Epidural blood patch in Trendelenburg position pre-medicated with acetazolamide to treat spontaneous intracranial hypotension

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Background: Spontaneous intracranial hypotension (SIH) is characterized by orthostatic headache, diffuse pachymeningeal enhancement on brain magnetic resonance imaging (MRI) and low cerebrospinal fluid (CSF) pressure. Treatment ranges from conservative management, such as bed rest, overhydration and caffeine, to invasive procedures, such as the autologous epidural blood patch (EBP), computed tomography (CT)-guided fibrin glue injection at the site of the leak and open surgical intervention. EBP has emerged as the treatment of choice for SIH when initial conservative measures fail to bring relief.
Methods: Forty-two patients with SIH were treated with lumbar autologous EBP in Trendelenburg position preceded by pre-medication with acetazolamide.
Results: A complete recovery was obtained in all patients after one (90%), two (5%) or three (5%) EBPs. After EBP, two patients (5%) also performed evacuation of bilateral chronic subdural hematoma with mass effect.
Conclusions: Spontaneous intracranial hypotension can be effectively cured by lumbar autologous EBP in Trendelenburg position pre-medicated with acetazolamide.

Introduction

Spontaneous intracranial hypotension is characterized by orthostatic headache, low CSF pressure and diffuse pachymeningeal enhancement on brain MRI [1–4]. Possible associated symptoms include neck or intrascapular pain, nausea and vomiting, change in hearing (echoed, distant, muffled), diplopia, visual blurring, bitemporal hemianopsia, upper limb paresthesias, parkinsonism [5], stupor and coma [6]. Atypical cases with normal CSF pressure [7], normal cranial MRI [8], nonpositional [9] or even absent headache [10] were also reported. SIH results from spontaneous CSF leakage, sometimes associated with underlying connective tissue disorders [11,12]. Although the spontaneous leak may occur at the level of the skull base, in the large majority of patients, it occurs at the spinal level, particularly the thoracic spine or cervicothoracic junction. Treatment is usually conservative, but autologous epidural blood patch (EBP) has emerged as the most important nonsurgical management [13–16]. We describe a series of 42 patients with SIH treated with autologous lumbar EBP in the Trendelenburg position preceded by pre-medication with acetazolamide.

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Methods

Since 1992, we have observed 82 patients with SIH according to the International Classification of Headache Disorder (2nd edn) 2004 criteria for headache attributed to spontaneous (or idiopathic) low CSF pressure [17]. The first 40 patients, after undergoing the usual conservative treatment (bed rest and overhydration), recovered, but only after some weeks or several months. The remaining 42 patients underwent lumbar EBP that has been started in our department since 2003 following reported experience of other authors [14]. After giving a full informed consent, these 42 patients (23 women, 19 men; aged 31–74 ; mean, 47 years) underwent lumbar autologous EBP, using 15–35 mL (mean 28 ml) of blood. Thirty-five patients performed EBP using blood mixed with contrast medium (1 mL of gadolinium in 12 patients and 5 mL of iopamidol in 23 patients). All of them performed spinal neuroimaging examination (spinal MRI or CT) after EBP to document the spreading of blood patch in the epidural space. The same anesthetist (I.A.) performed EBPs under strict aseptic conditions in an operating room. The EBPs were performed with a 18-g Tuohy needle via the

midline approach with the patient lying on one side (17 patients). Twenty-five patients performed EBP under fluoroscopic guidance on prone position. The blood was injected slowly in L2–L3, L3–L4 or L4–L5 spaces, as much possible, until the patient complained of severe lumbar pain, headache or nausea. The patients maintained a 30-degree Trendelenburg position an hour before procedure, during the procedure and 24 h after the procedure. All patients were pre-medicated with acetazolamide. The drug was given at dosage of 250 mg bid (18 and 6 h before EBP. The patients were asked to refrain from strenuous exercise for 2 weeks. Follow-up was obtained through clinical evaluation, after 1, 3 months and, later, through telephone calls. Follow-up ranged from 6 months to 5 years. The study was approved by our institutional review board.

