DOI: 10.5152/eurasianjmed.2018.17422

Manuscript Type: Original Article

Title: A Histopathological Investigation of the Effectiveness of Collagen Matrix in the Repair of Experimental Spinal Dura Mater Defects

Running Head: Spinal Dural Repair with Collagen Dura Matrix

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Cite this article as: Calikoglu C, Cakir M, Tuzun Y. A Histopathological Investigation of the Effectiveness of Collagen Matrix in the Repair of Experimental Spinal Dura Mater Defects. Eurasian J Med 2018; 50: 10.5152/eurasianjmed.2018.17422.

Abstract

Objectives: This study investigated the suitability of the collagen matrix as a dural graft in the repair of experimental spinal dura mater defects.

Materials and Methods: In the study, 30 New Zealand white rabbits were used. The rabbits were divided into a study and control group. In both groups, following exact laminectomy (Th 10 and 11) in rabbits under the isoflorane anesthesia, a spinal dural defect 1x0.5 cm in size was formed. In the study group, the dura mater defect was covered with collagen matrix; in the control group, the excised dura was sutured back to its original position. At the end of the follow-up period, the rabbits were sacrificed. In all subjects, the vertebral colon was excised completely, and it was fixed in 10 % formaldehyde solution. Sections 3 mm thick were taken from the specimens, stained with

hematoxylin and eosin, and examined under a light microscope. The stained sections were evaluated under light microscopy with regard to the cellular inflammatory response, fibroblastic proliferation, foreign body reaction, and capsule formation.

Results: The collagen matrix was completely absorbed, and it was easy to use since it did not require sutures. Foreign body reactions were minimal in the early period and were resolved entirely in the end. Inflammatory response against the collagen matrix was no greater than in the control group in which the dura was sutured primarily and then closed, eventually disappearing entirely, and no adhesion formation resulted. Collagen permits successful regeneration by combining with the dura mater. No capsule formation was observed in either group.

Conclusions: This study shows that collagen is suitable for duraplastic procedures and that it may be a useful agent in patients in whom the dura cannot be closed primarily due to retraction, constriction, or excision.

Keywords: *collagen*, *dural substitute*, *spinal dura mater*

Introduction

The repair of both cranial and spinal dural defects is still a problem frequently encountered by neurosurgeons. Spinal dural defects may arise in association with traumatic or neoplastic destruction, following routine spinal surgery procedures, after neurosurgical interventions requiring dural resection or for congenital reasons such as meningomyelocele, when duraplasty has to be performed [1–3]. If these defects are not repaired effectively, they may lead to meningoneural adhesions, greater scar tissue formation in the epidural region, pachymeningitis or soft tissue infections, cerebrospinal fluid (CSF) leaks or collections, decreased wound healing, neural herniations, tethered cord and pseudomeningocele development, and also to neurological deficits as a consequence [4].

The repair of dural defects with primary sutures may be problematic for reasons such as the defect site being unsuitable for repair or the residual dural quality being insufficient, and dural graft materials are frequently required [5]. Investigation of materials for the closure of dural defects goes back to the late 19th century [6].

The majority of materials involved in dural repair have been used in the cranial region, and relatively few studies concerning spinal duraplasty have been performed [6–13]. Factors such as the repair of dural defects using familiar suture methods that exacerbate the risk of CSF leaks, neural fiber damage, infection and meningoneural adhesion, or the defect being located in an area where suturing is not possible, have given rise to alternative dural graft materials and experimental evaluation [2, 3, 5].

The purpose of this study was to investigate the suitability, reliability, and potential superiority of the collagen matrix as a dural graft material not requiring sutures in the repair of experimentally induced spinal dural defects.

Materials and Methods

Approval for this experimental study was granted by the Local Ethical Committee. Thirty white New Zealand rabbits, aged 6–12 months and weighing 2.5–3.5 kg, were used. Animals who died during the surgical procedure or the follow-up period were replaced with new subjects. Experimental animals were divided into two main groups: one half as the study group and one half as the control group. The study and control groups were both further divided into three subgroups of 5 animals each for 1-, 2-, and 3-month follow-up periods.

