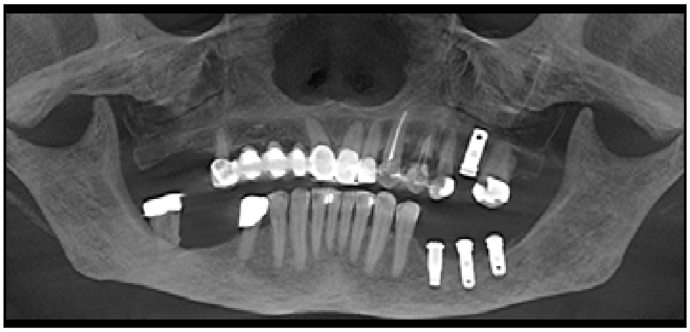


Figure 1: Panoramic radiograph of iatrogenically placed implants at sites 18, 19, 20.

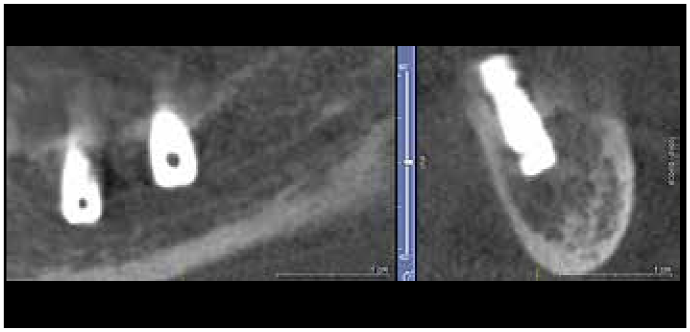


Figure 2: Radiographic image of iatrogenically placed implant at site 18.

Figure 3: Radiographic image of iatrogenically placed implant at site 19.

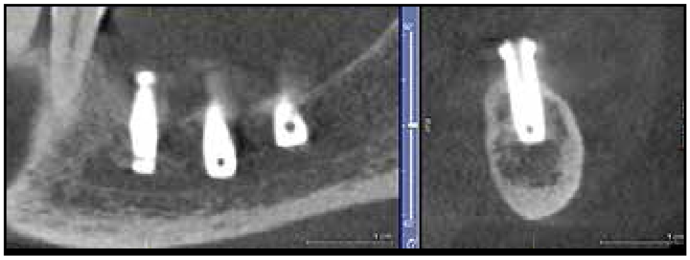


Figure 4: Radiographic image of iatrogenically placed implant at site 20.

Figure 5: Iatrogenically placed dental implants removed and injured left inferior alveolar nerve treated with amnion-chorion protocol.

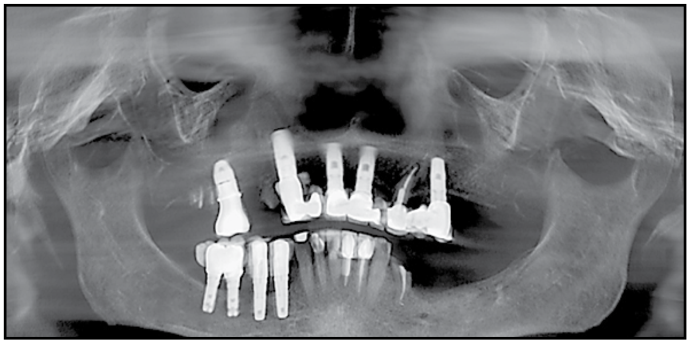


Figure 6: Panoramic radiograph of iatrogenically placed implants at sites 28, 29, 30

mental foramen (Figures 1-13). Following dental implant removal and treatment, three of the five patients were treated with the All-On-4™ style dental implant protocol and two patients had the offending implants replaced in the same exact spot with a shorter implant. During follow up appointments now extending up to 7 years post-treatment, each patient has reported significant and sustained improvement in their neurosensory recovery. With each patient, the most notable and appreciable neurosensory improvements occurred in the first 180 days after treatment.

