Application of Leukocyte and platelet-rich fibrin as a sealing material in endoscopic reconstruction of spontaneous CSF leaks

Original Article

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ABSTRACT

Objective: Different materials are used to repair skull base defects. Free grafts such as nasal mucoperiosteum, fascia lata, fascia temporalis, and adipose tissue are commonly employed and have satisfactory results. However, free grafts, particularly extra-nasal tissues implanted overlay, are usually not entirely integrated, resulting in excessive nasal crusting and patient discomfort in the postoperative months. We attempted in our study to use Leukocyte- and platelet-rich fibrin (L-PRF) membranes in skull base defect reconstruction.

Patients and Methods: This prospective controlled study was conducted on 42 patients with spontaneous CSF rhinorrhea who were randomly divided into 2 groups according to the materials used in skull base reconstruction. In group A, the defects were repaired by L-PRF membranes, fascia lata, and mucosal graft while fascia lata and mucosal graft were only used in group B.

Results: There was no statistically significant difference between the two groups regarding the early CSF leak. On the other hand, there was a difference related to the postoperative sinonasal crusting which shows a statistical significance.

Conclusion: L-PRF membrane was found to be a good sealing material in the repair of CSF leak as it encourages the healing of surrounding tissues and minimizes sinonasal morbidities such as severe crust formation.

Key Words: Leucocyte–platelet-rich fibrin, sealing material, skull base reconstruction, spontaneous CSF rhinorrhea.

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INTRODUCTION

Despite the fact of being relatively rare, spontaneous cerebrospinal fluid (CSF) leaks are considered to be life-threatening if complicated by ascending meningitis or brain abscess. A disruption in the dura and arachnoid matter, together with an underlying osseous defect can lead to a CSF leak in the presence of a considerable intracranial pressure (ICP) gradient, which exceeds the tensile strength of the disrupted membranes either continuously or intermittently. These defects are sometimes associated with dura, and to a lesser extent, brain parenchyma (encephalocele) herniation[1,2].

Since the 1920s, various strategies for the correction of skull base (SB) defects have been advised by surgeons. The main target of all of these novel techniques is to recreate a sturdy barrier between the extracranial and intracranial compartments thereby avoiding further complications of CSF leak. In the last decades, transnasal approaches have widely replaced the external approaches for nasal surgeries. Nowadays, endonasal endoscopic surgery expedites the reconstruction of the skull base defects through a minimally invasive approach[3].

The fascia lata application for skull base defects repair, on dealing with pneumocephalus, was reported for the first time by Dandy *et al*.[4] in 1926. Since then, tissue autografts have been used for repairing skull base defects including abdominal fat, temporalis fascia, septal mucosa, middle turbinate, and cartilage[5].

L-PRF is a second-generation platelet concentrate that does not require any biochemical changes or exogenous chemicals to be added to the blood sample[6]. Venous blood is collected and centrifuged without anticoagulants in a tube to separate three layers: red blood corpuscles at the bottom, L-PRF in the middle, and platelet-poor plasma at the top. A dense fibrin scaffold makes up the majority of L-PRF, allowing platelets and leukocytes to entangle. Platelets and leukocytes release cytokines and growth factors, which are important in the healing process[6,7]. In this study, we assess the reliability L-PRF membrane, an active autologous sealing material, for SB reconstruction.

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PATIENTS AND METHODS:

From June 2017 to May 2020, 42 patients with spontaneous CSF rhinorrhea were enrolled in this prospective controlled clinical research at the Otorhinolaryngology Department of Alexandria Main University Hospital. The study was carried out with the agreement of Alexandria University's Faculty of Medicine's Ethical Committee with IRB NO: 00012098.

Patients in this study were randomly divided into 2 subgroups, designated groups A and B, based on the method of repair of SB defect. Group A included patients with defects reconstructed using two layers of L-PRF membrane (one of them placed underlay if technically feasible) followed by fascia lata, and finally mucosal graft. Group B consisted of patients with defects repaired only by fascia lata and then mucosal graft.

Preoperatively, all patients had undergone a detailed review of the medical history and general examination with a thorough otorhinolaryngological and neurological assessment. CSF rhinorrhea was confirmed using the beta-2 transferrin and/or beta-trace protein with a value of 1.11 mg/ml for beta-trace protein is considered to be affirmative. Radiological assessment of the patients was done using multidetector computed tomography (MDCT) with multiplanar reconstruction (Figure 1) and high-resolution T2-weighted magnetic resonance imaging (MRI).