Half an hour before surgery, experimental subjects were injected intramuscularly with 5 mg/kg ketamine hydrochloride (Ketalar, 50 mg/ml, 10 ml vial, Eczacıbaşı ilaç Sanayi ve Ticaret A.Ş. Küçükkarıştıran, Luleburgaz, Tekirdağ, Turkey) for sedation. Anesthesia was induced with the administration by mask of 5% isoflurane (Forane, Abbott Laboratories Ltd., Queensborough, Kent, England). Anesthesia was maintained with 1%–3% isoflurane inhalation. The skin in the thoracolumbar region was shaved to a width of 6 cm along the midline. Following complete laminectomy at Th10 and Th11 with a vertical thoracolumbar midline incision, a section of dura mater approximately 1x0.5 cm in size was removed. In the study group, the collagen matrix (DuraGenTM, Integra LifeSciences Corporation, 105 Morgan Lane. Plainsboro, NJ 08536 USA) was cut in such a way as to overlap the dura mater defect margins, placed over the defect, and then wetted with 0.9% sodium chloride. In the control group, the excised section of dura mater was sutured back

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in its former position with 6/0 sutures. The muscle layer was closed with 3/0 vicryl suture material and the skin with 4/0 silk suture material. Following the surgical procedure, the animals were given 400,000 U penicillin G procaine (Pencain-K, Bilim İlaç San. ve Tic. A.Ş. Çerkezköy, Tekirdağ, Turkey) for protection against infection and 10 mg/kg intramuscular pethidine hydrochloride (Aldolan, Gerot Pharmazeutika GmbH Arnethgasse 3, 1160 Vienna, Austria) for analgesia. A prophylactic antibiotic and analgesic therapy was maintained for 5 days.

At the end of the various observation periods, subjects were sacrificed using intracardiac 10% formol solution. The skin of all subjects was opened, and the paravertebral region was entered with a transverse incision 2 cm proximal and 2 cm distal to the marker suture in the fascia. The ribs were severed using bone scissors. The vertebral column was extracted in one piece and fixed in 10% formaldehyde solution. Sections 3 pm in thickness were taken from specimens and stained with hematoxylin and eosin (H&E) under a light microscope. The stained sections were evaluated under light microscopy in terms of cellular inflammatory response, fibroblastic proliferation, foreign body reaction, and capsule formation.

A. Cellular inflammatory response: 0, No inflammation; 1, Minimal inflammation; 2, Moderate inflammation; 3, Severe inflammation.

B. Fibroblastic proliferation: 0, No fibroblastic proliferation; 1, Minimal fibroblastic proliferation; 2, Moderate fibroblastic proliferation; 3, Advanced fibroblastic proliferation.

C. Foreign body reaction: 0, No foreign body reaction; 1, Minimal foreign body reaction; 2, Moderate foreign body reaction; 3, Advanced foreign body reaction

D. Capsule formation: 0, Absent; 1, Present.

Statistical Analysis

Values obtained following histological analysis were subjected to statistical analysis using the chi-squared test on the SPSS 10.0 software.

Results

Histopathological results

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A. Cellular Inflammatory Response

At the end of the first month, moderate inflammatory response was present in 1 subject in the control group, and minimal inflammatory response was present in 2. The inflammatory response observed essentially consisted of mononuclear cells. There was no inflammatory response in the remaining 2 animals. In the study group, in which the dura mater defect was closed with collagen matrix, the moderate inflammatory response was present in 1 subject and the minimal inflammatory response in 3. The majority of cells constituting the inflammatory response were mononuclear cells. No inflammatory response was determined in the other animal.

In the control group in the second month, minimal inflammatory response was present in 1 animal, and none in the other 4. Minimal inflammatory response was present in 2 animals in the study group, and none in the remaining 3.

In the third month, no inflammatory response was observed in any animal in either group.

The cellular inflammatory response to collagen matrix in the first month was greater than in the control group, but the difference was not statistically significant (p=1.0) (Table 1).

The cellular inflammatory response was greater in the second month in the collagen matrix group, but the difference between the two groups was not statistically significant (p=0.49). In the third month, no cellular inflammatory response was present in any subject in either group (Table 1).

B. Fibroblastic Proliferation

In the first month, minimal fibroblastic proliferation accompanied by capillary proliferation was determined in 3 subjects in the control group, and moderate proliferation was determined in 2. In the study group, there was a marked fibroblast invasion of the collagen matrix covering the defect region, and collagen had begun accumulating. Advanced fibroblastic proliferation with new collagen formation was observed in 2 subjects, moderate proliferation in 2, and minimal proliferation in 1 (Figure 1).

