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Histopathological analysis of duragen collagen matrix over time in humans

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DuraGen is a widely used type I collagen matrix derived from bovine Achilles tendon that promotes fibroblast ingrowth and neovascularization. However, it remains unknown the time required for dura regeneration and reabsorption of the graft. We evaluate the histopathological characteristics of implanted DuraGen in humans across multiple time points. Patients who underwent a decompressive craniectomy and duraplasty with DuraGen at our institution between January 2020 and September 2021 were prospectively enrolled. At the time of the subsequent surgery, including cranioplasty, DuraGen and associated tissues removed from patients were sent for histopathological analysis. For each patient, time from index surgery to subsequent surgery was categorized into three groups: early (0–20 days), intermediate (21–30 days), and late (> 30 days). Baseline characteristics, primary disease, operative time, complication rate, and histopathological findings were compared between groups. A total of 28 patients were enrolled in the study. Seven specimens (25.0%) were collected within 20 days after craniectomy, 9 specimens (35.7%) between 21 and 30 days, and 12 specimens (39.3%) over 31 days. Histopathologically, implanted collagen matrix, erythrocyte infiltration, and fibrin layer decreased over time, whereas fibroblasts and endogenous collagen increased. Receiver operating characteristic analysis showed that the cut-off time post-implantation for presence of endogenous collagen was 34 days after DuraGen implantation (area under the curve = 0.810). We found that DuraGen was replaced by fibroblast-derived endogenous collagen as early as 34 days post-implantation. Although certain findings remain to be further validated, the present study substantiates DuraGen as a reliable substitute, with findings derived from clinical outcomes and histopathological changes.

Keywords Collagen matrix, Cranioplasty, DuraGen, Dural regeneration, Endogenous collagen, Fibroblast, Histopathology

Abbreviations

AUC	Area under the curve
CSF	Cerebrospinal fluid
ICP	Intracranial pressure
IQR	Interquartile range
ROC	Receiver operating characteristic

Background

Dural defects can frequently occur as a result of trauma, tumor involvement and surgery. If these defects are not effectively repaired, meningeal adhesions, epidural scarring, infection, cerebrospinal fluid (CSF) leakage, and neurological deficits may occur[1,2]. Dural repair with primary sutures is sometimes difficult due to the size and location of the defect. Other factors may also effect the ability to achieve a water-tight closure such as fragility of the dura due to aging and diabetes[3]. In cases where primary closure is not possible, often a dural-graft substitute is required.

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Autologous grafts such as tensor fascia lata, temporalis fascia, and pericranium are preferred as they do not cause as severe inflammatory or immunologic reactions as other types of grafts[4,5]. However, additional surgical-site incisions are required to harvest the graft, and large grafts may be difficult to obtain without adding significant post-operative morbidity along with time under anesthesia. For these reasons, a variety of nonautologous dural substitutes have been developed, with strategic physical properties of the grafts to aid in dural closure while simultaneously avoiding host tissue response[2,6,7].

The individual characteristics of the dural grafting material have significant implications for the ease of dissection and duration of the subsequent cranioplasty procedure[8]. An ideal graft should have none of the disadvantages associated with artificial dural substitutes, such as excessive tissue reaction, graft encapsulation, neural compression, seizures, or delayed hemorrhage[7,9–11]. Avoiding adhesion formation and foreign body reaction following the application of some artificial dural graft materials is especially important when performing the cranioplasty[12,13]. Such adhesions between the musculocutaneous flap and the underlying dural repair encountered during cranioplasty can prolong surgical time and may lead to dural tears[8].

DuraGen (DuraGen®, Integra LifeSciences, Princeton, NJ, USA) is one of the most widely used biologically derived dura substitute xenograft materials, a pure type I collagen matrix manufactured from atelocollagen fibers derived from the bovine deep flexor tendon. Type I collagen acts as a substrate for fibroblast migration and proliferation[14]. This property, coupled with the open porous structure of the collagen matrix, promotes fibroblast ingrowth and neovascularization (Fig. 1)[7]. Finally, fibroblasts entering the implanted matrix organize themselves into a layered structure of cells and secreted endogenous collagen fibers that acts as a new dura mater[15]. On histopathological analysis, this can be recognized as the presence of oriented connective tissue which indicates the replacement of DuraGen with endogenous collagen. In a porcine animal model study, implanted DuraGen in the lumbar spine was completely resorbed and replaced by collagen derived from infiltrating fibroblasts within 8 weeks[6]. However, it remains unknown at what time replacement occurs in the human brain following a duraplasty. Among the limited investigations on this topic, none have compared the histological changes across multiple times points. Additionally, all have been limited to single patient case reports[7,16–19].