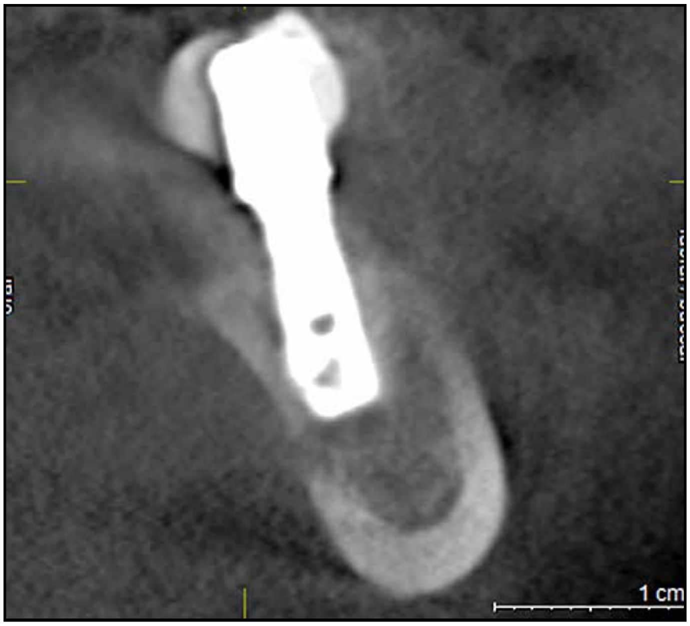


Figure 7: Radiographic image of iatrogenically placed implant at site 28.

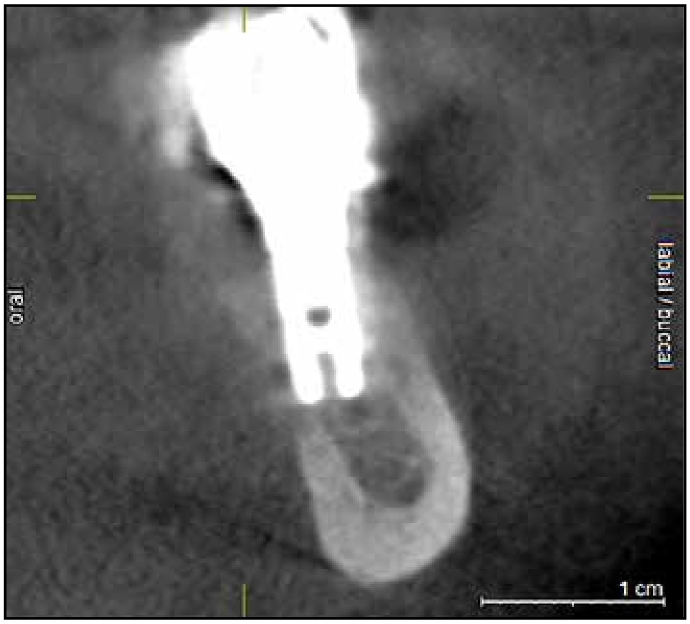


Figure 8: Radiographic image of iatrogenically placed implant at site 29.

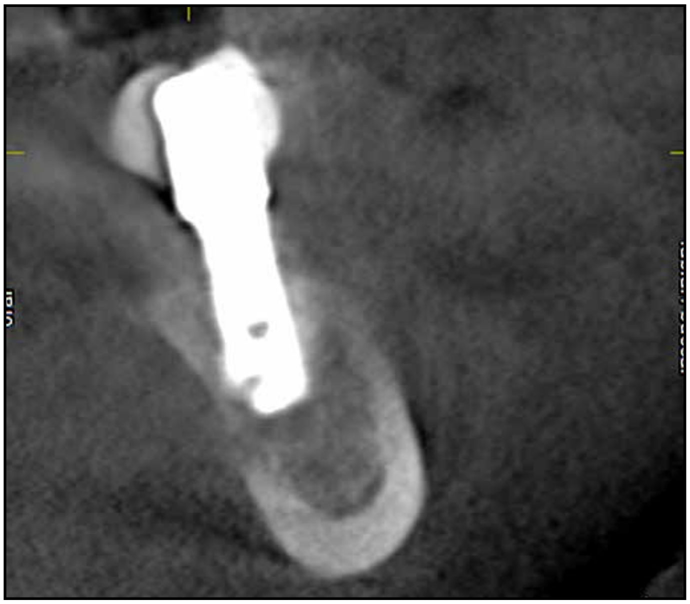


Figure 9: Radiographic image of iatrogenically placed implant at site 30.