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Examination of specimens from experimental animals sacrificed in the second month revealed minimal fibroblastic proliferation in 3 subjects from the control group, while no proliferation was observed in 2. In the study group, advanced proliferation and increased collagen deposition was determined in 1 subject, moderate proliferation in 2, and minimal proliferation in 1 (Figure 2). Vascularization persisted in both the study and control groups.

In the third month, minimal fibroblastic proliferation was present in 2 subjects in the control group, while no fibroblastic proliferation was observed in 3. In the study group, moderate fibroblastic proliferation was present in 2 subjects, and minimal proliferation in 3. Intensive collagen deposition (Figure 3) was observed in the defect region, and the collagen matrix was completely absorbed. Capillary structures had decreased in both groups.

Greater fibroblastic proliferation was observed in the collagen matrix group at Months 1, 2, and 3. However, the difference was not statistically significant (p 0.223, 0.079, and 0.074, respectively) (Table 1).

C. Foreign Body Reaction

The same degree of foreign body reaction was observed in both groups in the first month. In Month 2, no subjects in the collagen matrix group exhibited a foreign body reaction. The difference between the two groups was not statistically significant (p=0.287). In Month 3, no subjects in the collagen matrix group exhibited foreign body reaction, and the difference between the two groups was again not statistically significant (p=0.114) (Table 1).

D. Capsule Formation

No capsule formation was observed in either group at any observation period. There was no neomembrane formation determined.

Discussion

Numerous materials have been used to date for dural repair. However, the majority of studies have involved cranial dura defects, and far fewer have considered spinal duraplasty.

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The graft materials most commonly employed by neurosurgeons in the repair of dural defects are autogenous tissues such as the temporal fascia, pericranium, and fascia lata [4, 6, 12, 13, 14]. These autografts naturally confer a number of advantages, being easy to use, non-toxic and economical, and exhibiting perfect biological behavior [10]. However, it is not always possible to use these tissues as autografts. The fascia of the paravertebral muscle of pericranium may be damaged in the event of trauma, and a sufficient quantity to close the defect may not be available. The autologous fascia lata graft has become less popular due to requiring an additional operation, prolonged surgery time, additional scar formation, and adhesion in the region of application [15, 16].

Alloplastic materials have been reported to cause inflammatory reaction and to be expelled from the wound, while in the late period, they may lead to extraordinary vascularity and subsequently to hemorrhage [17, 18]. The use of entirely resorbable materials is therefore still essential for dural repair [14]

In their experimental study, Keller et al. [6] reported that silicone-coated Dacron was always encapsulated by connective tissue, that the thicker ventral part of the capsule extended inferiorly, frequently compressing the cord beneath, and that it is not suitable for duraplasty. Banerjee et al. [19] and Adegbite et al. [17] also published similar reports concerning silicone-coated Dacron.

There are various advantages to the use of absorbable materials as dural grafts. In theory, chronic foreign body reaction with membrane formation can be avoided with “biodegradable” implants. Resorbable synthetic materials such as vicryl (polyglactin 910) mesh and polydioxanone/polyglactin have been successfully used in dural repairs [15].

Collagen is another resorbable material tested in different forms, such as a film layer and sponge [2, 3, 11]. Collagen possesses numerous advantages: It is resorbable, degradation can be controlled with cross-linking, and it can be worked like a biomaterial. It is also hemostatic and capable of supporting cellular reproduction and tissue reconstruction. However, collagen must be highly purified to avoid immunological and severe inflammatory reactions, must not be pyrogenic, and must not contain telopeptides [14].

The collagen sponge was initially developed to protect the brain beneath the retractor [20]. Collagen sponge fibers behave like a scaffold for fibroblasts producing new collagen, and dural healing begins

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from inside the sponge rather than around it. Yet in most semisynthetic biomaterials healing begins around the dural repair graft. Dural repair is facilitated by the graft's natural pores, and previously used layering processes can reduce the biological properties of collagen necessary for fibroblasts to enter the graft. This also explains why graft encapsulation does not occur with the collagen sponge [7, 17, 21].

