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Beware, Red Heads Don't Numb!

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Abstract

Background: The use of topical anesthesia in the outpatient setting by Ophthalmologists has seen a dramatic increase since the development of anti-VEGF medications. Each year, there are an estimated 6-7 million anti-VEGF injections performed in the United States. People with red hair have a mutation of the MC1R gene, which has been associated with decreased effectiveness of local anesthesia. The purpose of this communication is to alert the ophthalmology community of potential for inadequate anesthesia for intraocular injections

Methods: IRB was obtained through OSU IRB. 175 patients receiving intravitreal injections were randomly surveyed to determine incidence of poor analgesia with injections.

Results: Overall, 19/175 patients were found to have decreased effectiveness of local anesthesia. We found a surprisingly high incidence (10.5%) of patients who require increased amounts of local anesthesia than is commonly used in those with natural red/auburn hair.

Conclusion: We encourage ophthalmologists who use local anesthesia for their patients to include an assessment of their response to dental anesthesia. These individuals need to be identified who have had previously bad experiences with poor responses to local anesthesia. We recommend using twice the amount of topical anesthesia in these patients.

Keywords: Intravitreal injections; MC1R Gene; Red hair; VEGF; Topical anesthesia

Introduction

The use of topical anesthesia in the outpatient setting by Ophthalmologists has seen a dramatic increase since the development of anti-VEGF medications. Each year, there are an estimated 2 million anti-VEGF injections performed in the United States for Medicare patients alone, estimating over 2 billion dollars in expenditures [1]. These injections, performed in the outpatient office, not only by retinal specialists, but also by most general ophthalmologists are becoming the most common ophthalmologic procedure.

Choroidal neovascularization is responsible for the vision loss in most patients suffering from AMD. Vascular endothelial growth factor is an important signal protein involved in angiogenesis in AMD, diabetic retinopathy, cancer, wound healing, and inflammation. It is believed that cytokine release from mast cells initiates the angiogenic cascade. The anti-VEGF antibody binds to soluble VEGF molecule which prevents its attachments to the surface receptors on the capillary endothelial cells.

In 2005, Philip Rosenthal observed regression of an active choroidal neovascular membrane (CNV) in a patient with wet age related macular degeneration (AMD) undergoing systemic Bevacizumab (Avastin) for metastatic carcinoma. He also discovered that intravitreal injections can control the angiogenesis in AMD. This has changed the landscape of management of AMD, and thus causing the dramatic increase in office intraocular injections.

While these injections are routine for all retinal specialists and many general ophthalmologists, they can be very traumatic for the patient. We report a cohort of patients that consistently have difficulty with local anesthesia, many requiring unusual amounts of topical agents to anesthetize the injection site. Interestingly, this group has a similar phenotype, most are those with natural red or auburn hair.

The MC1R gene, which determines skin, hair, and eye color is responsible [2-4]. People with red hair have a mutation of the MC1R gene, which has been associated with decreased effectiveness of local anesthesia and increased sensitivity to cold and heat [3] Most of the literature regarding the clinical effects of MC1R mutation has been studied in the dental field. The following scenario is not unusual when taking histories from patients with the MC1R gene mutation. They first experience

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Carrier of a red hair associated variant; higher risk of melanoma: This genotype raises the melanoma risk 42% higher than that among persons not carrying a similar allele rs1805007, known as Arg151Cys or R151C, one of the several SNPs in the MC1R gene associated with red hair color, and in redheaded females, linked to being more responsive to the anesthetics pentazocine, nalbuphine, and butorphanol, often used by dentists. The allele associated with red hair and increased anesthetic response (when homozygous) is rs1805007(T); the wild type, more common allele is rs1805007(C.). Note that in the studies of anesthetic response, having a single rs1805007(T) allele was equivalent to having none, because in both cases, in the absence of mutations elsewhere, the person still has a functioning MC1R receptor. The risk allele has also been reported in several studies to be associated with increased risk for melanoma.

Figure 1:

hypersensitivity to pain at the dentist. After several trips, they become sensitized to the unpleasant experience and frequently the mere sight of a needle is enough to cause anxiety and panic. The life-long painful experience with local anesthesia causes some patients with this mutation to experience significantly greater anxiety than those without the MC1R mutation [5]. The development of needle anxiety not only affects patients at the dentist, but can show significant effects on patients in other medical specialties as well.