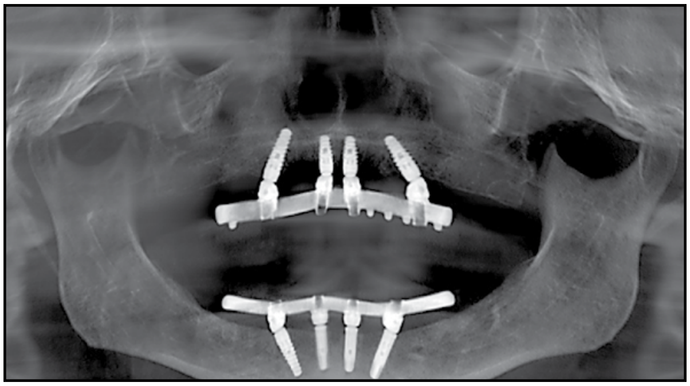


Figure 10: Iatrogenically placed dental implants removed and injured right inferior alveolar nerve treated with amnion-chorion protocol.

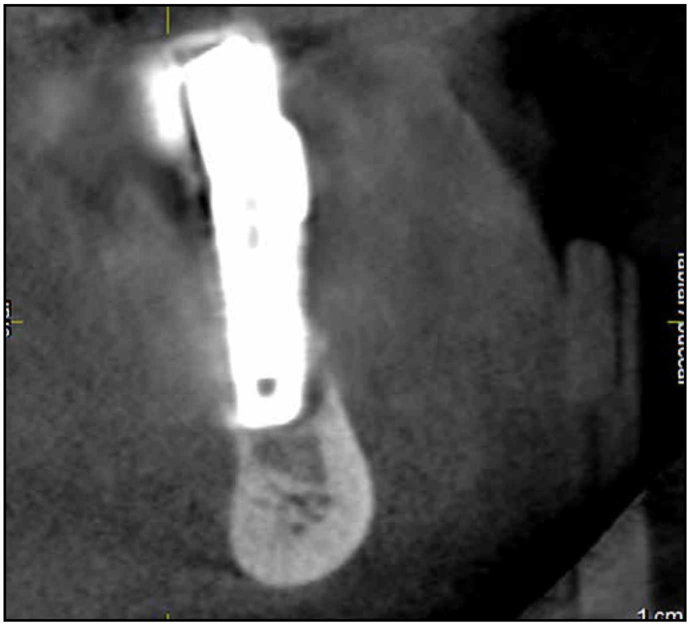


Figure 11: Iatrogenically placed dental implant penetrating mental foramen.

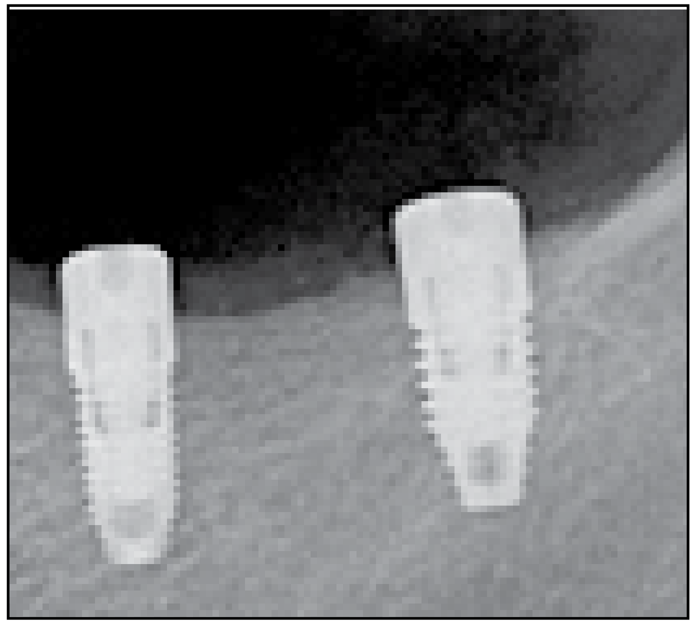


Figure 12: Iatrogenically placed dental implant (right) penetrating mandibular canal.

