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Non-Interventional Treatment of Post-Dural-Puncture Headache; High-Flow Oxygen and Pro-Serotonin Agents a Safe and Effective Alternative

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Introduction

Lumbar punctures are commonly performed for diagnostic and/or therapeutic purposes by threading a needle through the outermost layer of the meninges, the dura mater, and into the intrathecal space within the lumbar region of the spine [1]. The intrathecal space contains cerebrospinal fluid (CSF), a clear and colorless fluid, which surrounds the brain and spinal cord and can provide information regarding intracranial pressures, presence of diseases involving the central nervous system (CNS) or surrounding meninges [2-4]. A common complication of dural puncture is a post-dural puncture headache (PDPH) which is defined by The International Headache Society as a "headache that develops within 5 days of dural puncture and resolves within 1 week spontaneously or within 48 hours after effective treatment of the spinal fluid leak" [5]. Symptoms of PDPH classically include a frontal and/or occipital headache that improves in the supine position, worsened by sitting or standing, and may be associated with nausea, nick stiffness, vertigo, vision changes, dizziness, or auditory disturbances [6]. PDPH has the propensity to cause significant morbidity; among affected patients, 39% report a duration of at least one week of significant impairment of daily activities while severe PDPH may require hospital admission [7]. The gold standard treatment for PDPH is to administer an epidural blood patch (EBP), autologous blood collected in the periphery vessels and delivered in the area of suspected CSF leak within the spinal canal to "mechanically plug the leak" [8]. However, in order to perform this intervention safely, training and specific equipment are necessary but unfortunately not a common part of the armamentarium of most clinical settings.

Among cancer patients, access to the intrathecal space for diagnostic or therapeutic purposes may be part of the standard of care and occurrences of headaches associated with dural puncture in these scenarios are not totally unavoidable. Furthermore, many patients with cancer often have clear contraindications to accessing the epidural space to perform a therapeutic blood patch [9]. Under these circumstances, non-invasive alternatives should be considered (**Table 1**).

Table 1. Contraindications for EBP.
Coagulopathy
Thrombocytopenia
Anticoagulation
Suspected bacteremia
Infection at needle placement site
Untreated HIV
Unexperienced provider
Uncooperative patient

In this article, we describe commonly used non-invasive options to treat PDPH including high-flow oxygen-metoclopramide, Caffeine, Cosyntropin, Gabapentin, Indomethacin and Theophylline. Mechanisms of action associated with each treatment modality are highlighted (**Table 2**).

Pathophysiology of PDPH

There are several proposed mechanisms for PDPH including downward drag of pain-sensitive intracranial structures from

Table 2. Mechanism of action and common side effects of agents used to treat PDPH.

Agent	Mechanism	Side effects
High-flow oxygen	COX inhibitor PGE2 inhibitor Vasoconstriction	None
Metoclopramide	5-HT3 antagonist CGRP inhibitor Substance P antagonist	Akathisia Lower seizure threshold
Caffeine	Vasoconstriction Adenosine receptor antagonist	Diuresis Anxiety
Cosyntropin	Release of aldosterone to induce production of CSF	Fluid retention Electrolytes imbalance Hypertension Irregular heartbeat Increased growth hormone & Lipogenesis Nausea & anxiety Facial flushing & Diaphoresis
Gabapentin	Inhibits central neuronal hyperexcitability Inhibits release of substance P	Fluid retention Sedation Tremors Confusion & memory changes
Indomethacin	COX inhibitor PG inhibitor Nitric oxide modulation Intracranial precapillary vasoconstriction	Hypertension Peptic ulcer disease Increase bleeding
Theophylline	Vasoconstriction Adenosine receptor antagonist	Diuresis Anxiety & irritability Nausea & vomiting Seizures Arrhythmia

reduced buoyancy related to CSF hypotension, particularly in the upright position, contributing to the development of headache [10]. Additionally, compensatory vasodilation of intracranial blood vessels to maintain a constant intracranial volume and resultant headache from cerebral arterial and venous distention (Monro-Kellie Hypothesis) [11]. Furthermore, alterations in substance P, a modulator of pain perception, and regulation of neurokinin-1 receptors may play a role [12].

Non-Invasive Therapeutic Options

High-flow oxygen - metoclopramide

Oxygen concentration can influence prostaglandin synthesis via cyclooxygenase (COX) activity altering prostaglandin levels, notably prostaglandin E2 (PGE2), a vasodilator [13]. In hypoxic conditions, COX is activated with subsequent increase in PGE2 and downstream vasodilation [14] contributing to the development of a headache, commonly seen in high-altitude settings. Whereas in hyperoxic conditions, COX activity is diminished [15] which may result in downstream vasoconstriction. This vasoconstriction may explain the symptomatic improvement observed in patients with postdural puncture headaches receiving high flow oxygen (12L/min via a non-rebreathing mask) [16], as the effect counteracts the pathophysiologic hypothesis related to compensatory vasodilation of intracranial blood vessels in PDPH.

