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IN PATIENTS RECEIVING SPINAL ANESTHESIA, CAN HOMOCYSTEINE AND C-REACTIVE PROTEIN LEVELS PREDICT THE DEVELOPMENT OF POSTDURAL PUNCTURE HEADACHE?

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Abstract

Postdural puncture headache (PDPH) is a complication that may arise following spinal anesthesia. We investigated whether homocysteine and C-reactive protein levels may be associated in the development of PDPH in patients that received spinal anesthesia.

In order to determine homocysteine and C-reactive protein (CRP) levels, blood samples were taken from patients before and one day following spinal anesthesia. A total of 100 male patients were enrolled in the study. The mean age of the patients was 29 years old. Out of all the patients, a total of 6 developed headaches. The Mann-Whitney U-test was used to compare homocysteine and CRP levels between patients that did and did not develop headaches.

Homocysteine levels before and after the operation were higher in subjects that developed a headache as compared to patients that did not develop headaches ($p<0.001$). CRP levels did not differ significantly between patients with headaches and patients that did not experience them ($p>0.05$).

High blood levels of homocysteine in patients with PDPH might be used as a biomarker so to predict the development of PDPH. However, future larger, multi-center studies are needed to further elucidate this association.

Keywords: Spinal Anesthesia, Postdural Puncture Headache, Homocysteine, C-Reactive Protein

1. Introduction

Collecting cerebrospinal fluid (CSF) is achieved by puncturing the dura with a needle so to access the subarachnoid space, which contains the CSF. In routine clinical practice, accessing the subarachnoid space is necessary for the following procedures: performing spinal anesthesia, collecting CSF samples, measuring CSF pressures, draining CSF to treat idiopathic intrathecal hypertension, administering intrathecal chemotherapy, and injecting radiopaque substances so to perform myelography. However, while performing epidural anesthesia, the dura may be accidentally punctured, and CSF may be lost in excess (Bedirli and Akkaya 2010). Postdural puncture headache (PDPH) is one of the most common complications arising from diagnostic, therapeutic and even accidental lumbar punctures. The lumbar puncture was first performed by J.L. Corning in 1885 with sharpened bird quills. Later in 1891, Quincke was the

first to record the lumbar puncture technique still used today in his CSF study logs (Dakka 2011). PDPH was first described by August Bier in 1989 after attempting to perform spinal anesthesia on himself (Abdulla et al., 2011, Levine and Rapalino 2001). PDPH is defined as a headache that occurs after lumbar puncture and worsens 15 minutes after sitting or standing and is relieved by lying down for at least 15 minutes. Within three days 90% of PDPHs develop and 66% of them start within 48 hours of the procedure (Arevalo-Rodriguez 2013).

The pathophysiology of PDPH is still not fully understood (Arevalo-Rodriguez 2013, Ahmet et al., 2013); however, several theories have been generated. One such theory called the Monro-Kellie Doctrine posits that CSF volume loss causes compensatory intracranial vessel vasodilation and increased sensitivity to substance P, which intensifies the sensation of pain in sensitive structures. PDPH occurs when there is a relative decrease in CSF volume or due to a permanent CSF leak. A wider opening in dura causes greater volume losses during dural punctures, which increases the possibility of developing PDPH. A loss of approximately 10% of the predicted total CSF volume causes orthostatic hypotension. Certain anatomical and physiological patient characteristics are also believed to play important roles in developing PDPH, as some patients experience PDPH after minimal CSF losses while others remain asymptomatic after excessive CSF losses (Bezov et al., 2010a).

Risk factors for developing PDPH include utilizing a suboptimal needle that is dull with an inappropriately sized bore and no stylet, and poor technique in which the needle tip is oriented and angled improperly. Commonly used spinal needles are Tuohy, Sprotte, Quincke, Whitacre, and Atraucan needles. Needle size may be an important factor in increasing PDPH risk. The chances of developing PDPH after spinal anesthesia are the following: 36% with a 22 gauge Quincke sharp-pointed needle, 25% with a 25 gauge needle, 2-12% with a 26 gauge needle, and less than 2% with a 29 gauge needle or smaller. Bigger openings in the dura caused by large-bore needles are more difficult to seal and may lead to greater CSF losses (Bezov et al., 2010b). Needle sharpness may decrease the frequency of PDPH. Holes created by atraumatic Sprotte and Whitacre needles usually reseal after removing the needle. The ability of the hole to reseal spontaneously is most compelling reason as to why post-lumbar puncture headaches rarely develop with dural punctures performed with atraumatic needles (Bezov et al., 2010a).

