Vasovagal Reactions during Interventional Pain Management Procedures

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Contributor: Brian Malave , Bruce Vrooman

Vasovagal reactions—defined as a rapid drop in heart rate and/or blood pressure, usually in response to a stressful trigger—are a common complication of interventional pain management procedures. Three types of vasovagal responses have been described in the literature: a cardioinhibitory form (HR < 40 bpm), vasodepressor form (SBP < 80 mmHg or decrease by >30% without significant HR reduction), or mixed form (HR < 40 bpm and SBP < 80 mmHg or decrease by >30%). Typical symptoms of a vasovagal reaction are lightheadedness or dizziness, palpitations, weakness, blurred vision, nausea, feelings of warmth or coldness, and sweating. When a vasovagal reaction results in a loss of consciousness, it is termed vasovagal syncope. Although vasovagal reactions are usually benign in nature, they can lead to more serious complications for both patients and providers, such as aborted procedures, cardiac arrythmias, or fear of future procedures. It is thus useful for pain medicine clinicians to identify the risk factors, prevention, and management of vasovagal reactions in an outpatient setting.

vasovagal reaction epidural spinal injection antimuscarinic interventional pain management procedure

1. Pathophysiology

As mentioned previously, “vasovagal” reaction is a term that describes either “vaso-” depression (evident as hypotension), “vagally” mediated cardioinhibition (evident as bradycardia), or a combination of both. When loss of consciousness (i.e., syncope) occurs after a vasovagal reaction, it is term vasovagal syncope. Vasovagal syncope is the most common type of syncope, comprising up to 40% of all outpatient syncopal events. The most common explanation for why vasovagal responses occur is the Bezold–Jarisch reflex. The theory is that excessive venous pooling leads to decreased blood pressure sensed by baroreceptors on the aortic arch, carotid sinus, heart walls, and intrathoracic vessels, which relay the information to the nucleus tractus solitarius of the brain, ultimately inhibiting sympathetic response and increasing vagal tone. This leads to hypotension and bradycardia. This theory is supported by tilt-table testing, in which a patient lies down on a table and is then tilted upright at a specified angle, leading blood to pool in the leg veins secondary to gravity. If the patient exhibits a vasovagal response, it is likely due to the Bezold–Jarisch reflex [1].

The pathophysiology of vasovagal reaction to interventional pain management procedures specifically is multifactorial and not entirely understood. For epidural steroid injections, some have proposed that the epidural anesthesia may lead to sympathetic blockade, resulting in lower venous tone and decreased cardiac output [2][3]. Other known triggers of vasovagal reaction that may occur during interventional pain management procedures—but not specific to these procedures—are fear, anxiety, disgust, pain, imagined or real exposure to bodily harm, sight of blood, hunger, heat, and others. In all cases, these external stimuli lead to increased cardiac contractility despite an underfilled left ventricle, which is sensed by mechanoreceptors in the ventricle and relayed to the brain via vagal afferent nerves. The brain responds to the stimuli by increasing parasympathetic tone, leading to bradycardia and hypotension, much like in the Bezold–Jarisch reflex [4].

2. Prevention

2.1. Sedation

The American Society of Anesthesiologists defines the continuum of sedation as minimal, moderate, deep, or general anesthesia. Minimal sedation allows the patient to be responsive to verbal stimuli, and is usually achieved with oral

medications or nitrous oxide (“laughing gas”). In moderate or “conscious” sedation, the patient feels drowsy and may fall asleep, but awakens to verbal/tactile stimulation. This is usually achieved with IV medications. Deep sedation occurs when the patient is asleep through the procedure, but awakens to painful stimulation. General anesthesia occurs when the patient is unwakeable, even with painful stimuli [5].

