Prognostic factors affecting success rate in endoscopic management of spontaneous cerebrospinal fluid rhinorrhea

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Objective
Endoscopic sinus surgery has been established as the standard procedure for management of most cases of cerebrospinal fluid (CSF) rhinorrhea and meningoceles. Spontaneous leak represents the most common etiology, whether it is associated with idiopathic intracranial hypertension or not. Nevertheless, results of endoscopic repair of spontaneous CSF leaks represent the worst among other nonspontaneous etiologies in most literatures, with a wide range of success (25–87%).

Patients and methods
This is a retrospective study that included 52 cases of spontaneous CSF leak, which had been managed by endoscopic sinus surgery, in the last 8 years, in Kasr Alaini Hospital, Faculty of Medicine, Cairo University, and Shebin Alkom Teaching Hospital; and also some cases were done in New Kasr Alaini Teaching Hospital. Data collected included age, sex, manifestations of high intra cranial tension (ICT), duration of leak, site, method of repair, and whether repair was successful or not.

Results
In 52 cases with spontaneous CSF leak, successful repair was achieved in 73% (38 out of 52). There were 41 (78.8%) female and 11 (21.2%) male patients. Success in female patients was 70.7% (29 of 41 cases), and success in male patients was 81.8% (9 of 11 cases). Manifestations of increased ICT were found in 17 of 52 cases (32%), where nine of them failed (52%). Leaks in the ethmoidal region represented 27 (52%) cases, sphenoidal region 19 (36.5%) cases, and frontal region six (11.5%) cases. There were three methods of repair: in the first group, repair was done with fat and overlay mucosal graft in 17 (33%) cases; in the second group, repair was done with under lay epidural graft plus overlay mucosal graft in 29 (56%) cases; and in the third group, an underlay graft was used, and in addition, an overlay septal flap was put in six (11%) cases.

Conclusion
Spontaneous CSF leak represents a common cause of CSF rhinorrhea. Success rate is in general lower than in other etiologies of CSF leaks. The outcome of the surgical intervention could be related to variable demographic and preoperative factors.

Keywords:
cerebrospinal fluid leak, endoscopic sinus surgery, prognostic factors, spontaneous

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Introduction

Cerebrospinal fluid (CSF) leaks can occur owing to various etiological reasons, namely, congenital defects affecting the skull base, trauma whether accidental or iatrogenic, neoplastic lesions eroding the bones, surgery-produce defects, and lastly, the spontaneous leaks [1].

Results for endoscopic repair in spontaneous CSF are extremely variable in different publications, ranging from 25 to 87% [2].

The exact pathogenesis for spontaneous CSF leaks and meningoceles is still not certain. Most patient were found to have clinical symptoms and radiological signs of elevated intra cranial pressure (ICP) (normal pressure is 10–15 cm H_2O).

Elevated ICP commonly manifests in the syndrome of benign intra cranial hypertension (BIH), also known as pseudotumor cerebri. Patients may present clinically with pulsatile tinnitus, vertigo, headache, or visual symptoms. Radiological findings may include empty sella syndrome, encephaloceles, arachnoid pits, and optic nerve sheath abnormalities.

Patients with high-pressure spontaneous CSF leaks are clinically similar to those with idiopathic intracranial hypertension (IIH) [3]. It is possible that patients with thick skull base manifest as IIH, whereas those who have developed thinning of the skull base manifest with CSF rhinorrhea [4].

The sites most commonly affected by spontaneous leaks are lateral recess of the sphenoid sinus and lateral lamella of the cribriform plate [5].

Although large series had been found to assess the results of repair of CSF leaks in general, few were focused on the spontaneous type, and some of these research studies discussed how to improve success rate, in relation to different factors, such as medical control of high ICP, use of lumber drains, and multiple layer repair.

Patients and methods

Research was done according to ethics committee rules. The study included 52 patients, who had endoscopic repair of spontaneous CSF leak between October 2012 and January 2019. Repair was done in Kasr Alaini Hospital, Faculty of Medicine, Cairo University, and Shebin Alkom Teaching Hospital, and also, some cases were done in New Kasr Alaini Teaching Hospital.