The time from duraplasty-to-DuraGen reabsorption and replacement with endogenous collagen may have important surgical implications. Prior investigation into histopathological findings of DuraGen surrounding locations of cerebrospinal fluid leak revealed an absence fibroblasts infiltration[18]. Conversely, areas without leak displayed fibroblasts in the same patient samples, suggesting an important role this may have on clinical mangement[18]. Currently, controversy exists on the ideal time for performing a cranioplasty following a decompressive hemicraniectomy. A recent multi-institutional study reported similar functional outcomes between early and delayed cranioplasty timing, but patients had a significantly greater risk for post-operative hydrocephalus in the early intervention group[20]. In this study, the histopathological changes of DuraGen across different time points is compared, as the time at integration of the dural graft starts to occur may help guide cranioplasty timing, which remains an ongoing area of investigation[21].

Methods

This prospective clinical study was approved by the ethics committee of the Saitama Medical University International Medical Center (approval number, 20–181). The patients were provided with written informed consent for the histopathological study. Patients in the study were also given the opportunity to refuse to participate in the study by opting out. This study is based on the current version of the Declaration of Helsinki,

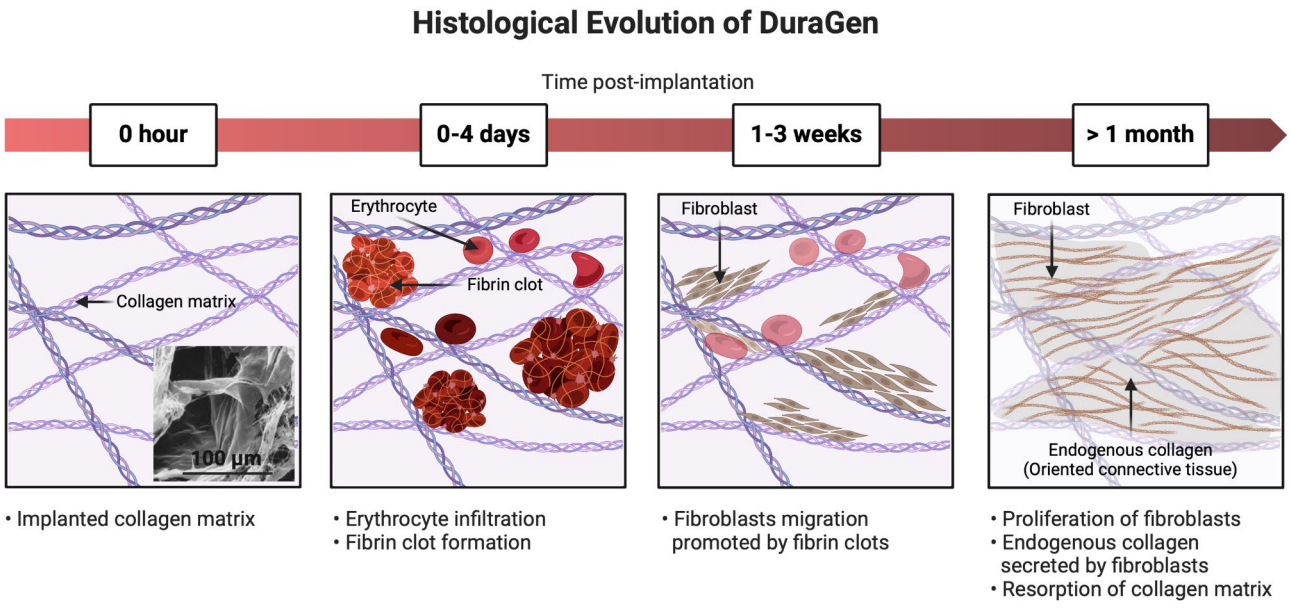

Fig. 1. Predicted histological evolution of DuraGen after implantation.

and all research processes are conducted in accordance with the relevant guidelines and regulations. Twenty-eight consecutive patients who underwent decompressive craniectomy and duraplasty for the treatment or prevention of medically refractory elevated intracranial pressure (ICP) and a subsequent surgery—either re-operation for the primary disease or cranioplasty—were included in this study. Patients were categorized into three groups according to the number of days since DuraGen implantation: early (0–20 days), intermediate (21–30 days), and late (> 30 days). Each group was compared on the following factors: the patients' age, sex, primary disease, operative time, surgical complication (cerebrospinal fluid leakage, infection), clinical complication, and histopathological findings.