Some evidence suggests that moderate sedation might reduce risk of vasovagal reaction, especially in patients with a history of vasovagal reactions. Kennedy et al., 2015 [6] performed 6364 spine injections, 214 of which were done with conscious sedation with midazolam and fentanyl. They found that none of the injections performed with sedation led to vasovagal reaction, while 3.3% of injections done without sedation led to vasovagal reaction. They analyzed the data further and found that 134 injections had been done on patients with a history of vasovagal reactions. Of these, 90 were done without sedation and 44 with moderate sedation. Those who received sedation did not experience any recurrent vasovagal reaction (vasovagal rate of 0), while those who did not receive sedation had a recurrent vasovagal reaction rate of 23.3%, suggesting that conscious sedation may be an effective measure to prevent the recurrence of vasovagal reactions.

However, sedation during interventional pain management procedures is associated with several risks. A sedated patient may not necessarily experience pain if a spinal nerve or the spinal cord is inadvertently contacted, and thus may not necessarily provide reliable feedback to the proceduralist who is attempting to ensure that there is no central neurological damage after the lidocaine test injection [7][8][9]. There are reported cases of traumatic spinal cord injury during interventional spine procedures in which sedation was used [10]. The frequency at which these iatrogenic injuries occur—and the role of sedation in predisposing to these injuries—is debated. Schaufele et al., 2011 [11] examined 2494 interventional spine procedures—half performed under conscious sedation and the other half without sedation—and found no significant difference in rates of adverse events at 1 day and 3 days postoperation. However, Rathmell et al., 2011 [12] examined ASA malpractice closed claims from 2005 to 2008 and found that 67% of cervical procedure claims associated with spinal cord injury involved the use of sedation or anesthesia. Of these claims, 25% of patients were nonresponsive during the procedure, indicating that they could not provide reliable feedback to the provider. Other complications of sedation include airway compromise, arrhythmia, hypotension, venous thrombosis, pulmonary embolism, nausea, vomiting, allergic reactions, and even death [7]. The possibility of putting patients’ health at risk makes sedation a less favorable choice for prevention of vasovagal syncope.

In summary, sedation has been shown to be an effective measure to prevent the recurrence of a vasovagal reaction in patients with a history of such. However, the routine use of sedation as a primary preventive measure for vasovagal reactions is likely not recommended, given its known risks and the overall low likelihood of a vasovagal reaction.

2.2. Anxiolytics

Anxiety is a well-established risk factor of vasovagal reactions, and fear of procedures increases the likelihood of a vasovagal response [13][14]. As such, anxiolytic medications, such as benzodiazepines, have been used in a variety of clinical settings—ranging from outpatient breast biopsy to dermatological procedures—to reduce preoperative anxiety levels [15][16][17]. Benzodiazepines have been shown not only to lower anxiety before procedures but also to lower vasovagal reaction rates during the procedure. Gebhardt et al., 2018 [18] retrospectively examined the charts of 2747 patients undergoing low-dose intrathecal anesthesia during outpatient procedures, with 1291 patients receiving anxiolytic premedication of 1–2 mg IV midazolam. Vasovagal reaction rates were 15% for patients who did not receive midazolam and 7.5% for those who did ($p < 0.001$), suggesting that benzodiazepines lower vasovagal rates [18]. James et al., 2005 [19] similarly found that giving 2–4 mg sublingual lorazepam to women undergoing stereotactic breast biopsies successfully prevented a recurrent vasovagal reaction in 95% who had previously had a vasovagal reaction during prior biopsy. The use of benzodiazepines for vasovagal reactions resulting specifically from interventional pain management procedures has not been studied to the researchers' knowledge, but merits research given its apparent benefit for lowering vasovagal reactions in other clinical settings.

There are side effects of benzodiazepines that might make them less favorable to use during interventional pain management procedures. Benzodiazepines are known to cause sedation and increase the risk of motor vehicle accidents, especially in the

elderly [20][21], which might prolong the time to achieve readiness for discharge. However, patients undergoing interventional pain management procedures under local anesthesia are not advised to drive for at least 12 h after their injection, even if sedation or anxiolytics are not used [22]. Gebhardt et al., 2018 [18] found that administration of 1–2 mg midazolam IV prior to low-dose intrathecal anesthesia for various outpatient procedures did not prolong time to achieve readiness for discharge. More studies should be done on the effects of benzodiazepines specifically for interventional pain management procedures, but it is suspected that the time to discharge should not be affected.