All patients were more than 16 years old and had spontaneous CSF rhinorrhea after excluding all known causes, previous skull base surgery, previous trauma, or known neoplastic lesion or congenital defect.

Data collected included patients' demographic data, BMI, the presenting symptoms, including the period of leak, radiological findings, manifestations of increase ICP (clinical and radiological), and intraoperative details of repair.

Moreover, data concerning postoperative management including hospital stay, use of acetazolamide, and lumbar drain were also collected.

Minimal follow-up period was 6 month, and repair was considered successful if no leak occurs till the end of this 6-month period.

Revision cases were excluded from the study, and cases that needed revision were considered as failed repair.

Results

Data were statistically described in terms of mean ± SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Mann-Whitney *U* test for independent samples. For comparing categorical data, χ^2-test was performed. Exact test was used instead when the expected frequency is less than 5. Multivariate logistic regression analysis was used to test for the independent predictors of success. Two-sided *P* values less than 0.05 were considered statistically significant.

In 52 cases with spontaneous CSF leak, successful repair was achieved in 73% (38 out of 52), so we considered successful cases (38) as group A, and failure cases (14) as group B, to compare the two groups regarding the different variables.

Age ranged between 16 and 62 years, with mean ± SD of 34.92 ± 13.39 years and median of 33.0 years. In the successful cases, mean ± SD age was 35.66 ± 13.14 years, and median was 36.5 years, whereas in failure cases, mean ± SD age was 32.93 ± 14.355 years and median was 28.50 years. Fig. 1 shows the mean age difference between the study groups.

Regarding sex distribution, the study included 41 (78.8%) females and 11 (21.2%) male. Success in females was 70.7% (29 out of 41 cases), and success in males was 81.8% (9 out of 11cases). Fig. 2 shows the sex distribution between the study groups.

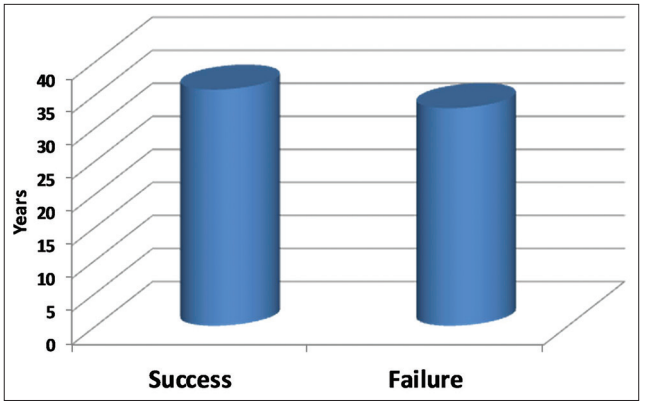
Mean ± SD BMI (kg/m^2) for all patients was 29.99 ± 2.778, and median was 30.00. In group A, mean ± SD BMI was 29.94 ± 2.661, and median was 29.85. However, in group B, mean ± SD BMI was 31.35 ± 2.720, and median was 31.30. Fig. 3 shows the mean BMI in the two study groups.

In all patients, there was no lumbar drains put before repair, so determination of increased ICP depended on clinical manifestations, in the form of tinnitus; balance disorders; headache; visual disturbance; radiological signs, such as meningoceles and empty sella; or optic nerve sheath abnormalities. Fig. 4 shows CT of a patient with meningoceles; there is fluid around the optic nerve sheath, suggesting of high ICP.

The number of patients with manifestations of high ICP in the study was 17, with success rate of 47.1% (8 out of 17), whereas patients without manifestations of high ICP were 35, with success rate of 85.7% (30 of 35).

Patients with high ICP represent 21.1% of group A and 64.3% of group B, whereas patients with normal

Figure 1



Mean age (years) between the study groups.

ICP represent 78.8% of group A and 35.7% of group B (Fig. 5).