Smaller diameter needles are sufficient to perform spinal or epidural anesthesia and myelography. For spinal anesthesia, 25 to 27 gauge needles are preferred as these sizes are associated with decreased procedure failure (Bezov et al., 2010b). Needle sizes and types utilized for spinal anesthesia in children are usually smaller than needles routinely used in adults, therefore such needles may have a limited contribution toward the development of PDPH. A study conducted by Apiliogullari et al. in 2010 revealed that the prevalence of PDPH was greater than previously thought, as PDPH occurred commonly in patients less than 13 years old (Apilioğulları et al., 2010a). Due to the relative high prevalence of PDPH, Apiliogullari et al. recommended in a 2013 publication that PDPH should be included in the second edition of International Headache Disorders (ICHD-II) (Apilioğulları et al., 2010b).

Appropriately orienting the sharp edge of the atraumatic needle with the stylet in place decreases the risk of PDPH (Bezov et al., 2010a). Yet, a study conducted with 639 patients by Sinikoglu et al. in 2013 demonstrated that stylet insertion did not decrease the risk of PDPH at all. For less experienced clinicians, large dural punctures may result from poor technique while performing epidural anesthesia. In addition to suboptimal dural puncture technique, young age, multiple dural punctures, female gender, pregnancy, low body mass index, and a history of chronic headache and/or PDPH all contribute to an increased risk of developing PDPH (Bezov et al., 2010a, Ghaleb et al., 2012). Several precautions can be taken to prevent PDPH such as correct patient positioning, good hydration, post-procedure bed rest, limiting the volume of CSF drained, and reducing the number of dural punctures. However, the benefits of these preventative

measures have not been clearly demonstrated. Moreover, there are several reports indicating that pretreatment with oral or intramuscular caffeine does not prevent PDPH (Bezov et al., 2010b, Halker et al., 2007).

There are four main approaches in treating PDPH including conservative medical treatment, aggressive medical treatment, conventional surgical treatment, and aggressive surgical treatment. Conservative medical treatment for PDPH has a benign prognosis and so is the preferred treatment method. Conservative treatment includes bed rest, hydration, and the use of analgesics and antiemetics (Bezov et al., 2010b). There have been reports demonstrating that to the contrary, post-procedural mobilization was better than bed rest in preventing PDPH (Thoennissen et al., 2001). Aggressive medical treatment consists of intravenous infusions of methylxanthines or ACTH (Kshatri 1997); occipital nerve blocks; and prescribing sumatriptan, mirtazapine, pregabalin (Zencirci 2010), gabapentin (Wagner et al., 2012), and corticosteroids (Bezov et al., 2010b). Administering an epidural injection of morphine has also been demonstrated to prevent PDPH (Al-metwalli 2008). Conventional surgical treatments are preferred when conservative treatments fail or when PDPH is severe. Often conventional surgical treatment is utilized to create an epidural blood patch. Studies with children and adults revealed that epidural saline is just as effective as an epidural blood patch (Abdulla et al., 2011, Gök and Apilioğulları 2009, Kakinohana et al., 2001). There are other studies that have reported that epidural dextran administration can be used to create a patch, but this method was found to be ineffective. Aggressive surgical treatment is necessary if the epidural blood patch fails two or three times, then a fibrin glue injection is administered via computerized tomography guidance (Bezov et al., 2010).

Homocysteine is composed of cysteine, which is formed after metabolizing the sulfur-containing aminoacid methionine that contains a sulfhydryl group (Isobe and Tereyama 2010). Hyperhomocysteinemia may be associated with increased risk of migraines (Gruber et al., 2010). Several patients with migraines demonstrated increased homocysteine levels, particularly in patients who suffered from migraines with aura. Homocysteine levels are also increased in patients with cardiovascular diseases as well (Isobe and Tereyama 2010).

C-reactive protein (CRP) is a marker of inflammation associated with cardiovascular diseases. Studies conducted on the relationship between migraines with aura and CRP levels did not reveal any association. However, research conducted with children suffering from headaches and migraines found that CRP and homocysteine levels remained high (Nelson et al., 2010). Even though there have been many studies regarding headache alleviation in patients with PDPH, studies investigating tests or biomarkers that predict the development of PDPH do not exist.

In our study, we investigated whether homocysteine and CRP levels can predict the development of PDPH.