Other side effects of benzodiazepines include confusion, anterograde amnesia, agitation, and increased risk of falling, all of which are increased in elderly persons [23][24]. Benzodiazepines have also been linked to teratogenic effects and poor outcomes on fetal health [24][25], although interventional pain management procedures are generally avoided in pregnancy unless conservative measures fail [26][27]. These side effects should be taken into consideration when determining whether to administer benzodiazepines to a patient prior to an interventional pain management procedure.

2.3. Antimuscarinics

Another pharmacological agent that has the potential to prevent vasovagal reactions is an antimuscarinic. To understand this, one must understand the pathophysiology of the vasovagal response. The vasovagal response is a reflex arc within the parasympathetic nervous system (PNS) that uses acetylcholine as its main postganglionic neurotransmitter. Thus, pharmacologic agents that block the effects of acetylcholine at its “muscarinic” receptor—i.e., antimuscarinics—should be expected to both treat and prevent the vasovagal response.

Atropine is an alkaloid extract and antimuscarinic agent derived from nightshade plants, including *Atropa belladona* (also known as “deadly nightshade”), Jimson weed, and mandrake. It can be administered ophthalmologically as a mydriatic agent or more commonly intravenously or intramuscularly for treatment of cholinergic crisis, symptomatic bradycardia, and inhibition of salivation and secretions during surgical procedures. Side effects include tachycardia, dry mucous membranes, anhidrosis, urinary retention, and constipation. Glycopyrrolate, a quaternary ammonium drug, is another antimuscarinic agent similar to atropine that is used primarily to inhibit salivary, tracheobronchial, and pharyngeal secretions preoperatively during induction of anesthesia and intubation [28][29][30]. Comparatively, it has greater potency and longer duration of action than atropine. An older study demonstrated differences in end-organ effects between atropine and glycopyrrolate. Glycopyrrolate had a selective and prolonged inhibitory effect at salivary and sweat glands, with minimal cardiovascular, ocular, and CNS effects compared to atropine [31].

Antimuscarinic agents have been studied in the treatment of vasovagal reactions. Santini et al., 1999 [32] demonstrated the efficacy of atropine in treating vasovagal symptoms in patients with the cardioinhibitory form of vasovagal syncope (i.e., characterized by bradycardia <40 bpm without significant blood pressure drop, as defined in the introduction). A selection of patients underwent the tilt test, in which they lay down on a table and were then tilted upright at a specified angle, leading blood to pool in the leg veins and potentially trigger a vasovagal response via the Bezold–Jarisch reflex. Patients with a positive tilt test underwent a second tilt test within 2 weeks of the first diagnostic test, and those with a negative second test were excluded from the group. Eighty-four patients with two positive tilt tests were divided into two groups—placebo or atropine at 0.02 mg/kg. After a repeat tilt-table test, symptoms resolved in 69.7% of patients administered atropine compared to 21.9% of patients on placebo, provided that their heart rate was less than 40 bpm, demonstrating the efficacy of atropine in resolution of cardioinhibitory vasovagal syncope. Atropine did not resolve vasovagal symptoms in patients with vasodepressor syncope, however (defined as significant drop in BP without bradycardia, as described in the introduction), suggesting that it may have more cardiac than vasopressor effects.

Antimuscarinic agents have not only been studied for the treatment but also the prevention of vasovagal reactions. Prophylactic administration of atropine and glycopyrrolate has been demonstrated to lower vasovagal reaction rates in several procedures, including removal of femoral arterial sheaths [33], cryoballoon ablation in patients with atrial fibrillation [34], C-sections [35], and ophthalmological surgeries [36][37]. Most of these studies have not described which type of vasovagal

reaction is prevented by antimuscarinics—i.e., cardioinhibitory, vasodepressor, or mixed. Of those that did, Sun et al., 2017 [34] found that preoperative administration of atropine prior to cryoballoon ablation for atrial fibrillation prevented all three forms of vasovagal syncope. However, Chamchad et al., 2011 [35] found that preoperative glycopyrrolate was effective in the prevention of bradycardia, with minimal to no effect on blood pressure, for women undergoing C-sections. More research needs to be done to clarify these conflicting results. It would also be useful to determine if antimuscarinics given in conjunction with IV fluids are more effective in resolving vasodepressor or mixed forms of syncope than antimuscarinics alone, since IV fluids should correct volume status.