Operative technique: Immediately before surgery, measurement of CSF pressure was routinely done. Cases with high opening CSF pressure (more than 30 cm H_2O) were either medically managed or referred to a neurosurgery team for shunting. Intraoperative confirmation of CSF leak was done using an intrathecal fluorescein injection, which was also used to detect the site of the leak and to confirm successful sealing at the end of surgery.

After induction of anesthesia, L-PRF was prepared by obtaining 20 ml of the patient's blood sample without any anticoagulant. The blood was left at room temperature for 10 minutes for complete clot formation and then was centrifuged for 10 minutes at 3000 rpm. After centrifugation, L-PRF was separated from the RBCs layer and compressed to form a membrane (Figure 2).

In patients of cribriform/ethmoid defects: Endoscopic identification of the defect was done through partial or complete ethmoidectomy. In most cases, Partial middle turbinectomy was needed to widen the surgical corridor and to utilize its mucosa in the repair. Additional nasal mucosa could be harvested from the nasal floor or nasal septum. The defect site was prepared for reconstruction through the removal of the mucoperiosteum around the defect. The application of L-PRF did not require any additional modification to the traditional technique (Figure 3). Reconstructive materials were further supported with Surgicel and/or Gelfoam. Then, Merocel was inserted.

In patients with sphenoid sinus defect: Medial to the middle turbinate, an endoscopic sphenoidotomy was performed. The opening was enlarged to allow for satisfactory exposure and to offer maximum support to the graft. Then, exposure of the skull base defect together with removal of all mucosa from the sinus was done. In the cases where an encephalocele was detected, cautious removal of the overlying mucosa was done, then careful reduction of the mass through the bony defect back to its anatomical site.

Postoperative: A quiet bed rest was offered to all patients, with a 45° elevation of the head of the bed. For the next 48 hours, patients were undercover of broad-spectrum IV antibiotics, and stool softeners were used to avoid any unnecessary strain. No lumbar CSF drains were used in any of the patients. If the first 48 hours passed uncomplicated, nasal packs were removed and the patients were kept hospitalized under observation for additional 24 hours and discharged afterward. A follow-up nasal endoscopy was done every two weeks in the first two months then monthly for one year. The absence of CSF leak during the follow-up period confirms the success of the repair.

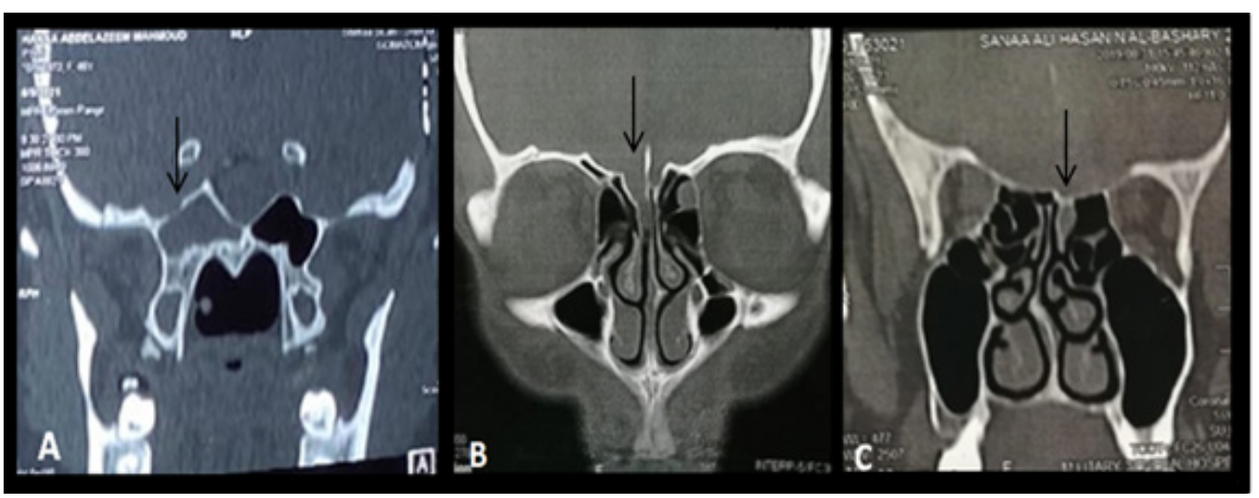

Fig. 1: Non-contrast HRCT: A) coronal view showing a defect in the roof of sphenoid, B) defect in the cribriform plate, C) defect in posterior ethmoid.