All surgical procedures were performed under general anesthesia. A standard decompressive hemicraniectomy was performed that consisted of a large frontotemporoparietal bone flap, which was removed as a single piece. The dura was widely opened and if necessary internal decompression was performed including lobectomy and intraparenchymal hematoma evacuation. Duraplasty was performing using a non-sutured onlay technique with one large sheet of DuraGen completely covering the exposed surface of the parenchyma. The reflected dural margins were reapproximated to their original locations over the surface of the implanted DuraGen. Fibrin glue (Beriplast P [CSL Behring K.K., Tokyo, Japan]) was then applied over the edges to form a seal. The bone flap was cryopreserved in the institution's biobank.

In cases of re-operation for the primary disease, the DuraGen placed during the initial surgery was removed and used for histological analysis. In the cases of cranioplasty, the cleavage plane for reinsertion of the bone was created between the myocutaneous flap and the fibrous dura-like tissue covering the brain. The bone margins were carefully exposed and the bone flap was placed. In the case of intraoperative CSF leak due to dural defect, additional collagen matrix was placed covering the defect. Removed DuraGen from patients requiring secondary duraplasty or removed excess DuraGen, such as overlapped area with native dura and tissue adhering to the flap, were used for histology. Samples were not collected from patients with complete dural remodeling at the time of cranioplasty to avoid unnecessary damage. All patients received perioperative antibiotic coverage with cefazolin from 1 h before surgery until at least 24 h after surgery, and wound drains were placed in both the craniectomy and cranioplasty procedures.

Histopathological study

The tissue was fixed in formaldehyde solution at a concentration of 10%. Tissue sections were prepared from the specimens and stained with hematoxylin and eosin (H&E). The sections were examined by one pathologist and one neurosurgeon under light microscopy and evaluated in terms of the presence or absence of the following histological features: (1) implanted collagen matrix, (2) erythrocyte infiltration, (3) fibrin layer (suggesting fibrin glue), (4) fibroblasts, (5) endogenous collagen, (6) neutrophil reaction, (7) external thrombus, (8) fibrosis, (9) foreign body present, and (10) native dura. For each specimen, serial sections were prepared, and the presence or absence of features was assessed through a comprehensive review of all sections (generally between 8 and 16 sections). No attempt was made to quantify the area or volume of the various features identified; scoring was based on the presence of absence of the feature described from all the sections obtained from each patient. This observational study is based on cellular morphology and nuclear staining, which are effectively demonstrated by H&E.

Statistical analysis

Quantitative variables are expressed as mean ± standard deviation. The Fisher's exact test and Bonferroni correction were used to identify covariates that could be used as binary categorical dependent variables. Kruskal-Wallis test was used for nonparametric data. The receiver operating characteristic (ROC) analysis were evaluated to determine the days after the implantation predicting the histopathological finding. Statistical significance was set at $P < 0.05$. SPSS version 29 (IBM Corp., Armonk, New York, USA) was used for all the statistical analyses.

Results

A total of 28 patients were included in the study. Baseline patient characteristics are summarized in Table 1 and Figure S1A. The median age of the patients was 71 (interquartile range [IQR], 52–74) years; there was a

	All	Early	Intermediate	Late	*P* value
Number of patients	28 (100)	7 (25.0)	9 (32.1)	12 (42.9)	
Age (years), median [IQR]	71 [52–74]	58 [50–74]	72 [66–78]	69 [50–73]	0.505
Female	15 (53.6)	3 (42.9)	7 (77.8)	5 (41.7)	0.242
Primary disease					
Brain injury	6 (21.4)	1 (14.3)	3 (33.3)	2 (16.7)	0.61
Cerebral infarction	4 (14.3)	2 (28.6)	1 (11.1)	1 (8.3)	0.533
Intracerebral hemorrhage	8 (28.6)	2 (28.6)	1 (11.1)	5 (41.7)	0.277
Subarachnoid hemorrhage	8 (28.6)	1 (14.3)	4 (44.4)	3 (25.0)	0.508
Others	2 (7.1)	1 (14.3)	0 (0)	1 (8.3)	0.714
Elapsed time since implantation (day), median [IQR]	27 [20–37]	15 [5–18]	25 [21–27]	38 [34–55]	< 0.001

Table 1. Baseline characteristics in 28 patients. Values are number (%) except where indicated otherwise. *IQR* interquartile range.