It is interesting to note that a randomized, placebo-control study on prevention of vasovagal syncope during ophthalmological (squint) surgery found fewer side effects associated with glycopyrrolate than atropine. Mirakhur et al., 1982 [36] randomized 160 children (1–14 years old) undergoing ophthalmological (squint) surgery to receive atropine, glycopyrrolate, or placebo at various doses and routes of administration (IV or IM). They found that IV administration of either glycopyrrolate or atropine significantly lowered rates of oculocardiac reflex (a type of vasovagal syncope defined as reduction in HR by >20%), but that glycopyrrolate was associated with a smaller magnitude of tachycardia than atropine. Yang et al., 1996 [37] similarly wrote that glycopyrrolate is less likely to cause tachycardia or dry mouth than atropine when given for ophthalmological surgeries. The lower side-effect profile of glycopyrrolate may make it a more favorable option than atropine for prevention of vasovagal syncope.

While all the aforementioned studies examined the utility of antimuscarinics in prevention of vasovagal reaction resulting from various procedures, no study to the researchers' knowledge has evaluated the utility of prophylactic antimuscarinics specifically for interventional pain management procedures. Mahajan 2008 [38] recommends giving IV glycopyrrolate in increments of 0.2 mg for prevention of vasovagal syncope during interventional pain management procedures for patients with a history of vasovagal episodes, but did not provide references to support his recommendation. This represents a large gap in the literature that merits more attention.

2.4. Hydration and IV Fluids

The possibility of using sedation, anxiolysis, or antimuscarinic agents to prevent vasovagal reactions raises the question of whether an IV line with fluids running should be placed prior to interventional pain management procedures. This would allow IV medications to be given promptly during the procedure if needed, without needing to stop the procedure to insert an IV line. Additionally, IV fluids in and of themselves might prevent vasovagal syncope for patients with baseline hypotension, bradycardia, dehydration, or anxiety. This is especially important to consider if a patient has fasted prior to the procedure. As per ASA guidelines, patients undergoing procedures with moderate sedation should not have clear liquids or solid foods 2 h or 6 h before their procedure, respectively, to mitigate the risk of airway compromise or aspiration [39]. Patients choosing to receive sedation for prevention of vasovagal reaction may thus be dehydrated at baseline, and IV fluid administration may help to further prevent vasovagal reactions.

For these reasons, some have advised obtaining IV access prior to interventional pain management procedures for patients with a high risk of vasovagal syncope [38][40][41]. However, no studies to the researchers' knowledge have evaluated whether IV fluid administration during interventional pain management procedures can prevent vasovagal reactions. More research should be done on the benefit of obtaining IV access prior to these procedures, both as a stand-alone preventive measure with IV fluids and in conjunction with other pharmacological agents.

3. Management

Most—if not all—patients undergoing interventional pain management procedures should have vital sign monitoring, including pulse oximetry, an electrocardiogram, and blood pressure monitoring, prior to and during the procedure. This is especially important for patients who report a history of vasovagal reactions to similar procedures. For patients who develop bradycardia and/or vasodepression, the first step is to stop the procedure immediately. The patient should have a cold compress (e.g., ice

pack) placed on his or her neck. The patient can then either be placed supine or in the Trendelenburg position (with the table at an angle such that the patient's head is declined below their feet at roughly a 15–30 degree angle). The patient can also be asked to perform counterpressure techniques, such as squatting or leg crossing, which may improve venous return and cardiac output. If these conservative measures do not work, IV fluids should be started (if they were not started preoperatively) and vasoactive medications considered, such as ephedrine in 5–10 mg increments, glycopyrrolate in 0.2 mg increments, or atropine in 0.4–1.0 mg increments. If the patient continues to have SBP < 90 mmHg, MAP < 65 mmHg, or HR < 50 bpm, then he or she should be transported to an emergency department [40].

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