2. Materials and Methods

We enrolled a total of 100 male patients that were scheduled to receive spinal anesthesia with ASA (American Society Anesthesiologists) Risk Classification score of I-II in the operating rooms of Department of Anesthesiology and Reanimation at Mengücek Gazi Teaching and Research Hospital. Patient ages ranged between 18-57 years, and the average age was 29 years old. Patients fasted for 8 hours prior to surgery. Venous blood samples were taken from patients one hour preceding the operation and one day following the surgery. Homocysteine and CRP levels were measured from the blood samples. Exclusion criteria were patients that had more than two attempts to achieve spinal anesthesia; patients with a history of cardiovascular disease and/or headaches and/or migraines; patients that suffered excessive blood loss intraoperatively; and patients that received a blood transfusion.

A 25 gauge pencil point guided a 90 mm needle (Egemen International Medical İzmir) that delivered 15 mg of bupivacaine (0.5% heavy spinal Marcaine, Astra Zeneca) for spinal anesthesia. A total of 500 mL of 6% hydroxyethyl

starch (Voluven Fresenius Kabi) was administered intravenously to every patient 2 hours preceding spinal anesthesia in the antecubital area. During and after the operation, non-invasive arterial blood pressure, pulse oximetry, heart rate, and serial ECGs were monitored in all patients. The mean duration of surgery was 41 minutes and vitals were monitored until the patients recovered purposeful motor function. A 5 mg intravenous bolus of ephedrine was administered if the patient exhibited a sudden drop in blood pressure during surgery, and that dosage was repeated as necessary. Hemodynamic parameters were kept within normal limits throughout surgery. Bed rest, hydration, oral paracetamol with caffeine treatment were all used for patients that developed a headache. All headaches resolved within 3 days and every patient responded to therapy. None of the patients required an epidural blood patch.

We investigated whether homocysteine and C-reactive protein levels differed significantly between patients that developed post-spinal anesthesia headache or not. Normal homocysteine levels in patients range from 5.46-16.20 umol/L. Reference CRP levels range from 0-1 mg/dL. Homocysteine levels were measured by the Abbott Architec 2000 device and CRP levels were determined with the Coulter Immage 800 device.

Putative PDPH biomarker levels (homocysteine and CRP) were compared via the Mann-Whitney U-test. Monte Carlo p-values were calculated so to determine whether the p-value was significant.

The study protocol was reviewed and approved by the Erzincan University Ethics Committee (No: 10.09.2012, 2012/1) and the Erzincan University Scientific Research Program Project No: 2012/12.01.08)

3. Results and Discussion

The study subjects had ASA risk classification scores ranging between I-II and 100 male patients. A total of 6 participants developed a headache.

Table 1. Homocysteine and CRP levels in patients with and without post-spinal anesthesia headache

			HOMOCYSTEINE		CRP	
			PRE-OP	POST-OP	PRE-OP	POST-OP
Without Headache	n		94	94	94	94
	Mean		11.935	11.853	0.596	0.852
	Std. Deviation		3.609	2.958	0.625	0.824
	Minimum		5.710	5.610	0.080	0.163
	Maximum		27.910	17.130	4.218	4.916
	Percentiles	25	8.830	9.270	0.175	0.283
		50 (Mean)	12.310	12.150	0.392	0.618
		75	13.953	14.500	0.840	0.999
With Headache	n		6	6	6	6
	Mean		20.623	23.432	0.337	0.527
	Std. Deviation		4.090	2.793	0.228	0.418
	Minimum		16.390	20.840	0.128	0.192
	Maximum		27.180	28.130	0.727	1.170
	Percentiles	25	16.878	21.073	0.129	0.208
		50 (Mean)	20.350	22.640	0.292	0.332
		75	23.618	25.925	0.524	0.986

Table 1 shows the descriptive statistics for the 94 participants that did not develop headache and for the 6 patients that did develop headache following spinal anesthesia.

Table 2. Comparison of homocysteine and CRP levels in patients that did and not experience post-spinal headache before and after the operation

	Headache	n	Mean±SD	U	*p*-value[a]
H_PRE-OP	Without Headache	94	11.935±3.609	16.0	0.000*
	With Headache	6	20.623±4.09		
H_POST-OP	Without Headache	94	11.853±2.958	0.0	0.000*
	With Headache	6	23.432±2.793		
CRP_PRE-OP	Without Headache	94	0.596±0.625	208.0	0.290
	With Headache	6	0.337±0.228		
CRP_POST-OP	Without Headache	94	0.852±0.824	199.0	0.244
	With Headache	6	0.527±0.418		

[a] :Monte Carlo *p*-value, H_PREOP: pre-operative homocysteine level, H_POSTOP: post-operative homocysteine level, CRP_PREOP: pre-operative CRP level, and CRP_POSTOP: post-operative CRP level. These are based on 10,000 sampled tables with a starting seed of 2,000,000. *$p<0.001$