For all these reasons, in our study, we compared the collagen matrix still in clinical use as a dural graft in spinal dural graft repair with experimental animals' own dura excised by us. Since silk is a suture material widely used in our and many other clinics, we closed the dural defects induced in the control groups in a waterproof manner with the excised dura and 6/0 atraumatic silk. Our objective in doing this was to evaluate the foreign body reaction in areas through which the silk suture material passed and areas through which it did not pass.

Meddings et al. [22] used collagen Vicryl (bovine collagen coated vicryl mesh), Zenoderm (procine dermis), and Lyodura (lyophilized human cadaveric dura [LHD]) to close defects established in the rabbit dura mater. They reported that vicryl remained visible under microscopy up to 8 weeks after surgery, but that no sign of the implant material remained after 3 months. They also revealed that during this time, a new dura layer formed reminiscent of the dura mater in size and appearance.

In an experimental study in which double-layered human collagen as a dural graft was assessed, Laquerriere et al. [14] reported that the material began being absorbed macroscopically on Day 30, disappearing on Day 90, and that histologically, both collagen graft materials disappeared on Day 90, being entirely replaced by fibrocallogenous tissue resembling a newly formed dura.

Matsumoto et al. [23] used a membrane composed of polyglycolic acid mesh, collagen sponge, and gelatin sponge to close dura mater defects induced in dogs. At observations 2 months after the implantation, they reported that the graft material had been partially resorbed and that a thin fibrous membrane had formed in the implant region. However, 4 months after implantation, the implanted membrane was completely resorbed, and no membrane residue remained.

In the present study, the collagen matrix was visible in the first month, but resorption had begun in places. At 2 months, the collagen matrix was still visible but was well absorbed, while at 3 months,

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the collagen matrix was no longer visible and was entirely resorbed. These findings were very similar to those by Meddings et al. [22].

Differing results concerning the emergence and severity of the host reaction to the dural graft materials used, and varying interpretations of these, have been reported. Abbott et al. (7) observed findings suggesting minimal foreign body reaction in cases of dural defect in which they used LHD grafts, while Crawford et al. [24] compared skin grafts and preserved homologous dura and skin grafts in dural defects induced in animals and reported few chronic inflammatory cells in areas close to homologous dura mater sutures.

In their experimental models, Meddings et al. [22] maintained that no foreign body reaction to collagen/Vicryl occurred after 3 months, but that foreign body reaction to LHD and swine skin persisted. Cantore et al. [25] emphasized that no rejection was observed after dural homotransplantation.

Narotam et al. [2] reported no astrocytic and inflammatory reaction in lower brain sections from autopsy specimens on Day 40. They determined a mild inflammatory cell reaction to Vicryl sutures and a foreign body giant cell reaction. They reported no inflammatory cell or foreign body giant cell in 1 patient undergoing repeat meningioma 5 years subsequently.

Several studies have examined concerns about the safety of dural grafts due to septic complications. Studies of dural graft materials have generally reported no increase in infection rates [3, 7, 22, 26], with Abbot and Dupree [7] reporting a figure of 6%, and Cantore et al. [25] a figure of 11%.

In another study by Narotam et al. (3), no acute or chronic inflammatory cell infiltration or foreign body giant cell reaction were observed at 1, 3, or even 9 months. We obtained similar results. This indicates that the collagen sponge is inert. Also, no rejection reaction developed in our study. Similar rates of foreign body reaction were observed in the collagen matrix and control groups at 1 month. No foreign body reaction was observed in any subject in the collagen matrix group at 2 months. The difference between the two groups was not statistically significant. At 3 months, no foreign body reaction was determined in any member of the collagen matrix group. The difference between the two groups was again not statistically significant. Our study corroborates the thesis that the graft we

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employed does not increase wound infection. Our studies were similar to those by Noratam [2, 3, 27], Abbott [7], Cantore et al. [25], and Crawford [24].

Crawford (24) stated that metal layers such as gold, silver, platinum, aluminum, nickel, and stainless steel reported as being first used in 1890 led to encapsulation and severe meningocerebral adhesion. Capsule formation arising in the long or short term with graft materials employed can give rise to compression findings and may appear as hyperdense lesions reminiscent of meningioma at computerized tomography [17, 28, 29]. Indeed, some authors have reported observing subdural and subarachnoid bleeding after quite lengthy periods in cases in which silastic material was used [29]. Şengül et al. [16] determined no capsule formation due to the collagen matrix. We also observed no capsule formation due to the collagen matrix used as a dural graft in our study.