The duration of CSF leak before repair was done ranged from 1 week up to 18 months, and the average duration in group A was 3.8 ± 4.3 and in group B was 7.5 ± 7.1. Fig. 6 shows the difference in duration of the leaks in the two groups.

In 52 cases of spontaneous CSF leak, the sites of the leaks were as follows: cribriform plate of the ethmoids (27 cases), with success rate of 70.4% (19 out of 27); sphenoid sinus (19 cases), with success rate of 78.9% (15 out of 19); and frontal sinus (six cases), with success rate of 66.7% (four out of six).

In group A, ethmoids, sphenoid, and frontal represent 50, 39.5, and 10.5% respectively, whereas in group B, the percentage is 57.1, 14.3, and 28.6, respectively. Fig. 7 shows the distribution of leak sites within the study groups.

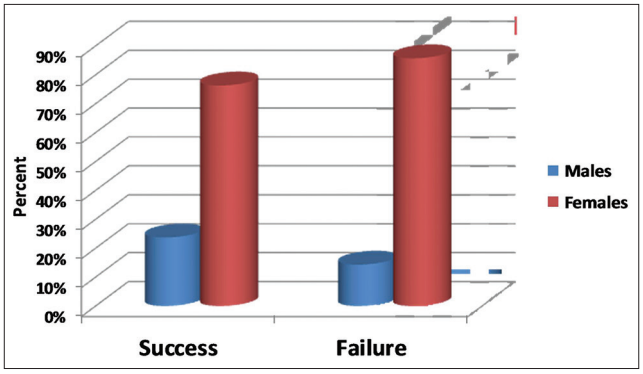
Operative details for the 52 patients revealed that repair was done in one of three ways: in 17 cases, repair was done using fat plug and overlay mucosal graft (group 1); in 29 cases, repair was done using underlay epidural mucosal graft with additional overlay mucosal graft (group 2); and in six cases, repair was done using underlay epidural flap and septal mucosal flap (group 3). Figs. 8–11 shows examples of repair techniques.

Success rate was as follow: 64.7% in group 1, 79.3% in group 2, and 66.7% in group 3. Fig. 12 shows the distribution of groups of repair techniques, in relation to the success of repair.

The different factors studied (age, sex, BMI, ICP, duration, site of leak, and type of repair) are summarized in Table 1, with their effect on result of repair. Table 2 shows select multivariate analysis-logistic regression model.

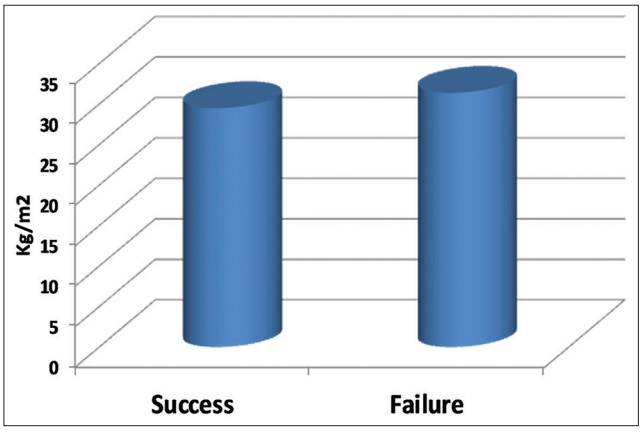
The fourteen patients who had recurrent leaks were transferred to the neurosurgical department for evaluation of the ICP, where 10 of them proved to have high ICP, and four had normal pressure, for whom second repair was scheduled; out of the 10 patients with high ICP, four had ventriculo peritoneal (VP) shunting, and six were managed medically (mainly using acetazolamide) to control the high ICP.

Figure 2



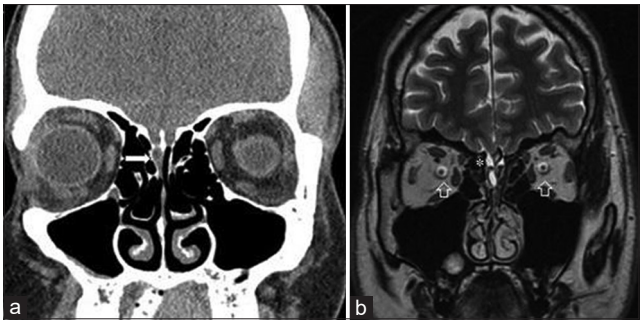
Sex distribution.