	All	Early	Intermediate	Late	*P* value
Operative time of subsequent surgery (min), median [IQR]	79 [50–118]	81 [73–123]	77 [43–139]	75 [53–110]	0.791
Surgical complication	3 (10.7)	0 (0)	2 (22.2)	1 (8.3)	0.447
CSF leakage	1 (3.5)	0 (0)	0 (0)	1 (8.3)	1.000
Wound infection	1 (3.5)	0 (0)	1 (11.1)	0 (0)	0.571
Meningitis	1 (3.5)	0 (0)	1 (11.1)	0 (0)	0.571
Clinical complication	3 (10.7)	0 (0)	0 (0)	3 (25.0)	0.161

Table 2. Surgical outcomes of all patients. Values are number (%) except where indicated otherwise. *CSF* cerebrospinal fluid, *IQR* interquartile range.

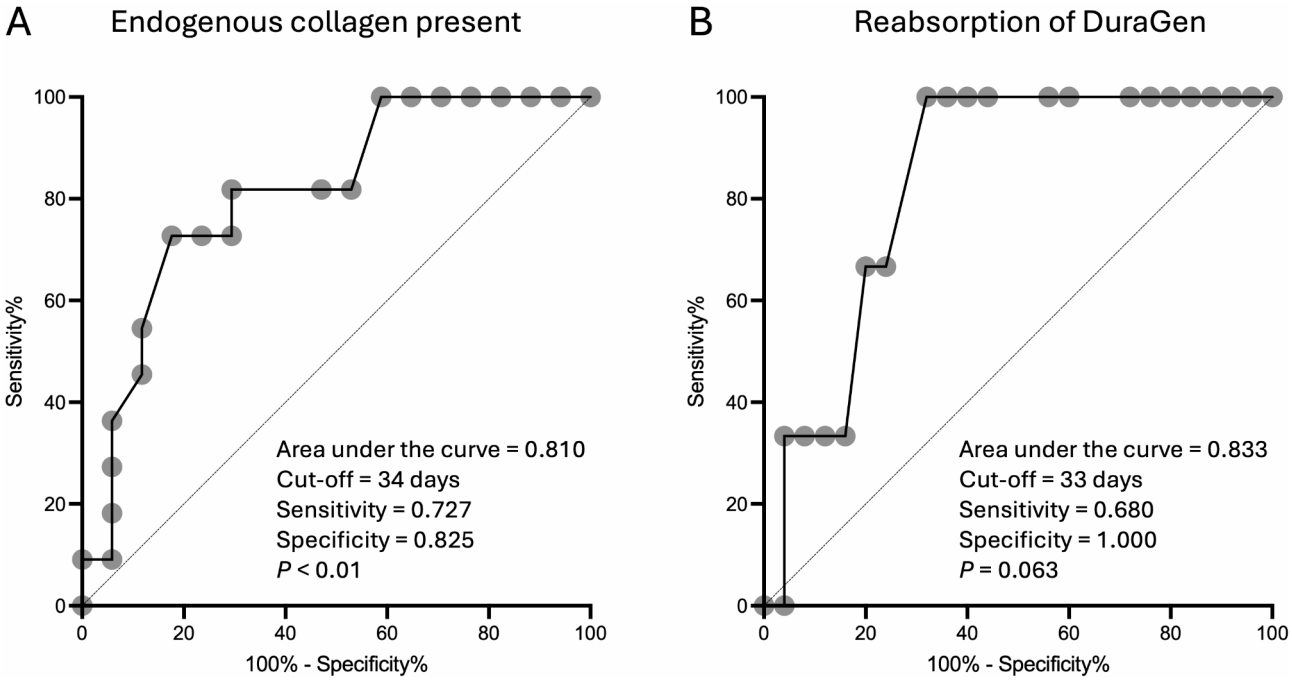

Fig. 2. Receiver operating characteristic curve for predicting the presence of endogenous collagen (A) and reabsorption of collagen matrix (B).

slight females (53.6%) predominance. The most common causes of elevated ICP requiring a decompressive craniectomy were intracerebral hemorrhage (28.6%, 8/28) and subarachnoid hemorrhage (28.6%, 8/28), followed by traumatic brain injury (21.4%, 6/28). A total of seven specimens (25.0%, 7/28) collected within 20 days after DuraGen implantation (early group, Range 3–19 days), 9 specimens (32.1%, 9/28) between 21 and 30 days (intermediate group, Range 21–30 days), and 12 specimens (42.9%, 12/28) over 31 days (late group, Range 33–121 days).