Homocysteine levels preceding and following the operation were greater in subjects that developed a headache when compared to patients that did not develop a headache ($p<0.001$). Homocysteine levels in participants without headaches before the operation was 11.853±2.958 umol/L with an average value of 12.310 umol/L, while homocysteine levels in participants with headache were 20.623±4.09 umol/L with a mean value of 20.350 umol/L. Homocysteine levels in participants without headaches after the operation was 11.935±3.609 umol/L with an average level of 12.150 umol/L. Homocysteine levels in participants that developed headache was 23.432±2.793 with an average value of 22.640 umol/L. CRP levels did not differ significantly between patients that did and did not develop headaches ($p>0.05$).

Even though it has been more than 100 years since PDPH was first described (Zencirci 2010), only a few theories have been postulated regarding its pathophysiology and the actual mechanism remains unknown (Ahmed et al., 2006, Bezov et al., 2010a, Sinikoğlu et al., 2013, Grände 2005). Age, sex, increased body mass index, and a history of headaches and/or migraines all play important roles in developing PDPH. Several studies have demonstrated that needle diameter and type modulate the risk of getting PDPH (Bezov et al., 2010a). However, individual anatomy and overall health may contribute to the risk of developing PDPH. For example, some patients may experience PDPH after experiencing minimal CSF losses, while other patients do not experience headaches following relatively greater CSF losses (Bezov et al., 2010a). Other risk factors for developing PDPH may include a history of chronic headaches and having experienced PDPH previously (Bezov et al., 2010a, Ghaleb et al., 2012).

Several studies have reported an association between chronic headache and certain biomarkers. Isobe et al. identified significant increases in homocysteine levels in the cerebrospinal fluid of patients that suffered from migraines with aura (Isobe and Tereyama 2010). Catecholamines are also significant in the pathogenesis of migraines. Dopamine agonists cause migraine-like symptoms, which supports the hypothesis that dopamine contributes to the development of migraines (Gruber et al., 2010, Akerman and Goadsby 2007). Gruber et al. reported that increased dopamine levels triggered the development of migraines and that dopamine was highly correlated with cGMP and the homocysteine-folate pathway. Also, they determined that dopamine levels had increased during headache-free periods. Oterino et al. found

that smoking, hypertension and dyslipidemia did not affect homocysteine levels in patients suffering from migraines with aura. Moreover, no correlation was determined between age and homocysteine levels. At baseline, normal homocysteine levels are higher in male patients as compared to female patients. Homocysteine levels have been found to be higher in patients suffering from migraines with aura, and folate-related enzymes are thought to contribute to this increase (Oterino et al., 2010).

In a study conducted by Lea et al. it was demonstrated that lowering homocysteine levels with vitamin supplementation might reduce the development of migraines. Cheap, effective prophylactive vitamin administration such as folic acid might improve the quality of life of patients with migraines. Moreover, it has been reported that patients with a B12-dependent methylenetetrahydrofolate reductase genotype may derive greater benefits from taking folic acid (Lea et al., 2009). In a study conducted in the United States on children with headaches, Nelson et al. found that hyperhomocysteinemia was associated with low folate levels, high CRP levels, and increased body mass index. In contrast, Hanit et al. found no relationship between hyperhomocysteinemia and migraines. Moreover, Gudmundsson et al. determined that CRP levels were not elevated in patients with migraines.

We investigated homocysteine and CRP levels before and after surgery in patients that received spinal anesthesia and developed subsequent PDPH. A similar study has not been reported in the literature. Our study included 100 patients and we found a significant difference in homocysteine levels in patients that developed headaches as compared to patients that did not. There was not a significant difference between headache-free patients and those that experienced dural puncture-related headaches when examining CRP levels. Patients that underwent more than two attempts to achieve spinal anesthesia; previously experienced PDPH; and had a history of cardiovascular disease, myocardial infarction, chronic headache, and migraine were excluded from the study so to eliminate confounding variables. Moreover, a 25-gauge pencil point was used to guide a 90 mm needle for spinal anesthesia in every patient so to avoid variability introduced by using different needle types.

4. Conclusion

We posit that high blood levels of homocysteine may be utilized as a biological indicator of PDPH. Precautions against developing PDPH may improve patient comfort, prevent work absences, and shorten the duration of hospital stay. Moreover, it may be possible to avoid PDPH if high homocysteine levels are detected, which might increase the quality of care delivered by anesthetists. However, further studies must be performed with larger patient samples and multiple health centers to better illuminate the association between increased homocysteine levels and the development of PDPH.

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