Results

Ten patients reported as a triggering factor physical effort ($n = 2$), coughing ($n = 2$), sneezing ($n = 1$), mild trauma ($n = 3$) and cervical manipulation ($n = 2$). Forty patients had orthostatic headache, one patient had chronic daily headache and one patient had no headache. Intensity of headache was variable from a moderate (10 patients) to a severe (32 patients) degree. Other manifestations were nausea, vomiting, mild neck stiffness, tinnitus, blurred vision, hemianopsia, diplopia, bilateral upper limb numbness and coma (GCS: 5 state). Spinal taps had been performed in 10 patients. Eight patients showed low CSF opening pressure. The implemented diagnostic imaging studies are listed in the Table 1. The level of the leak was determined in 17 patients and the actual site of the leak in seven, see Table 2. All patients performed a brain CT scan. Brain MRI with gadolinium was performed in 40 patients (one patient did not perform brain MRI because he had a pacemaker, an other one performed a brain MRI without gadolinium because of an allergy to nickel). Spinal neuroimaging was performed: spine MRI (37 patients), MRI myelography (25 patients), CT myelography (three patients) and radioisotope cisternography (two patients). Spinal neuroimaging post-EBP (MRI or CT scan) was performed in 36 patients (Fig. 1). Brain CT scan showed bilateral fluid collections in 15 patients (35%), increased attenuation along the tentorium cerebelli and in the basilar cisterns/sylvian fissures in three patients (7%). Brain MRI (41 patients) showed diffuse pachymeningeal enhancement in 38 patients (92%), bilateral chronic subdural hematomas (CSH) in 15 patients (36%) and brain sagging in eight patients (19%). Spinal MRI (37 patients) or MRI myelography (25 patients) or CT myelography (three patients) or radioisotope cisternography (two patients) showed the CSF leakage site in 17 patients [at the cervical level ($n = 6$), at the cervicothoracic junction ($n = 7$), at the dorsal level ($n = 1$) and at the lumbar level ($n = 3$)]. The spinal site of CSF leakage was not determined in 25 patients. The spinal neuroimaging examination post-EBP (MRI in 14 and spiral CT scan in 23 patients) showed the blood patch spread from the lumbar to cervical epidural space in 26 (63%) of 41 EBP. All 42 patients had failed to recover during an initial period of conservative non-invasive management that ranged from 9 days to 13 months (median 62 days) and consisted of one, but often more of the following: bed rest,

Table 1 Diagnostic imaging studies in 42 patients with spontaneous intracranial hypotension (SIH)

Parameters	No. of patients
Diagnostic study	
Brain computed tomography (CT) scan	42
Brain magnetic resonance imaging (MRI)	41
Spine MRI	37
MRI myelography	25
Myelogram/CTM	3
Radionuclide cisternography	2

CTM, CT myelography.

Table 2 Level and site of spontaneous cerebrospinal fluid (CSF) leaks in 42 patients

Neuroimaging studies	Level of the leak determined	Actual site of the leak also identified	CSF leak site/No. of patients	No. of patients
Spine magnetic resonance imaging (MRI)	13	–	Cervical/5 Cervicothoracic/8	37
MRI myelography	–	5	Cervical/2 Thoracic/1 Lumbar/2	25
Computed tomography (CT) myelography	–	3	Cervical/1 Cervicothoracic/1 Lumbar/1	3
Radionuclide cisternography	–	2	Lumbar/2	2

Figure 1 Multiplanar reconstruction on sagittal view of the spine obtained by reformatted axial computed tomography (CT) slices acquired after epidural blood patch (EBP) and after Trendelenburg position: at cervical level, there is a hyperdense collection of the injected solution (blood mixed with iodinated contrast medium) into the anterior epidural spaces (white open arrow-heads); at lumbar level, some air collections into the epidural spaces (white open arrows) are recognizable.

overhydration, analgesic, non-steroidal drugs, steroids and antidepressants. Amongst 42 patients who underwent a lumbar EBP 41 patients (97%) had immediate relief and orthostatic headache disappeared within 24 h. One (patient with SIH resulting in coma) did not improve. This patient underwent a second EBP with transient improvement for 15 days, and then a third EBP with complete recovery. Amongst 41 patients with immediate relief, 37 (88%) remained pain free at the end of follow-up period, whilst four had a relapse within a few days. Of these four patients, one with atypical SIH (pachymeningeal enhancement absence on brain MRI but at multiple lumbar sites of CSF leak) had a recurrence after 10 days. She underwent a second EBP with a transient improvement for 2 weeks and, finally, a third EBP with complete recovery. The second patient affected by joint hyperflexibility after 7 days relapsed. She underwent a second EBP with recovery. The third and the fourth patient with bilateral CSH relapsed, respectively, after 20 and 7 days, because of a continuous headache by increased volume of the bilateral CSH that caused mass effect and were therefore evacuated. The third patient relapsed again after 30 days for non-postural headache by CSH with mass effect that was evacuated again. The fourth patient underwent a second EBP 3 days after CSH operation, before he stood in an upright position, as a precaution. In fact, in our experience, some patients with CSH by SIH have a recurrence of CSH after evacuation. EBP had been given at the level of the leak in three instances, at a different level in 14 [patients with CSF leak at cervical (six cases), cervicothoracic junction (seven cases) or thoracic level (one case) who received EBP at lumbar level] and as 'blind' in 25 patients in whom the spinal level of the leak had not been identified. No complication was observed.

Discussion

Forty-two patients with SIH received lumbar autologous EBP in Trendelenburg position preceded by premedication with 500 mg of acetazolamide. Thirty-eight patients (90%) recovered after one, two patients (5%) after two and two patients (5%) after three EBPs. After EBP, two patients (5%) also underwent evacuation of bilateral CSH with mass effect. For one of them, the CSH with mass effect relapsed and needed to be evacuated again. The other patients with CSH recovered spontaneously after EBP. CSH frequency in our sample was higher (36% vs. 20%) than previously reported [18,19]. Follow-up ranged from 6 months to 5 years. About 50% of patients had been referred from other centers.