The surgical outcomes of the patients are shown in Table 2 and Figures S1B and S1C. The median operative time was 79 (IQR, 50–118) minutes in all patients. There was no significant difference in operative time between early, intermediate, and late groups (81 vs. 77 vs. 75 min, $P=0.791$). Three patients (10.7%, 3/28) experienced a surgical complication as follows: wound infection (3.5%, 1/28), meningitis (3.5%, 1/28), and CSF leakage (3.5%, 1/28), with no significant difference between the groups. CSF leakage resolved in 12 days without treatment including head wrapping, forced head-up position, or prolonged antibiotic coverage. Three patients (10.7%) developed post-operative aspiration pneumonia that was successfully treated with antibiotics.

Histopathological findings

The earliest time when there was histopathological evidence indicating replacement of DuraGen with endogenous collagen was at 21 days post-duraplasty ($n=10/28$). At 28 days or later, more than half (64.2%) of specimens analyzed displayed endogenous collagen. ROC analysis revealed a cut-off for identifying patients with endogenous collagen at 34 days after DuraGen implantation (area under the curve [AUC] = 0.810, Fig. 2A). As expected, the presence of endogenous collagen between the three groups increased in a stepwise manner (0% vs. 33.3% vs. 66.7%, $P=0.016$). The earliest time at which no collagen matrix was found (indicating complete or near complete reabsorption) was at 34 days ($n=20/28$). There was a lower tendency for collagen matrix to be present in the late group without a statistical difference (100% vs. 100% vs. 75.0%, $P=0.161$). ROC analysis

	All	Early	Intermediate	Late	*P* value	Range (days)
Main findings						
Collagen matrix	25 (89.3)	7 (100)	9 (100)	9 (75.0)	0.161	3-121
Erythrocyte infiltration	24 (85.7)	7 (100)	9 (100)	8 (66.7)	0.068	3-121
Fibrin layer	16 (57.1)	6 (85.7)	7 (77.8)	3 (25.0)	0.012†	5-121
Fibroblast	19 (67.9)	3 (42.9)	7 (77.8)	9 (75.0)	0.346	11–121
Endogenous collagen	11 (39.3)	0 (0)	3 (33.3)	8 (66.7)	0.016††	21–121
Other findings						
Neutrophil reaction	2 (7.1)	1 (14.3)	0 (0)	1 (8.3)	0.714	3–38
External thrombus	12 (42.9)	2 (28.6)	3 (33.3)	7 (58.3)	0.427	5-121
Fibrosis	3 (10.7)	1 (14.3)	1 (11.1)	1 (8.3)	1.000	19–35
Foreign body	5 (17.9)	1 (14.3)	1 (11.1)	3 (25.0)	0.831	19–38
Native dura	2 (7.1)	0 (0)	1 (11.1)	1 (8.3)	1.000	28–34

Table 3. Histopathological characteristics in each group. Values are number (%) except where indicated otherwise. †Early vs. Intermediate, $P = 1.000$; Early vs. Late, $P = 0.059$; Intermediate vs. Late, $P = 0.098$. ††Early vs. intermediate, $P = 0.638$; Early vs. Late, $P = 0.038$; Intermediate vs. Late, $P = 0.595$.