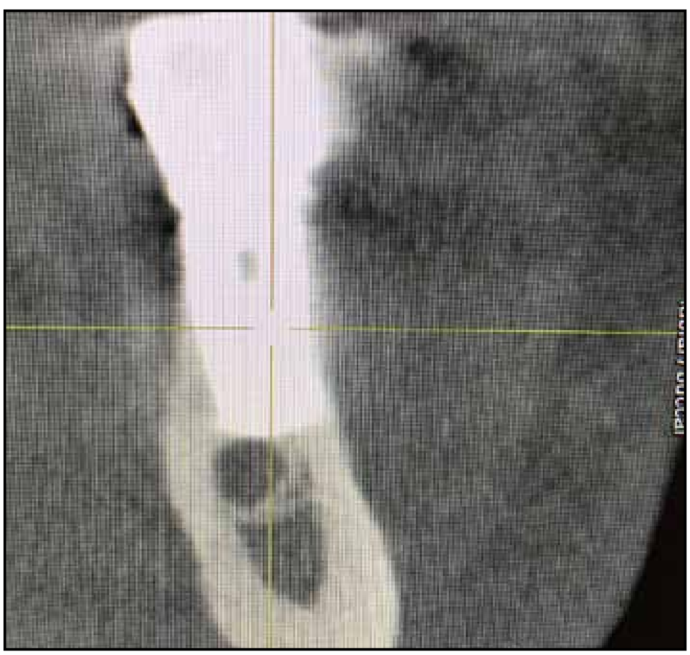


Figure 13: Radiographic image of iatrogenically placed implant at site 30.

Over follow-up periods ranging from 3 to 7 years, no patients have reported any regression in the improvements attained following treatment of their neural maladies. Furthermore, at no point during treatment or follow-up did any patient report any worsening of their neurosensory symptoms.

DISCUSSION

Neurosensory disturbances following the placement of dental implants are common with up to 73% of dentists encountering such issues in during the course of their practice.[9] The inferior alveolar nerve consistently ranks as the nerve most commonly affected by the placement of dental implants with rates of altered sensation reaching as high as 43.5%.[31] Accordingly, iatrogenic damage to the inferior alveolar nerve following the placement of dental implants is one of the most common dental malpractice claims.[32] Neurosensory disturbances of the inferior alveolar nerve

Table 2: Misch and Resnik[9] Treatment Protocol
1. Pre-surgical subjective nerve mapping of affected sites.
2.Repositioning or removal of any irritant in close approximation to the neurovascular bundle.
3. Topical application of 4mg/ml dexamethasone solution.
4. No bone graft materials placed into osteotomy site.
5. Cryotherapy ice applied to surgical site for one week.
6. Place patient on 6-day post-surgical regimen of oral dexamethasone.
7. Place patient on post-surgical NSAIDs (600-800mg, TID for up to 3 weeks).
8. Post-surgical subjective nerve mapping of affected sites.

range from transient to permanent with varying degrees of intensity depending on the etiology of the cause. Temporary and lower grades of neural disturbances are sometimes seen with non-iatrogenic post-surgical healing. Post-surgical bleeding, edema, and/or hematoma occasionally cause nerve compression resulting in paresthesia that typically resolves spontaneously over time.[33] A 2016 meta-analysis of the incidence of altered nerve sensation after mandibular dental implant surgery indicated that up to 91% of patients would return to "normal sensation" within one year of surgery when damage to the inferior alveolar nerve was non-catastrophic.[33] Over the past decade, a handful of protocols have been proposed to treat and conservatively manage neurosensory disturbances following dental implant treatment. In 2010, Misch and Resnick[9] proposed treating mandibular neurosensory impairment with a combination of implant removal, irritant removal, topical steroid application, systemic corticosteroids, NSAIDs, and cryotherapy (Table 2). In 2011, Juodzbalys et al.[11] proposed the IANIDIS protocol for dental implant related impairment of the inferior alveolar nerve. The IANIDIS protocol incorporated implant and irritant removal, topical steroid application, systemic corticosteroids, NSAIDs, diuretics, vasodilators, antihistamines, and B-group vitamins (Table 3). In 2013, Kim et al.[12] proposed a conservative treatment protocol (Table 4) for management of dental implant induced inferior alveolar nerve injury that included implant and irritant removal, systemic corticosteroids, vitamin B-12, anti-convulsants, low dose NSAIDs, and heat therapy. Of these treatments, the IANIDIS protocol showed neurosensory improvement in all patients after 3 months while the protocol of Kim et al. showed no improvement in nearly 70% of treated patients. One significant difference of note between the Kim et al. and IANIDIS study of Juodzbalys et al. is the time elapsed between inferior alveolar nerve injury