The porous structure of the collagen sponge has been reported to facilitate fibroblastic proliferation and dural repair [9]. The main criticism of the collagen sponge is that, due to its porous nature, it may be insufficiently resistant to the CSF leakage. However, Narotam et al. [3] observed no CSF fistula in any animal in their study.

A pattern of fibroblastic proliferation inside the collagen sponge in 5 days at the earliest, and being well observed on the 15th day, confirms that graft porosity is indeed an essential feature in the success of dural repair [2]. In addition, since the collagen sponge is sufficiently porous to allow cell proliferation, it is superior to the collagen film in terms of tissue regeneration [23]. The porosity of the material is responsible, not only for its good use characteristics, but also permits fibroblasts to enter the graft to establish tissue repair [30].

Although it has long been known not to provide waterproof dural closure, the use of non-porous grafts still has its adherents [7, 14, 22, 31]. Narotam et al. [2] reported that the collagen sponge is very useful in the repair of such dural tears, on condition that this is done in a layer-on-layer manner. Narotam et al. [2, 3] suggested that the pores in the collagen sponge and its sponge-like structure facilitate the direct and early penetration of fibroblasts into the collagen sponge. The proximity of fibroblasts to the collagen sponge has suggested that it behaves like a scaffold for new collagen deposition.

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Fibroblastic proliferation in our study was greater in the collagen matrix group on Months 1, 2, and 3, although the difference was not statistically significant. Other studies have also reported that the collagen sponge can be easily used and shaped without a lengthy saturation process and difficulty in application [11, 16, 27].

Suture use is reduced by the use of coated grafts. These coated grafts not only reduce operative time, but also and most importantly reduce foreign body giant cell reaction [11]. Since the collagen sponge is inert, it does not encourage foreign body reactions, and it has been reported to be superior to other collagen products [2, 3]. In our study, although the difference was not statistically significant, cellular inflammatory response in the group in which we used sutures was greater than that in the collagen matric group, in which sutures were not employed. This finding is in agreement with other studies using coated grafts.

In spinal surgeries, where it is usually difficult to suture a graft, the use of Duradry has been reported to be beneficial in terms of reducing surgical time. Moreover, no fistula has been reported in such cases [12, 27].

Several synthetic and biological materials have been unsuccessful in research aimed at identifying the ideal dural graft. From that perspective, the collagen sponge appears promising. It establishes a sufficient barrier, does not give rise to inflammatory reaction in the host, is easy to use, and can be easily shaped depending on the dural defect. It coalesces early with the dura, and no suture removal is required. Fibroblasts use the fibers of the collagen sponge as a skeleton and perform dural repair without the risk of graft encapsulation or fragile neomembranous capillaries.

Investigation being an animal-based study and an inadequate number of rabbits used in the experiment were the most important limitations of this study. Therefore, the effects of collagen matrix should be further investigated with more clinical studies.

We think that, in spinal duraplasty in particular, autologous grafts not requiring secondary incisions, such as the patient's paravertebral muscle, should be implanted, but that if this is not possible, the collagen matrix can be safely used. This study shows that, as described, the collagen sponge is suitable for duraplastic procedures and is a useful agent in patients in whom the dura cannot be closed primarily due to retraction, shrinkage, or excision.

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References:

1. Kadioglu HH, Takci E, Arik M, Gündogdu C, Aydın IH. İmmun response to dehydrated human dura mater : evaluation in a rabbit model. Neurol India. 2002 ;50:256-61

2. Narotam PK, Van Dellen JR, Bhoola KD: A clinicopathological study of collagen sponge as a dural graft in neurosurgery. J Neurosurg 1995; 82: 406-412.

3. Narotam PK, Van Dellen JR, Bhoola KON et al. Experimental evaluation of collagen sponge as a dural graft. Br J Neurosurg 1993;7: 635-641.