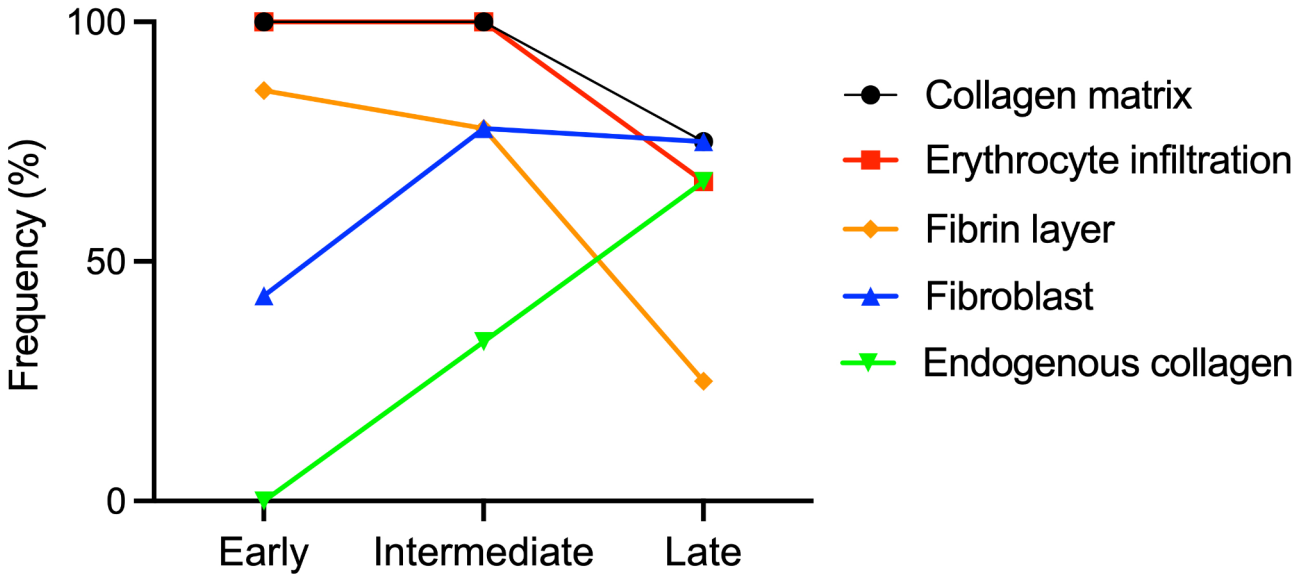

Fig. 3. Significant histopathological changes over time.

demonstrated that the cut-off for correctly predicting complete reabsorption of collagen matrix was 33 days post DuraGen implantation (AUC = 0.833, Fig. 2B). Resolution of a surrounding fibrin layer occurred in the majority of patients in the late group (presence of fibrin layer: 85.7% vs. 77.8% vs. 25.0%, $P = 0.012$). Table 3 shows the histopathological findings of all patients for each time point. Fibroblasts colonization of the material was higher in the intermediate (77.8%) and late (75.0%) groups compared to the early group (42.9%), although there was no statistical difference ($P = 0.346$). In other words, five patients (23.8%) had no fibroblasts even in the intermediate or late group. The median age of these patients without fibroblasts was older (77 [IQR, 71–79] years) than those with fibroblasts (69 [IQR, 61–73] years), although there was no significant difference ($P = 0.093$). Figure 3 represents the major histopathological changes over time. Foreign bodies and the reactions to them were observed in 17.9% (5/28), suture material was observed in 4 patents and unidentified fibers (possibly suture) observed in 1 patient. No post-operative infections or complications occurred in this group of patients with foreign body reactions. In the two patients who developed a post-operative infection, there were no specific findings such as neutrophil infiltration and foreign body reaction at the time of cranioplasty. Figure 4 shows representative histopathological findings of the patients at each time point.

Ad-hoc analysis of histopathological findings

We additionally performed two-group comparison by (1) setting the time window to one month and (2) introducing an interval between the groups (Tables S1 and S2). In both analyses, the presence of endogenous collagen was significantly increased in the later group (18.8% vs. 70.0%, $P < 0.05$, 0% vs. 75.0%, $P < 0.05$, respectively). Furthermore, for specimens in which the sampling site could be clearly identified retrospectively,

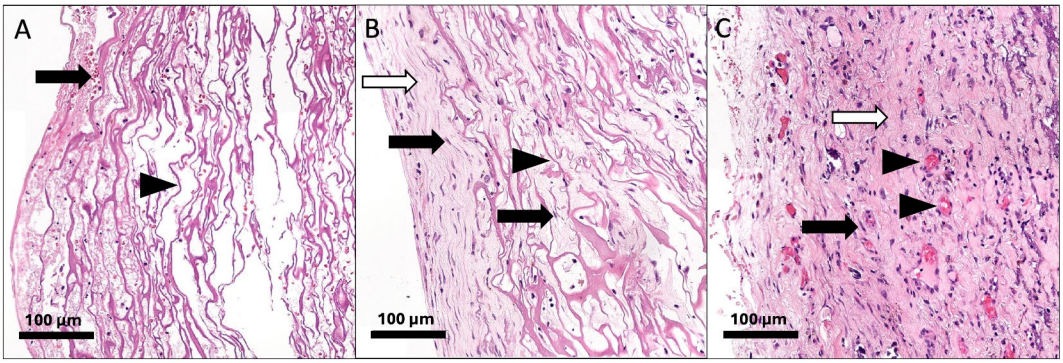

Fig. 4. Representative histopathological findings of the patients' implanted collagen matrix in each group. A (early group, day 16), erythrocyte infiltration (black arrow) on surface of collagen matrix (black arrowhead). B (intermediate group, day 28), fibroblasts (black arrows) migrating into the collagen matrix, which is in the absorption process (black arrowhead). Endogenous collagen secreted by fibroblasts is found mainly on the surface layer (white arrow). C (late group, day 35), fibroblastic infiltration and proliferation are evident (black arrow). The interstices of the trabecular network are filled with endogenous collagen (white arrow) and new capillaries (black arrowheads).