Figure 3



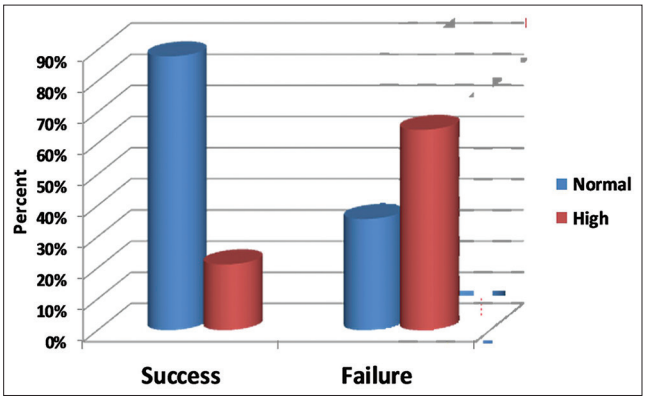
Mean BMI (kg/m^2).

Figure 4



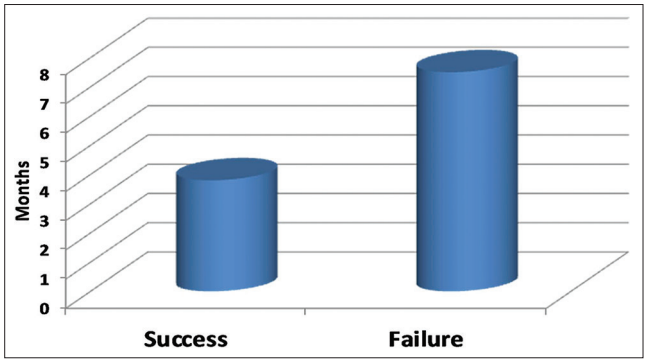
Radiological manifestations of high ICP. White arrow in (a) meningocele Hollow white arrows in (b) CSF around optic nerve

Figure 5



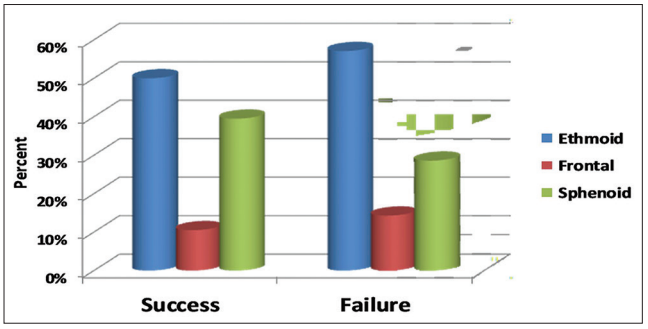
Distribution of ICP results.

Figure 6



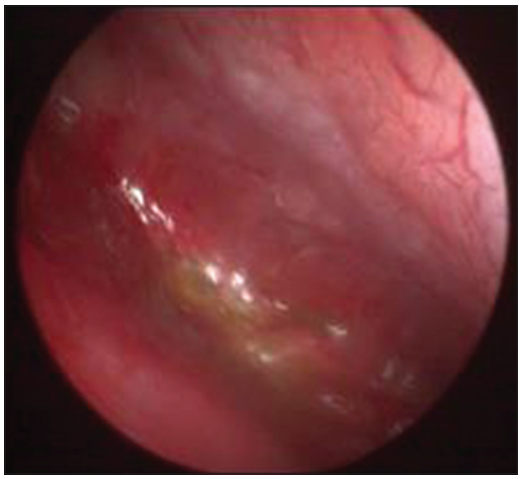
Mean duration (months).