4. Fang Z, Tian R, Jia Y, Xu TT, Liu Y. Treatment of Cerebrospinal fluid leak after spine surgery. cjtrauma 20 (2017) 81-83

5. Palm SJ, Kirsch WM, Zhu YH, Peckham N, Kihara Si, Anton R, Anton T, Balzer K, Eickmann T. Dural closure with nonpenetrating elips prevents meningoneural adhesions: An experimental study in dogs. Neurosurg 1999; 45: 875-882.

6. Keller JT, Ongkiko CM, Saunders MC, Mayfield FH, Dunsker SB. Repair of spinal dural defects: an experimental study. J Neurosurg 1984; 60: 1022-1028.

7. Abbott WM, Dupree EL Jr: Clinical results of lyophilized human cadaver dura transplantation. J Neurosurg 1971; 34: 770-773.

8. Keller JT, Dunsker SB, Mc Whorter JM, Ongkiko CM Jr, Saunders MC, Mayfield FH. The fate of autogenous grafts to the spinal dura: An experimental study. J Neurosurg 1978; 49: 412-418.

9. Thammavaram KV, Benzel EC, Kesterson L. Fascia lata grafts as a dural substitute in neurosurgery. South Med J 1990; 83: 634-636.

10. Sabatino G, Pepa GMD, Bianchi F, Gennaro C, et all. Autologous dural Subtitutes: A prospective study. Clin Neurol Neurosurg 2014(116):20-23

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11. Esposito F, Grimod G, Cavallo LM and et all. Collagen-only biomatrix as dural substitute: What happened after a 5-year observational follow-up study. Clin Neurol Neurosurg 2013 (115):1735-1737

12. Costa BS, Cavalcanti-Mendes GA, Abreu MS, Sousa AA. Clinical experience with a novel bovine collagen dura mater substitute. Arq Neuropsiquiatr 2011;69(2-A):217-220

13. Pettorini BL, Tamburrini G, Massimi L, Paternoster G, Caldarelli M, Di Rocco C. The use of reconstituted foil dura mater substitute in paediatric neurosurgical procedures – Experince in 47 patients. Br J Neurosurg, February 2010; 24(1): 51-54

14. Laquerriera A, Yun J, Tiollier J, Hemet J, Tadie M: Experimental evaluation of bilayered human collagen as a dural substitute. J Neurosurg 1993; 78: 487-491

15. Nussbaum CE, Maurer PK, Mc Donald JV: Vicryl (polyglactin 91O) mesh a dural substitute in the presence of pia arachnoid injury. J Neurosurg 1989; 71: 124-127.

16. Çetin B, Şengül G, Tüzün Y, Gündoğdu C, Kadıoğlu HH, Aydın İH. Suitability of collagen Matrix as a dural repair of experimental posterior fossa dura mater defects. Turkish neurosurg 2006; 16(1): 9-13

17. Adegbite AB, Paine KWE, Rozdilsky B: The role of neomembranes in formation of hematoma around silastic dura substitute (Case report). J Neurosurg. 1983; 58: 295-297

18. Simpson D, Robson A: Recurrent subarachnoid bleeding in association with dural substitute. Report of three cases. J Neurosurg. 1984; 60: 408-409.

19. Banerjee T, Meagher JN, Hunt WE: Unusual complications with use of Silastic dural substitute. Am Surg.1974; 40: 434-437.

20. Kurze T, Apuzzo MLJ, Weiss MH, et al: Collagen sponge tor surface brain protection. Tecnical note. J Neurosurg 1975; 43: 637-638.

21. Keener EB: An experimental study of reactions of the dura mater to wounding and loss of substance. J Neurosurg. 1959; 16: 424- 447.

22. Meddings N, Scott R, Bullock R, French DA, Hide TA, Gorham SD: Collagen vicryl-a new dural prothesis. Acta Neurochir (Wien) 1992; 117: 53-58

23. Matsumoto K, Nakamura T, Fukuda S, Sekine T, Ueda H, Shimizu Y: A Gelatin Coated Collagen-Polyglycolic Acid Composite Membran as a Dural Substitute. ASAIO Journal. 2001; 47: 641-645.

24. Crawford H: Dura replacement. An experimental study of derma autografts and preserved dura homografts. Plast Reconst Surg. 1957; 19: 299-320.