Author & year	Age (yrs)/sex	Primary disease	Post-implantation time	Main findings	Complication
Khorasani et al., (2008)[16]	17/M	Acute lymphoblastic leukemia	3 months	Dense connective tissue with prominent neovascularization	–
Tamura et al., (2022)[17]	66/F	Meningioma	1 year	Collagen fibers, neovascularization, meningioma cell invasion	–
Nagata et al., (2022)[18]	N/A	Tuberculum sellae meningioma	21 days	Neovascularization, fibroblast infiltration*	CSF leakage
Ono et al., (2022)[19]	83/M	Acute subdural hematoma	16 days	Collagen matrix, RBC, Neutrophil, lymphocyte, fibroblast proliferation	–
Ono et al., (2022)[19]	54/F	Intracerebral hematoma	32 days	Collagen matrix, RBC, Neutrophil, lymphocyte, fibroblast proliferation	–
Ono et al., (2022)[19]	81/M	Intracerebral hematoma	44 days	Collagen fiber bundles with microcalcification, foreign body, edema, hemorrhage	–

Table 4. Histopathological findings of duragen in previous studies. *CSF* cerebrospinal fluid, *RBC* red blood cell. *These findings were confirmed in the non-CSF leak area but in the CSF leak area.

we conducted a site-specific comparison (frontal lobe vs. temporal lobe, Table S3). The frontal lobe specimens tended to exhibit higher proportions of endogenous collagen (50.0% vs. 25%, $P=0.576$) and fibroblasts (100% vs. 75.0%, $P=0.333$) compared with the temporal lobe specimens, although these differences did not reach statistical significance.

Discussion

In this study, the histopathological changes following DuraGen implantation were compared in a cohort of patients that underwent duraplasty and subsequent surgeries across various time points (Range 3-121). It is well-known that fibroblasts migrate into dural defect area, and infiltrate into the porous structure of the DuraGen collagen matrix, which serves as a scaffold for the attachment of the cells to deposit the endogenous collagen and reform an effective barrier to CSF leakage[7,22]. However, the time when this occurs and how it might differ between patients has not been previously reported. Among the histopathological changes identified in this study, we found a high predictive accuracy of 34 days after DuraGen implantation for having evidence of endogenous collagen and thus the onset of co-optation of the collagen matrix dural substitute by host fibroblast cells. We also found the cut-off of 33 days for reabsorption of the DuraGen graft. This investigation represents the largest human clinical study on this topic and first to compare histopathological findings at different post-operative times[16–19]. Regrowth of the water-tight native dura (endogenous collagen) prior to the resorption of the dural graft is important to prevent postoperative CSF leakage[23]. Information regarding these important time points may be helpful for cranioplasty timing.

Prior investigations into the post-implantation histopathological findings of DuraGen in humans have varied from 16 days to 1 year (Table 4)[16–19]. There were only two of six cases of early post-implantation time within one month in previous studies. In addition, DuraGen-derived new dura mater, such as connective tissue and collagen fibers, was only confirmed in two cases at 3 months and 1 year after implantation[16,17]. The actual timing of these formation was unknown due to the limited number of previous reports. Nagata et al. (2022) reported the histopathological findings of the patient experienced CSF leakage 3 weeks after extended transsphenoidal

surgery for tuberculum sellae meningioma[18]. Interestingly, fibroblast infiltration was not detected in DuraGen from the CSF leakage area, while it was detected from non-CSF leakage area, suggesting the important role of fibroblasts in the formation of new dura mater[18]. We proposed the cut-off to predict the formation of new DuraGen-derived dura mater, endogenous collagen, as 34 days after implantation.