Metoclopramide is a dopamine antagonist used in the treatment of nausea and vomiting and has also evolved to be utilized as an effective analgesic medication during migraine exacerbations [17]. The pain-relieving mechanism underlying metoclopramide may be influenced by its antagonistic role at the serotonin type 3 (5-HT_3) receptor as several studies indicate 5-HT_3 receptors are expressed in primary afferent nociceptors [18-20]. Furthermore, 5-HT_3 receptor antagonists have been shown to inhibit calcitonin gene-related peptide (CGRP) release in the rat spinal cord [21]. In the CNS, CGRP is involved in pain modulation, perception, and central sensitization [22]. CGRP potentiates the release of substance P from primary afferent terminals and promotes nociceptive signaling induced by noxious stimuli [23]. Additionally, CGRP is implicated in promoting vasodilation on arterial smooth muscle [24]. Therefore, metoclopramide may produce analgesia by its antagonistic activity at 5-HT_3 receptors, inhibiting CGRP release and downstream influence on substance P and arterial vasodilation.

Caffeine

Caffeine is a central nervous stimulant of the methylxanthine class and is used worldwide to enhance concentration and memory [25], with first report of usage as a treatment for PDPH in 1949 [26]. Caffeine is hypothesized to treat PDPH by inducing cerebral vasoconstriction as an adenosine receptor antagonist [27,28] since adenosine receptor activation can produce downstream vasodilatory effects via its G protein-coupled receptor activity [29]. In forty postpartum patients with postdural puncture headache who were randomly assigned to receive oral caffeine or a placebo, assessment using visual analogue pain scale four hours after administration was significantly improved regarding headache intensity in the group receiving oral caffeine [30].

Cosyntropin

Adrenocorticotropic hormone (ACTH) is produced by the pituitary gland of the brain and controls the production of cortisol, the primary physiologic stress hormone [31]. Cosyntropin is the synthetic version of adrenocorticotropic hormone. Cosyntropin is hypothesized to be effective in the treatment of PDPH by stimulating the release of aldosterone and influencing the downstream production of CSF [32]. In twenty-eight patients who were diagnosed with PDPH and randomized to receive EBP (gold standard) or intravenous Cosyntropin, effectiveness was similar for each intervention arm immediately after treatment, along with days 3 and 7 regarding headache intensity and function [33].

Gabapentin

Gabapentin is an anticonvulsant medication that serves as a ligand for voltage-gated calcium channels and functions as a gamma aminobutyric acid (GABA) analogue [34,35]. The role of gabapentin for analgesic relief is not yet fully elucidated but may be related to inhibition of central neuronal hyperexcitability [36] along with the observation that gabapentin reduces the release of substance P in rats [37,38]. These factors may have contributed to the analgesic effect seen in twenty patients diagnosed with PDPH who were randomized to receive either gabapentin or placebo, with the gabapentin group reporting improved pain relief during the four-day study period [39].

Indomethacin

Although better known for its absolute effectiveness on a heterogeneous group of primary headache disorders, Indomethacin has been used on the treatment of PDPH. By inhibiting COX, it reduces PG synthesis possibly via calcium channel blockade with a more potent anti-inflammatory effect than aspirin [40]. Other mechanisms include reduction of cerebral blood flow via modulation nitric oxide (NO) pathway and causing intracranial precapillary vasoconstriction which can reduce intracranial pressure by 37% [41].

Theophylline

Theophylline is a member of the xanthine family and is used primarily in the treatment of respiratory diseases (e.g. COPD and asthma) [42]. In PDPH, theophylline is thought to work similarly as caffeine via its action as an adenosine antagonist with downstream vasoconstriction since there is overlap in structure and pharmacologic properties of xanthine's (e.g. theophylline) and methylxanthines (e.g. caffeine) [43,44]. In forty patients diagnosed with PDPH and randomized to receive either conservative treatment or oral Theophylline, assessment using visual analogue scale score for pain demonstrated significantly better relief for those receiving theophylline [45].

Conclusion

The pathophysiology of PDPH is not yet precisely known, but CSF volume loss, intracranial blood vessel vasodilation, and substance P may play a role. The gold standard of treatment is an epidural blood patch, which may not be an accessible option at all practice settings or contraindicated depending on the clinical context. Therefore, treatment options that are non-invasive and readily accessible should be considered and may include high-flow oxygen, metoclopramide, caffeine, Cosyntropin, gabapentin, indomethacin or theophylline in the management of PDPH.

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