Figure 7



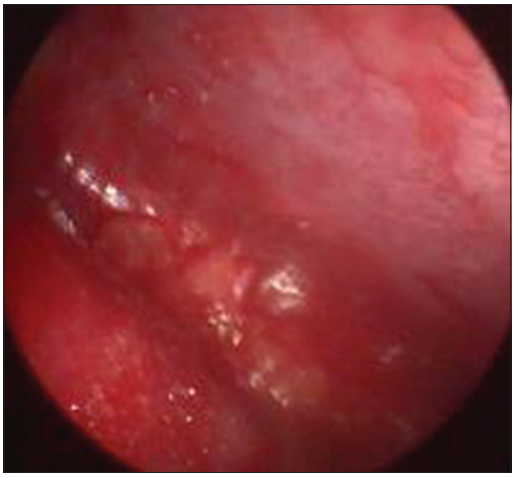
Site distribution between the study groups.

Figure 8



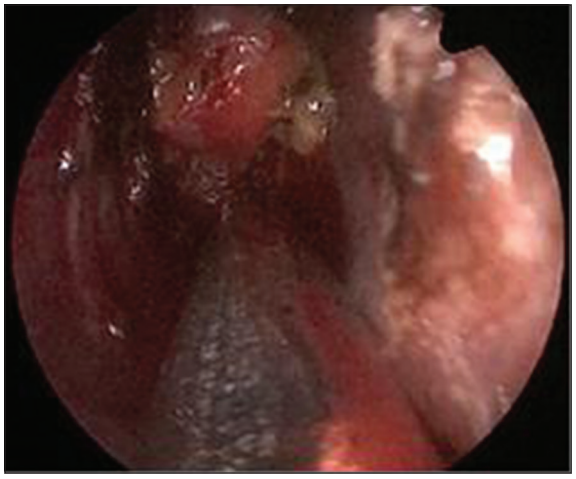
Cerebrospinal fluid leak.

Figure 9



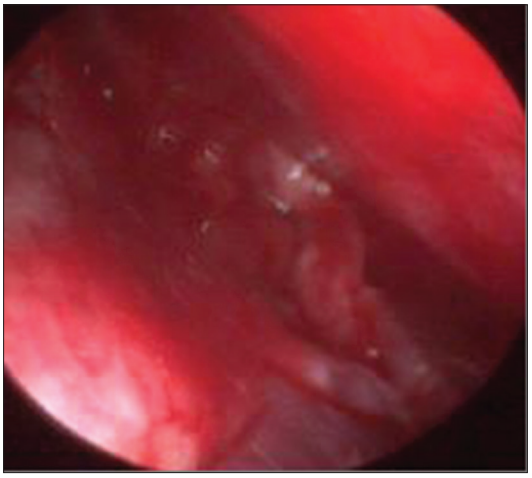
Fat plug.

Figure 10



Epidural graft.

Figure 11

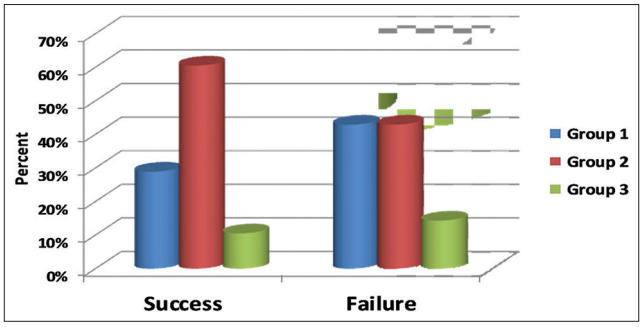


Overlay mucosal graft.

Discussion

Spontaneous CSF leak had been considered as one of the common causes for CSF leaks. Many theories had been postulated to explain the pathogenesis of spontaneous CSF leaks, and the most accepted is IIH; this is owing to the demographic similarities between both [6]. According to most publications, both patients with IIH and spontaneous CSF leaks are often middle-aged obese females. Obesity (BMI higher than 30) is associated with increased ICP in several ways: obesity leads to high intra-abdominal pressure with subsequent increase in ICP by decreasing

Figure 12



Distribution of repair between the study groups.