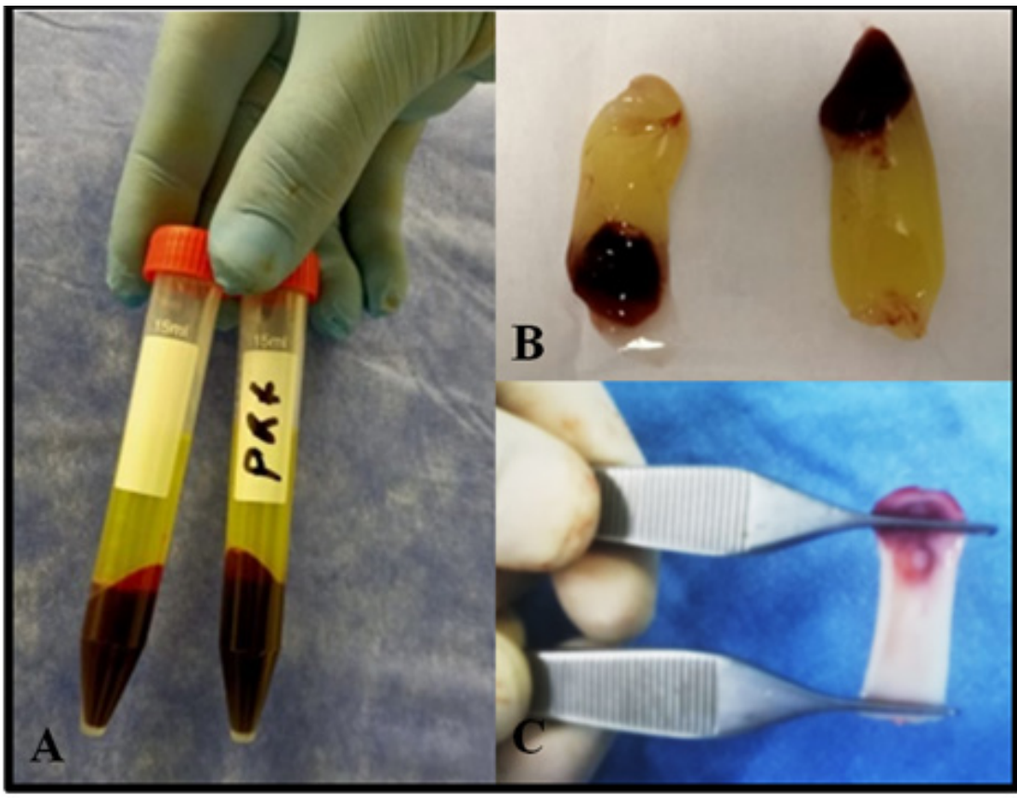

Fig. 2: (A) blood after centrifugation (B) cuff of RBCs and L-PRF (C) L-PRF membrane