Table 3: IANIDIS[11] Treatment Protocol
1. Confirmation of injury with patient.
2. Identify related risk factors.
3. Identify likely etiologic risk factors.
4. Pre-surgical subjective nerve mapping of affected sites.
5. Repositioning or removal of any irritant in close approximation to the neurovascular bundle.
6. Topical application of 4mg/ml dexamethasone solution.
7. Place patient on post-surgical NSAIDs (400-800mg, TID for 1-3 weeks).
8. Place patient on 6-day post-surgical regimen of oral dexamethasone.
9. Place patient on post-surgical diuretics for 5 days.
10. Place patient on post-surgical vasodilators for 10 days.
11. Place patient on post-surgical antihistaminic drugs.
12. Place patient on post-surgical B-group vitamins.
13. Post-surgical subjective nerve mapping of affected sites.

and neural treatment initiation. While all but one patient in the IANIDIS study were treated within 10-52 hours of neural injury, the mean interval between nerve injury and treatment in the Kim et al. study was 10.91 months. This significant difference in time between neural injury and treatment initiation is a possible reason for the vastly different outcomes between these two studies. The work of Khawaju and Renton[34] may support this statement as their study suggested that early treatment within 36 hours of dental implant related neural injury could greatly minimize post-surgical neuropathy.

While mild neurological deficits of the inferior alveolar nerve may occur secondary to iatrogenic placement of dental implants, more severe neurological complications may occur as well. Most cases of advanced neuropathy following the placement of dental implants tend to be iatrogenic in nature and are rarely seen with non-iatrogenic placement of dental implants. In some cases, overpreparation of the implant osteotomy may lead to drill penetration into the mandibular canal.[35,36] Juodzbalys et al.[10] described 5 degrees of implant drill penetration into the mandibular canal that could result in varying severity of damage to the inferior alveolar nerve. It is important to note that dental implant drills are often longer than their corresponding depth markings and may

Table 4: Kim et al.[12] Treatment Protocol
1. Pre-surgical subjective nerve mapping of affected sites.
2. Repositioning or removal of any irritant in close approximation to the neurovascular bundle.
3. Place patient on post-surgical Prenidsolone prescription for 7 days.
4. Place patient on post-surgical NSAIDS ("aspirin" TID).
5. Place patient on post-surgical B-group vitamins.
6. Place patient on post-surgical Neurontin TID.
7. Place patient on post-surgical narcotics as needed.

mislead inexperienced dental implant surgeons to overprepare dental implant osteotomies to excessive depths.[37] Just as overpreparation of the implant osteotomy can damage the inferior alveolar nerve, placement of the actual implant fixture into the mandibular canal can do the same. Six degrees of dental implant penetration into the mandibular canal have been noted.[10] In cases where dental implants penetrate the mandibular canal, removal of the fixture is advocated.[34,37,38] Neurosensory deficits of the inferior alveolar nerve will vary depending on the amount of drill or implant penetration into the mandibular canal. While it does happen in cases of gross negligence, complete drill or implant transection of the inferior alveolar nerve is rarely seen due to clinicians following standard peri-operative dental implant protocols of acquiring and analyzing both pre-operative and intra-operative radiographic measurements relative to the mandibular canal. In the rare cases of known complete nerve transection, immediate referral to a nerve repair specialist is recommended as conservative treatment of such injuries has minimal positive effect.[9] Because the majority of implant surgeons follow standard peri-operative treatment protocols, if iatrogenic complications arise, they tend to be related to partial penetration or near penetration into the mandibular canal. Partial or near penetration into the mandibular canal may occur due to drill slippage, varying degrees of bone density coronal to the mandibular canal, improper radiographic angulations, and patient movement.[35,36] Such penetration injuries may result in a variety of possible injuries including complete resection, crushing, stretching, or entrapment injuries to the inferior alveolar nerve.[9] Because the nerve fibers are not completely severed in such scenarios, conduction capability remains and less invasive treatment remains an option. When initiated early, typically within 36 hours of injury, prognosis is generally good. In a systematic review and meta-analysis of altered sensation following mandibular dental implant surgery, Lin et al. noted that 91% of affected patients regained "normal sensation" one year after treatment while only 3% of affected patients reported continued altered sensation.[33] Gregg et al. noted that 8% of patients with dental implant related inferior alveolar nerve damage had permanent neurosensory deficits.[4] Juodzbalys et al. noted that "all patients were successfully treated" for implant induced neural impairment with the IANIDIS protocol.[11] However, careful analysis of the data in the Juodzbalys et al. article reveals that 8 of the 16 patients in the study "completely healed", 7 of the 16 patients had moderate sensory alteration, and 1 of the 16 patients continued to have severe sensory alteration after treatment. Casual skimming of this article or just reading the abstract may lead one to believe that this treatment protocol cured all affected patients as the article states that all patients in the study "were successfully treated with the IANIDIS protocol." In reality, while all patients in the study did show improvement, only 50% of the patients fully recovered neurosensory function. It is important to note that the remaining 50% of patients treated for iatrogenic dental implant damage to the inferior alveolar nerve retained some degree of neurosensory impairment after treatment. These findings are actually in line with the findings of Kim et al. who noted that 70% of patients with inferior alveolar nerve damage showed no improvement with non-surgical neural treatment.[12]