Table 1 Different factors affecting success rate of endoscopic repair of spontaneous CSF leak

	Success (*n*=38) [*n* (%)]	Failure (*n*=14) [*n* (%)]	*P*
Age	35.7±13.1	32.9±14.4	0.516
Sex			
Males	9 (23.7)	2 (14.3)	0.705
Females	29 (76.3)	12 (85.7)	
BMI	29.5±2.7	31.4±2.7	0.049
ICP			
Normal	30 (78.9)	5 (35.7)	0.006
High	8 (21.1)	9 (64.3)	
Duration	3.8±4.3	7.5±7.1	0.046
Site			
Ethmoid	19 (50.0)	8 (57.1)	0.756
Frontal	4 (10.5)	2 (14.3)	
Sphenoid	15 (39.5)	4 (28.6)	
Repair			
Group 1	11 (28.9)	6 (42.9)	0.521
Group 2	23 (60.5)	6 (42.9)	
Group 3	4 (10.5)	2 (14.3)	

Table 2 The effect of each single factor on success rate

	OR	SE	*P*	95%CI for OR	
				Lower	Upper
Sex	1.310	1.016	0.791	0.179	9.589
Age	1.030	0.032	0.344	0.968	1.096
BMI	0.989	0.069	0.867	0.863	1.132
ICP	0.112	0.851	0.010	0.021	0.595
Duration (months)	0.884	0.078	0.112	0.759	1.029
Site	1	2	0.402	0	11
Repair	4.158	1.022	0.163	0.561	30.837

CI, confidence interval; OR, odds ratio.

the venous return from the heart; also, obesity is associated with higher incidence of sleep apnea, with alteration of respiratory mechanics with hypoxemia, which may trigger cerebral vasodilatation and increase in the cerebral blood flow; and lastly, obesity may cause neuroendocrinal disturbance from extraovarian estrone production, with increased androstenedione conversion to estrone, a relative hypoadrenalism could then change vascular transport and drainage channels across arachnoid villi, with more resistance to cerebral blood flow [7].

In our study, the mean age in group A was 35.66 years, whereas in group B was 32.93 years; this means that most patients are middle aged with no difference between the two groups.

Regarding the sex, it is obvious that females were dominant, representing 78.8%. The success in females was less than in males (70.7 and 81.8%, respectively), but still not statistically significant.

Considering the BMI, it was found that in group A, it was 29.49, whereas in group B, it was 31.35. This means that failure goes more with higher BMI. Regarding sex, we found that the mean BMI in males was 29, whereas in females was 30.2. In a meta-analysis of three studies, patients with spontaneous CSF leaks were 2.85 times more likely than patients with nonspontaneous CSF leaks to have obstructive sleep apnea [8].

So, our results indicated that spontaneous leaks are more common in middle age, especially females who carried worse prognosis, especially if associated with higher BMI.

Patients with high ICP showed poorer prognosis than others, being 47.1 and 85.7% respectively, and this result was highly statistically significant (*P*=0.006). It is still not completely understood why some patients with IIH develop CSF leaks, whereas others do not. It is likely that long duration of high ICP is needed. Some patients with intracranial tumors distant from skull base, but leading to high ICP, may also develop CSF leaks [9]. Persistent elevated ICP can produce remodeling of the skull base, with resultant meningoceles; moreover, spontaneous CSF is more associated with meningoceles, than does other causes of CSF leaks [10].

This explains why the longer duration of the leak is associated with poorer results. In our study, the mean duration in group A was 3.78 m, whereas that of group B was 7.52 m.

In a study that included 46 patients with spontaneous CSF leak, including 21 patients who recurred after primary repair, all patients had evidence of high ICP at time of reoperation, with mean ICP of 32.3 H_2O, so these patients were managed postoperatively with acetazolamide in 50% of cases, whereas 41% needed VP shunt; some patients had another recurrence after stopping of acetazolamide [11]. In another study, long-term use of acetazolamide was not associated with decrease in recurrence rate [12].