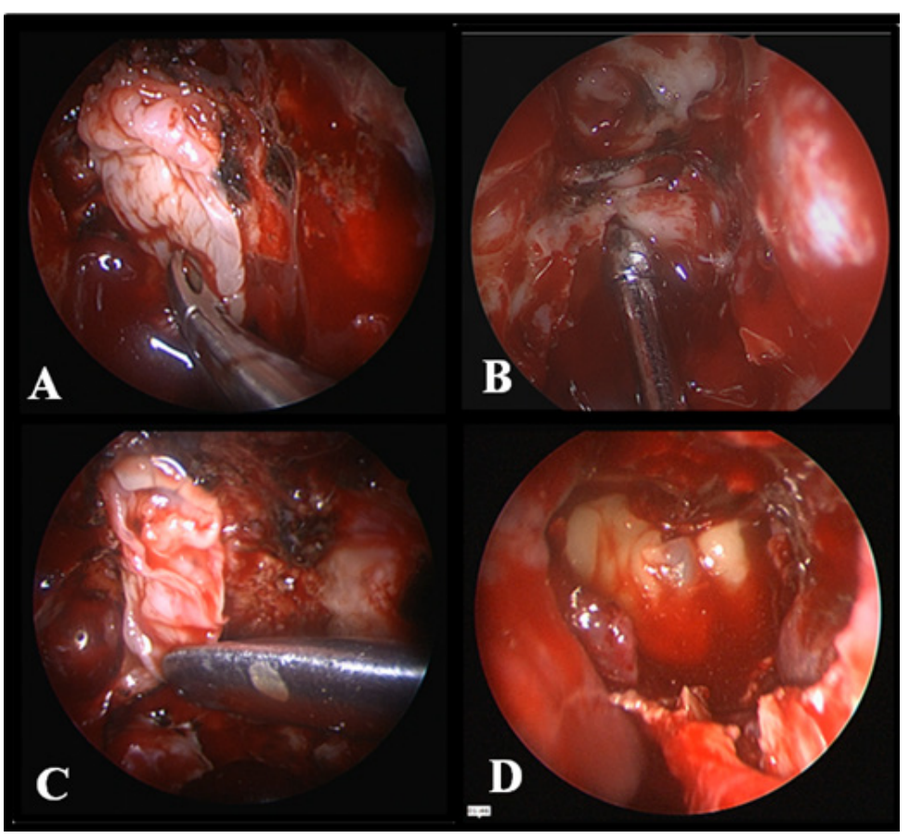

Fig. 3: Endoscopic view of application of L-PRF membranes in different sites (A) Cribriform defect (B) Ethmoid roof (c) Lateral lamella (D) Sphenoid defect

RESULTS:

This study included 42 patients, 36 (85.7%) females and 6 (14.3%) males, with ages ranging from 35-71 years old (mean 51 years) and the BMI ranged from 23 to55.4 kg/m2 with an average of 30.5kg/m2. 16 (38%) patients were obese with BMI>30, 20 (47.6%) were overweight (BMI 25-30), and 6 patients were at normal weight (BMI <20). Table 1 demonstrates the clinical manifestations of the studied cases. The main clinical symptom was watery rhinorrhea. All patients had continuous or intermittent watery rhinorrhea. Twenty-four patients had headaches and 15 patients complained of tinnitus. None of the patients reported having visual disturbances. Additionally, ten patients experienced history of meningitis, three of whom had recurrent attacks.

CSF leak was confirmed in all cases using either Beta2-transferrin or B trace protein. Non-contrast high-resolution CT nose and MRI sinuses with IV gadolinium showed that (90.47%) of patients had bony dehiscence on CT scan, and four patients had normal CT scan. 25(59.52%) patients had an empty sella detected on MRI (14 in group A, 11 of group B), 18 patients had meningocele (8 in group A, 10 in group B), and seven patients had optic nerve edema.

CSF pressure measurement was done preoperatively. The opening ICP pressure ranged from 12 to 29 cm H_2O, with a mean of 22.56 cm H_2O. The pressure was categorized as high (≥ 20 cm H_2O) or normal (less than 20 cm H_2O), with ten patients (6 in group A, 4 of group B) having a normal pressure leak and the rest having a high-pressure leak. Table 2 summarizes some of the characteristics of the defects. Only three patients had two defects. The most common site of the leak was the cribriform plate (38%) followed by the sphenoid sinus (26.19%). The size of the defect was measured intraoperatively by a cottonoid pledget that was properly cut out to simulate the defect area. Twenty-nine (69%) patients had a defect less than 1cm, while the defect size ranged from1-2cm in ten (23.8%) patients, and > 2cm in three patients.

As for the postoperative complications, as shown in (Table 3), only two patients in the study had experienced a recurrence of CSF leak at the primary site of the repair. The first patient had an 18 mm cribriform defect repaired using fascia lata and mucosal graft, with an opening ICP 20cm H_2O, and experienced the recurrence two months after surgery. The second patient had a 13 mm defect in the lateral lamella of the middle turbinate which was repaired using fascia lata and L-PRF, with an ICP 25 cm H_2O, and the recurrence occurred two weeks after surgery. These results did not show any statistical significance.

More patients in group B experienced severe sinonasal crusting in comparsion to group A, and this result was statistically significant. On the other hand, the results did not show any significant difference between the two groups regarding the incidence of epistaxis, headache, and postoperative meningitis, where the latter has occurred in one patient of group B.

Table 1: Clinical symptoms of patients with CSF rhinorrhea.

Symptoms	Number of patients
Watery rhinorrhea	42
Headache	24
Tinnitus	15
Visual disturbance	0
Meningitis	10

Table 2: Comparison between the two groups regarding the characteristics of SB defects.