Baseline characteristics of our patients are similar to those reported in other large series: female prepon-

derance, mean age of about 40 years, triggering factors and symptoms [2]. There are no controlled studies about application of EBP in CSF leak. Utilization of EBP has been based on the clinical observation of its effectiveness [20]. The criticism of lack of control for spontaneous recovery can also be extended to our study. There is no consensus regarding the management of SIH. In mild form, conservative treatment (bed rest, hydration, analgesic, non-steroidal drugs, steroids, antidepressants) is generally sufficient. In moderate and severe cases, EBP can be considered the treatment of choice for patients in whom conservative management has failed [13–16].

In these cases, some authors prefer to perform EBP precociously, few days after the beginning of symptoms [15]. We agree with this method and, usually, we recommend 10 days of conservative treatment before using EBP. We avoid lumbar puncture in typical cases because such a procedure can aggravate SIH and normal CSF pressure does not exclude the diagnosis of SIH.

Currently, we make invasive tests, lumbar puncture and/or CT myelography only in unusual atypical cases with normal brain MRI. Our cases show that, if the second lumbar EBP failed, even in the cases with complications as coma, the invasive tests are not necessary to look for the CSF leak, to perform later a targeted EBP which, according to some authors, is more effective than the lumbar one [21].

Our study, in contrast with cases reported in literature, shows that the results of EBP in spontaneous spinal CSF leak are similar to those reported in cases with CSF leak secondary to diagnostic lumbar punctures [20]. Our data confirm the efficacy of EBP in the SIH, also when it is given far from the CSF leak site (cervical or cervicothoracic junction level) and also when the site of CSF leakage is not determined. Thus, in light of our experience, we treat patients with CSF leakage undetermined with a 'blind' EBP in Trendelenburg position pre-medicated with acetazolamide. In fact, we currently do not perform more invasive examinations, as CT myelography, to identify the CSF leak site because we believe that targeted EBP at the CSF leak site is not mandatory, also because this site often remain unknown, even after performing several invasive examinations. This is an other argument to avoid spinal imaging investigation in typical cases. Furthermore, our study suggests that the blood patch spread in the epidural space can be easily traced with spinal neuroimaging (MRI or CT, using blood mixed with contrast medium), underlying the importance of the Trendelenburg position to favor the blood patch spread from lumbar to cervical epidural space on [26 (63%) of 41 EBPs] [22]. This is very important when the leak site is at the cervical level, that is the more frequent site of CSF leakage [22]. So, in these cases, it may not be necessary to perform a targeted EBP, given at the level of the leak and generally considered more effective than given at a distant site [21]. The targeted EBP is a more complex procedure possibly associated with a higher risk. No one amongst our patients needed a surgical correction of the leak [23]. The patients who needed more than one EBP were complicated and atypical cases (a complicated case with CSH with mass effect, a case with coma, a case with joint hyperflexibility and a case with normal brain MRI but multiple lumbar CSF leak on radioisotope cisternography). These cases represent a significant therapeutic challenge.

Although we have previously reported our experience with lumbar EBP in few cases, this is the first report that describes our own experience in the whole sample of patients who were diagnosed as having SIH. Our approach differs from that used by others because our procedure (EBP) was preceded by administration of acetazolamide and each patient was kept in prolonged Trendelenburg position.

Our 90% success rate after one epidural blood patch is higher than that (57%) observed in the Lariboisière Hospital in Paris (a series of 30 patients) [15] and also greater than that (36%) observed in the Mayo Clinic in Rochester (a series of 25 patients) [14], possibly because these patients underwent epidural blood patch in a horizontal position and remained recumbent for only 2 h after EBP. Furthermore, the patients of the Mayo Clinic series received a smaller quantity of blood (10–20 mL) in contrast to 15–35 mL in our series.

Acetazolamide is a sulfonamide with carbonic anhydrase inhibitory activity, and it decreases production of CSF reducing intracranial pressure. We chose the use of acetazolamide and the Trendelenburg position during EBP performance from the neurosurgical procedure for the spinal liquoral leakage repair. In fact, they place a catheter to drain CSF reducing the spinal pressure, thus closing the CSF fistula. It may be that pre-medication with acetazolamide associated with keeping the patient in prolonged Trendelenburg position might reduce the flow of spinal CSF fistula and might cause collapse of dura mater favoring the approach of borders of the dural hole producing the sealing of the hole. Because it has been reported that an anti-Trendelenburg position increased the flow of CSF leak [24], it is possible that a Trendelenburg position has the opposite effect. Furthermore, pre-medication with acetazolamide might avoid the rebound intracranial hypertension sometimes reported after the EBP [25]. In fact, none of our patients had a rebound of intracranial hypertension after EBP. We acknowledge that this complication is rare. However, acetazolamide at low doses may further prevent the rebound of

intracranial hypertension. This, to our knowledge, is the first report that describes the use of acetazolamide in the treatment of SIH in a large case series. In conclusion, we performed a lumbar large volume EBP in Trendelenburg position pre-medicated with acetazolamide in 42 patients. Our experience suggests that the procedure is safe and highly effective for patients suffering from SIH by spinal CSF leak.

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