A recent Cochrane review failed to find sufficient evidence for use of acetazolamide in IIH [13].

It is clear that not all patients with spontaneous CSF leaks have IIH, nor all patients with IIH develop CSF leak. The overall incidence of IIH has been estimated as 0.9 per 100 000/year in general population, and as 1.6 per 100 000 female/year; the incidence increases with increase in BMI [14].

Spontaneous CSF leak cases may develop increased ICP once the leak is closed. Some studies have shown that the mean CSF pressure is elevated (between 25 and 32 cm H_2O) after repair of the leak [15]. A prospective study measuring ICP through lumbar drain, after endoscopic repair of spontaneous CSF leak, found that most patients had increased ICP after leak repair, whereas none of the patients who had repair for traumatic CSF leak had abnormal ICP values [16]. Treatment of high ICP may lead to spontaneous resolution of spontaneous CSF leak; however, the risk of bacterial meningitis with its lethal complications requires additional surgical repair of the bony defect responsible for the leak [17]. Furthermore, the incidence of spontaneous resolution in primary spontaneous CSF leaks is low, and endonasal repair is the standard of care [18], keeping in mind that these cases carry higher failure rate than other causes of CSF leaks [19].

The most common site of the leak, as goes with most publications, is the cribriform plate of the ethmoids (52%), followed by the sphenoid (36.5), and lastly the frontal sinus (11.5%). Success rates were 70.4, 78.9, and 66.7% respectively. This shows more favorable prognosis in sphenoid sinus, but with no statistical significance. Location of the leak can occasionally be difficult to classify, as the pattern of pneumatization is unique in each person, and also changes with time. In particular, sphenoid pneumatization can extend quite lateral according to increased pterygoid process pneumatization, but this was not associated with poor prognosis [20]. Leaks in more than one sinus are much more associated with high recurrence rate; multiple leaks can affect two sinuses either in contiguous fashion, or as two discrete locations. Another may be important, but missed issue is the size of the defect, as it is difficult to determine in radiological studies, or even objectively during surgery [21].

Many reconstructive techniques have been discussed in the literature; however, there are little data comparing success rate by reconstructive technique for patients with spontaneous CSF leak. In most series, all recurrent cases were attributed to unrecognized elevated ICP, or inability to control ICP with medications, thus requiring VP shunting [22]. In a study conducted on 48 cases with spontaneous CSF leak, where repair was done by various surgeons, univariate analysis showed that use of acellular dermis and multilayer closure were found to be favorable factors in repair [21].

In our study, patients were divided into 3 groups according to repair method: group 1 (17 cases), where repair was done using a fat plug and overlay mucosal graft, with success rate of 64.7%; group 2 (29 cases), where repair was done using underlay epidural graft, with overlay mucosal graft, leading to a success rate of 79.3%; and group 3 (six cases), where repair was done using underlay graft, and overlay septal mucosal flap, with success rate of 66.6%. It is clear that the second method gave the best results.

To improve the prognosis in cases with spontaneous CSF leak, it is recommended that any patients with known high ICP at time of diagnosis of CSF leak should have a shunting procedure before leak repair, as well as monitoring the CSF pressure after repair to recognize cases with elevated pressure. As high BMI is a risk factor for both IIH, and spontaneous CSF rhinorrhea, weight loss should be strongly encouraged in these patients. The strong association between IIH, and spontaneous CSF leaks, in most publications, supports systematic screening for manifestations of high ICP, after surgical repair of the presumed spontaneous CSF leak. Early identification of these patients helps to prevent failure of leak repair, and moreover prevents visual problems owing to papilledema [23].

Conclusion

Spontaneous CSF rhinorrhea repair still represents a challenging issue, with variable success rates, which are less favorable than other nonspontaneous causes of CSF leaks. Factors contributing to bad worse prognosis include female sex, high BMI, unrecognized high ICP, long period before intervention, affection of more than one site, and lastly, failure to obtain a multilayer repair.

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Conflicts of interest

There are no conflicts of interest.

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