	Group A (n =22)	Group B (n = 20)
Side of leak		
Right	12	9
Left	10	11
Multiple defects	1	2
Site of defects		
Cribriform plate	7	9
Lateral lamella	5	4
Ethmoidal roof	2	1
Sphenoid sinus	6	5
Posterior frontal table	2	1
Size of defects		
< 1cm	16	13
1-2 cm	4	6
>2 cm	2	1

Table 3: Comparison between the two groups regarding the postoperative (PO) complications.

	Group A (n =22)		Group B (n =20)		*p. value*
	NO.	%	NO.	%	
Recurrence of CSF leak	1	4.54	1	5.00	.4721 N.S.
Severe crusting	5	22.72	12	60.00	.0069*
Headache	9	40.90	8	40.00	.47608 N.S.
Meningitis	0	00	1	5.00	.14457 N.S.

N.S: Not Significant
(*): statistical significant

DISCUSSION

Cell processing technology has been enormously progressing over the last three decades; consequently, autologous stem cell therapies have widely replaced heterologous therapies. The availability of bioactive and biomedical surgical additives together with a predictable successful outcome has encouraged the processing of peripheral blood as a raw material for obtaining a viable tissue capable of controlling inflammation, enhancing homeostasis, and promoting the physiological process of healing[8,9].

L-PRF has been assessed for the first time regarding its potential utility for SB reconstruction by Soldatova *et al*.[10] in 2017 who demonstrated a great improvement in the healing process thus a better crusting scale score. Moreover, the role of L-PRF in neoossification, being an adjuvant material used in SB reconstruction, has been highlighted in more recent studies[11]. In 2018, Rasmussen *et al*.[12] documented the application of LPRF as a reconstructive material for SB defects following a transsphenoidal endoscopic approach for sellar lesions. Regarding the spontaneous CSF leak, Khafagy *et al*.[13] in 2018 endorsed the successful use of the L-PRF membrane for endoscopic repair of these defects.

The ability to attain an immediate water tight seal, by the rapid clotting property of L-PRF, renders it to be a suitable sealing material in the underlay technique in which the CSF flow washes out the graft, and thus promotes the mucosalization and enhances the postoperative healing[13].

In our study, the cribriform plate of the ethmoid is the most commonly affected site. The bone at this area is remarkably thin and the dura is strongly adherent to the bone rendering it a common site for spontaneous CSF leaks. Sphenoid defects were less common. This finding is similar to that in most of the literature. The cribriform plate is the commonest site of defects and

contributes to about 83.3% and 62.3% of cases in Gilaat *et al*.[14] and Ye *et al*.[15] respectively. The cribriform plate and fovea ethmoidalis also represent a common site for post-traumatic nonsurgical CSF leaks[16].

It was found that there was no statistically significant difference between the two groups regarding the early recurrence of CSF leak (i.e. within a three-month period) and postoperative meningitis. This could be explained due to the small size of the studied population. The incidence of recurrent leaks may possibly increase in these patients over time, thus long-term follow-up is necessarily needed[17]. As regards the postoperative healing, which was assessed by the severity of crusting, there was a statistically significant difference between the two groups. These results worship the role of L-PRF in enhancing tissue healing in cases of SB defect repair.

Upon reviewing the literature, the success rate of endonasal CSF leak repair is high, and revision surgery is even better. In our study, group B had a 95% success rate, while group A had a 95.5% success rate. According to a systematic review[18], Endoscopic CSF leak repairs were successful 70% to 100% on the first surgery, and 86% to 100% on the second.

The small sample size stands out as the main point of limitation in this study, where it hinders against proving a statically significant difference between the two groups regarding the success rate of the repair. Other limitations include the lack of the long-term follow-up needed to detect the delayed CSF leak.

CONCLUSION

We proposed the use of L-PRF membrane as a sealing material for the repair of SB defects in spontaneous CSF rhinorrhea. L-PRF membrane is an inexpensive available autologous biological active membrane that enhances the healing process of the repair of SB defects and reduces the postoperative sinonasal morbidities such as crusting.

ABBREVIATIONS

L-PRF: Leukocyte- and platelet-rich fibrin

SB: skull base

CSF: cerebrospinal fluid

ICP: intracranial pressure

MDCT: multidetector computed tomography

CONFLICT OF INTEREST

There are no conflicts of interest.

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