When treating implant induced neural injuries, published literature suggests that time is of the essence for improved chances of recovery. Khawaja and Renton[34] suggests a magic window of 36 hours post dental implant nerve injury while Juodzbalys et al.[11] showed benefits when treating patients within 52 hours of injury. Kim et al.[12] treated patients nearly 11 months after dental implant induced nerve injury and noted that only 16.4% of these patients experienced improved neurosensory outcomes. The patients treated in the current case series had an average of 6.25 years elapsed from the time of iatrogenic dental implant injury to presentation for treatment. Although the patient population in the current report is very small, it is interesting to note that all patients treated with the amnion-chorion protocol experienced significant improvement in neurosensory outcomes despite the very long interval between nerve damage and nerve treatment. The amnion-chorion protocol utilized for the treatment of these patients is based on the protocols initially proposed by Misch[9] and Juodzbalys et al.[11] The concepts of irritant removal, localized and systemic anti-inflammatory treatment, and cryotherapy are retained with the addition of localized application of placental growth factor.

Placental growth factor was specifically chosen for this protocol based on published medical studies that have shown positive results when the material was used for nerve repair. Animal studies involving the complete transection of sciatic nerves have shown dramatic improvements in physical, electrophysiological, and histologic assessments when amnion membranes were applied to the damaged nerve.[21-26] Sadriae et al. found that physical movement was dramatically improved by 8 weeks in limbs of damaged nerves that were treated with amnion and steroid application.[21] These results were consistent with multiple other studies that found similar physical improvements within 2-12 weeks of neural treatment.[23,24,26] Concerning electrophysical results, numerous studies show improved neural conduction amplitudes 8-12 weeks after amnion treatment.[26,39,40] Finally, multiple studies show histologic improvements in damaged nerves treated with amnion. Meng et al., Zhang et al. Mohammadi et al., and Sari et al. all found significantly increased numbers of myelinated axons, less inter-axonal fibrosis, improved axonal diameters, improved myelin thickness, and improved neurite densities when damaged nerves were treated with amnion.[24-26,40,41]

The encouraging results of these animal studies for amniotic neural treatment have been tested and confirmed in human subjects. Utilization of amnion membranes has been used in a number of studies evaluating prostatectomy treatment. In a 2015 case controlled study by Patel et al.,[18] dehydrated human amnion-chorion allograft was wrapped around the neurovascular bundle during robot assisted radical prostatectomy. Traditionally, radical prostatectomy has been associated with long convalescent periods due to incontinence and impotence caused by inflammatory responses secondary to traction of the neurovascular bundle.[19,20] In this study, patients treated with amnion-chorion had faster returns to continence and potency compared to conventionally treated patients. A 2017 study by Pinies et al.[17] also evaluated the use of dehydrated human amnion-chorion allograft in the treatment of robot assisted radical prostatectomy. This study with a large experimental 235 patient population, was compared to a control group of 705 patients. While the controlled patients received traditional treatment, the experimental group had amnion-chorion grafts applied to the neurovascular bundle at the time of surgery. Measures of potency, the ability to achieve and maintain erections firm enough for sexual intercourse, were significantly lower in the experimental group. While both of these studies showed significant benefits with the use of amnion-chorion membranes, neither study showed any detrimental effects with use of the material.