25. Cantore G, Guidetti B: Neurosurgical use of human dura mater sterilized by gamma rays and stored in alcohol: Long-term results. J Neurosurg. 1987; 66: 93- 95

26. . Mian M, Beghe F, Mian E: Collagen as a pharmacological approach in wound healing. Int J Tiss React XIV (Suppl). 1992; 1-9.

27. Narotam P, Reddy K, Fewer D, Qiao F, NathooN. Collagen Matrix Duraplasty for Cranial and Spinal surgery: Aclinical and imaging study. J Neurosurg 2007;106:45-51

28. Ongkiko CM, Keller JT, Mayfield FH, Dunsker SB: An unusual complication of dura film as a dural substitute. J Neurosurg 1984; 60:1076-1079.

29. Siccardi O, Ventimiglia A: Fibrotic-haemorrhagic reaction to synthetic dural substitute. Acta Neurochir. 1995; 132: 148-149.

30. Laun A, Tonn JC, Jerusalem C: Comparative study of lyophilized human dura mater and lyophilized bovin pericardium as dural substitutes in neurosurgery. Acta Neurosurg. 1990;107: 16-21.

31. Bang-Zong XU, Hong-Xue P, Ke-Ming L, Xi-Jin C, Ying-Dei T, Yong-Lin L, Jian L: Study and clinical application of a porcine biomembrane for the repair of dural defects. J Neurosurg 1988; 69: 707-711.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Calikoglu C, Cakir M, Tuzun Y. A Histopathological Investigation of the Effectiveness of Collagen Matrix in the Repair of Experimental Spinal Dura Mater Defects. Eurasian J Med 2018; 50: 10.5152/eurasianjmed.2018.17422.

Figure Legends

Figure 1. Graft Residue and Foreign Body Reaction 1 Month After Collagen Matrix Implantation (H&E, x100).

Figure 2. Marked Fibroblastic Proliferation 2 Months After Collagen Matrix Implantation (H&E, X100)

Figure 3. Intensive Collagen Deposition Three Months After Collagen Matrix Implantation (H&E, X100).

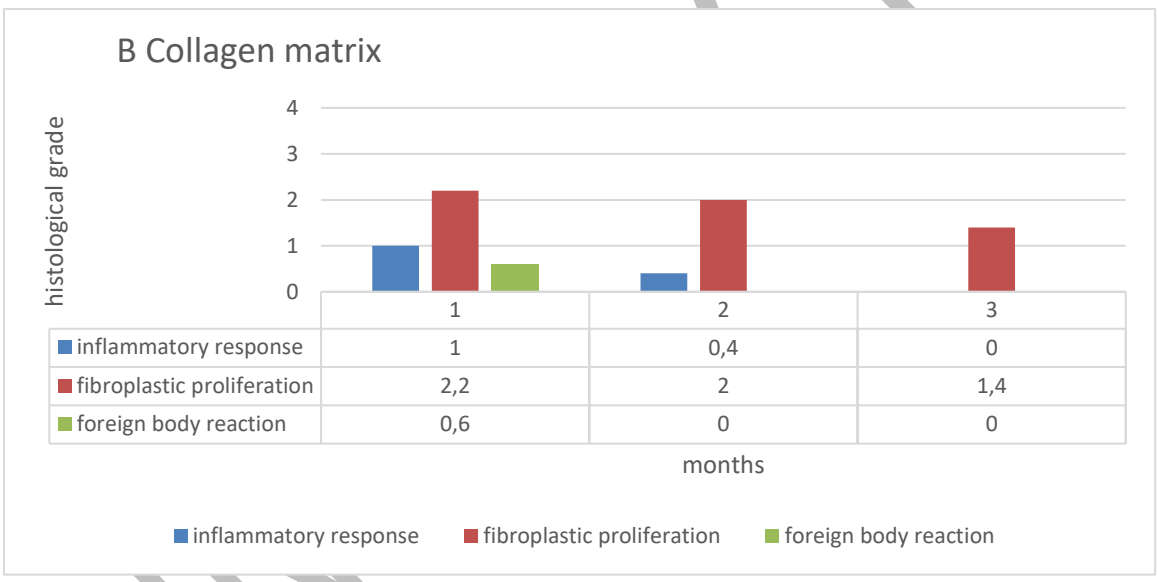

Table 1: Means of inflammatory response, fibroblastic proliferation, and foreign body reaction gradings in the control (A) and collagen matrix (B) groups.