Decompressive craniectomy and duraplasty are routinely performed following traumatic brain injury or stroke to alleviate increased intracranial pressure. During dural healing the formation of a water-tight seal across the dura edges may still have an impact on the reabsorption of CSF. This is important regarding cranioplasty timing as early surgery timing has been associated with a greater rate of post-operative hydrocephalus[20]. The presence of endogenous collagen, which is the primary structural component of the dura matter, may represent a possible surrogate for the presence of water-tight seal around the duraplasty borders and the native dura[24]. Although beyond the scope of this study, we suspect patients who have developed a water-tight seal and thereby confining CSF to the subarachnoid and intraventricular spaces, would have a lower rate of developing hydrocephalus following a cranioplasty if they had not already. It is also likely the histopathological changes over time may differ between the onlay versus inlay techniques. Though all patients in this study underwent the onlay technique, this may be an important area for future investigation. The onlay technique requires an overlap of at least 1 cm beyond the edges of the defect and does not require suturing according to the manufacturer's instructions. The simplicity of onlay technique makes it suitable for larger defects or areas where the dura is difficult to approximate. However, for the regions with higher intracranial pressure, the onlay graft can be at a slightly increased risk of developing CSF leaks[25]. In contrast, the inlay technique was followed by suturing or gluing the tissue edges together. This subdural positioning is hypothesized to offer a more robust seal, as the graft is anchored by both the underling CSF pressure and the natural dural rims. But the systematic review and Meta-Analysis in endoscopic endonasal skull base surgery showed no superiority over other methods without inlay[26]. Another study advocated a "double grafting technique" with a combination of inlay and onlay, with a reported CSF leak rate of 3.3%[27]. Further studies are warranted to determine the appropriate surgical methods which may effect the rate of fibroblast migration and replacement of DuraGen with endogenous collagen.

Although first introduced in the U.S in 1999, DuraGen was only recently approved in Japan for dural reconstruction in 2019. Histopathological and clinical results from this study support its effective and safe use at our institution. Regarding the foreign body reaction, previous studies have shown that DuraGen typically does not elicit a foreign body reaction, which can lead to encapsulation and adhesion formation around artificial dural grafts[7,28–31]. However, five patients did exhibit foreign body reactions, which may be attributed to nearby scalp closure sutures or excessive fibrin glue application over the DuraGen graft[6,7,32]. Despite these reactions, severe adhesions and prolonged operative times were not observed. Infection rates were consistent with previous reports for decompressive craniectomies, and histopathological analysis revealed no evidence of infection on the implanted DuraGen[7].

While we have demonstrated the timing of endogenous collagen replacement following collagen matrix placement, drawing a definitive conclusion regarding the optimal timing of cranioplasty is challenging due to the limited sample size beyond 3 months—which previous studies classified as "late" cranioplasty[33]. Based on our histopathological findings, a robust shield formed by endogenous collagen is expected to begin developing approximately one month after DuraGen placement. Although not the focus of this study, intraoperative CSF leakage was observed in the early and intermediate groups, which could potentially lead to postoperative CSF leakage and infection. Taken together, it may be preferable to avoid performing cranioplasty too early unless there is a specific indication.

Limitations

We acknowledge several limitations. First, the sample size ($n = 28$) is relatively small and was obtained from a single institution. We did not collect samples from patients with a fully healed dura to avoid unnecessary damage, which further limited the number of samples, especially for patients more than two months after implantation. Due to the limited sample size in each group, conducting multivariate analysis was challenging. Second, patients in the early group may not have required decompressive craniectomy. However, we performed preventive decompressive craniectomy using broad criteria at the time of the initial surgery—a strategy we believe is far preferable to waiting until it is too late. This study limitations also include having not completely standardized specimen sites in location and size, which may have affected the results. Although findings are limited to the collected tissue samples, it is likely this applies to other locations of the graft if not throughout, though additional investigation is needed to substantiate this. Furthermore, the findings presented in our study are solely applicable to collagen application on the cerebral surface or convexity. It should be noted that the results are not translatable to other applications, such as skull base reconstruction, whether performed via transcranial or endonasal approaches. In skull base reconstruction, the DuraGen will be in direct contact with the basal cisterns, creating a markedly different environment that will likely influence the reabsorption of DuraGen. Finally, we did not assess the thickness of the new dura mater, which is an important factor in durability. Despite these limitations, the present study is largest intracranial human study conducted and the first to compare histopathological characteristics at various time points following implantation of DuraGen.

Conclusions

In this investigation, the histopathological changes of DuraGen across different time points were compared for the first time. Although some results were preliminary and require further validation, our study findings support DuraGen as a reliable substitute are based on clinical outcomes and histopathological changes. Evidence of DuraGen being replaced with fibroblast-derived endogenous collagen was identified as early as 34 days

post-implantation. Further studies taking into account the maturation and expansion of new dura mater are warranted to determine the appropriate timing of cranioplasty.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
This prospective clinical study was approved by the ethics committee of the Saitama Medical University International Medical Center (approval number, 20–181). The patients were provided with written informed consent for the histopathological study. Patients in the study were also given the opportunity to refuse to participate in the study by opting out.

Consent for publication
Patients in the study were given the opportunity to refuse the publication in the study by opting out.

Additional information
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