In the present study, multiple patients with longstanding damage to the inferior alveolar nerve were treated with minimally invasive protocols that employed the benefits of amniotic membranes. Following removal of the suspected irritants, the damaged nerves were treated with a combination of anti-inflammatory medications and amniotic membranes. In all cases, patients experienced significant improvements in neurosensory function. Multiple studies indicate that treatment of damaged inferior alveolar nerves should occur within 36-52 hours to provide the best chance of recovery and that minimal improvement may be achieved with long-standing nerve damage.[11,34,42,43] The patients in this report had nerve damage of an average of 6.25 years duration prior to the initiation of neural treatment. How then, did these patients experience improvements to neurological function? Prior studies involving irritant removal and anti-inflammatory treatment have found minimal improvement to neurosensory deficits when the damage was long-standing.[12] The current study, however, found results that differed from these findings. The most significant variable between the protocol in this paper and those previously published is the addition of amnion-chorion placental based growth factors. Was it the addition of amnion-chorion that allowed for the improved neurosensory results for the patients presented in this report? As this is simply a retrospective observational report and not a prospective case-controlled study, it is impossible to say. However, the documented benefits of amniotic membranes for the treatment of nerve damage in multiple other studies and the promising findings of the current paper suggest that this is a strong possibility.

The mechanisms by which amniotic membranes possibly aid neural recovery is multifaceted. Inflammatory reduction is one of the initial ways that amnion may aid neural recovery. The anti-inflammatory effects of placental membranes are well documented. Solomon et al.[42] cultured human corneal limbal epithelial cells on either freshly frozen and thawed human amniotic membrane or tissue culture plastic. These cells were plated on amnion tissue and assayed for the expression of inflammatory cytokines. The cultures demonstrated that cryopreserved amnion directly suppressed the expression of pro-inflammatory cytokines at the protein and mRNA levels. In another study of transepithelial photorefractory keratectomies in rabbits, the application of fresh amnion showed a significant reduction in the number of leukocytes and less keratocyte death compared to controls, demonstrating the anti-inflammatory effects of amnion.[43] When studying the effects of amniotic membrane on corneal wounds in rabbits via histopathologic, proteinase assay, and zymography, Kim and colleagues[44] reported decreased polymorphonuclear leukocyte (PMN) infiltration, decreased macrophage chemotaxis, and inhibited proteinase activity at treated sites. In reviewing the use of amniotic grafts for ocular surface reconstruction, Tseng[45] noted the anti-inflammatory effects of the graft as did Güell et al.[46] in their treatment of symptomatic bullous keratopathy. Koob and colleagues have performed multiple studies evaluating amniotic tissues such as dHACM for anti-inflammatory modulators via enzyme linked immunosorbent assays (ELISA) with significant findings.[47,48] These numerous studies demonstrate the significant anti-inflammatory effects of placental membranes. So how do these help with neural damage? Upon being injured, the inflammatory response often induces conduction blocks in affected nerves causing temporary paresthesia. Continued or excessive edema may eventually lead to segmented demyelination of affected neural sheaths and axonal damage, resulting in longer bouts of neurosensory deficits.[49] Certain inflammatory factors such as phospholipase are thought to be involved in the process of myelin degeneration.[41] Inhibition of phospholipase and other inflammatory factors is the reason for localized and systemic administration of corticosteroids following neural injury.[9-11,21] The addition of amniotic membranes to the sites of neural injury add to the anti-inflammatory effect.

In cases of injury without complete nerve transection, as was the case with the patients in this report, impaired neural transmissions may result in sensory disturbances. If the extraneural tissues are damaged, placental allograft tissues may act as a substrate for axon growth.[49] Multiple studies have shown amnion may be used as a peripheral nerve conduit and aid neural regeneration.[50-53] The histomorphometric studies amnion treated transected nerves in rats have shown robust axonal healing compared to non-amnion treated sites.[21-26] Upon removal of the source of irritation, placing amniotic membranes at the site of damage to the inferior alveolar nerve may indeed follow these same patterns and aid in the healing of damaged neural tissue.

CONCLUSION

As more dental implants are placed by dentists with varying levels of training, skill, and experience, the risk of iatrogenic damage to adjacent nerves such as the inferior alveolar nerve remains a concern. The application of growth factors such as amnion-chorion to existing conservative protocols provides a minimally invasive option for the treatment of nerve damage. The promising results of the current report, in addition to the positive results of previously published animal and human studies in medical literature, provide basis for further exploration of the use of placental tissues for repair of nerve damage secondary to the placement of dental implants. Case controlled animal studies with physical, electrophysical, and histomorphometric analysis would provide valuable insight into the use of this material for the treatment of dental implant induced neural injuries.

Correspondence:
Dr. Dan Holtzclaw
Email: dholtzclaw@jiacd.com

Disclosure
Dr. Holtzclaw has a financial interest in Snoasis medical and serves as a clinical advisor for the company.

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