Methods

In an attempt to determine the impact of having an altered response to local anesthesia, we recorded the incidence of inadequate topical anesthesia in an unselected group of patients being treated with antivegf injections. This study was funded in part by the Patti Blow Research Fund. IRB was obtained through OSU Wexner Medical Center and is considered exempt status. One hundred and seventy-five patients were included from a group of patients receiving injections. They were questioned to determine hypersensitivity to pain with prior local anesthesia experiences.

Results

Patient J.J. requires frequent anti-VEGF injections to control Choroidal neovascular formation in both eyes. In spite of using increased local anesthetic, the injections create extreme anxiety for the patient. He has difficulty sleeping two days prior to routine injections. He decided to undergo testing and was found to have a MC1R mutation. Similarly, nineteen of these 175 patients surveyed, have reported inadequate analgesia, most of whom had natural red/auburn hair. This equates to over 10% of patients receiving antivegf injections! In this group that reports difficulty, we now give twice the amount of local anesthesia that is routinely administered. J.J. was the only patient to have genetic testing for the mutation in this cohort, the results of which are pictured below in Figure 1. His results showed a mutation in Arg151Cys, which is consistent with MC1R mutation, consistent with the known association between poor analgesia with MC1R mutation and red heads. In the population examined, there is a strong history of difficulty with dental anesthesia in all of the patients.

Discussion

Natural red hair is an autosomal recessive trait that results from the mutation of the melanocortin-1 receptor gene, MC1R [4]. It is estimated that 1-2% of the world's population has natural red or auburn hair. In humans, MC1R is expressed on the surface of melanocytes, regulating melanin and pigment formation [2-4] Hair and skin is determined by a ratio of pheomelanin (yellow/red) and eumelanin (dark brown) pigments [2-4] Red hair is the result of excess pheomelanin production, due to loss of function of one or more alleles on the MC1R gene [2-3]. People with two variants of the

MC1R alleles have pure red hair, while those with a single variant have auburn or strawberry blonde hair [3]. Patients with both single and double variants of the MC1R alleles have the potential to experience decreased effectiveness of anesthesia and hypersensitivity to pain [3].

The mutation of the MC1R gene affects the central nervous system, which has a concentration of melanocortin receptors (MCR) in the orbitofrontal cortex, amygdala, and periaqueductal gray matter, all of which are involved with pain perception [3]. It is unclear why the MC1R mutation should affect anesthetic requirements. One possible explanation for this relationship is that the MC1R mutation up-regulates production of the receptor's primary ligands [5]. This stimulates other melanocortin receptors, including the MC4R receptors which are heavily concentrated in the CNS and regulate thermal and mechanical pain sensitization [3]. Therefore, pain sensitivity may be more prevalent in those with MC1R mutation.

It is important for all physicians to be aware of this phenomenon. From the hypersensitivity to pain and anxiety, patients with red hair are more likely to report discomfort with non-painful sensations such as pressure and vibrations [5]. Due to increased sensitivity to pain caused by this mutation, redheads often require twice the amount of local anesthesia in order to receive adequate analgesia. This can be problematic, especially during ophthalmic procedures, which require the patient to remain very still for the duration. Inadequate analgesia can be potentially disastrous for patients, with the potential for complications during the procedure [6].

Most of the literature regarding the clinical effects of the MC1R mutation has been studied in the field of dentistry. The following scenario is not unusual when taking medical histories from people with the MC1R gene mutation. They first experience pain during dental procedures despite having appropriate local anesthesia. After several experiences with these painful episodes, many become sensitized and frequently panic at the mere sight of a needle. This life-long painful experience with local anesthesia causes some patients with this mutation to have significantly greater medical anxiety than those without the MC1R mutation [5]. The development of needle anxiety not only affects patients at the dentist but in all aspects of medicine. Therefore, it is important that medical professionals ask patients about prior experiences with dental work prior to administering local anesthesia.

Conclusion

It is important for all ophthalmologists to be aware of this phenomenon. This paper discusses the ineffective local anesthesia within the field of ophthalmology presumptively due to a mutation in the MC1R gene. The purpose of this communication is to alert the ophthalmology community of potential for inadequate anesthesia

for intraocular injections. Antivegf injections are one of the most common procedures in all of medicine! We found a surprisingly high incidence (10.5%) of patients who require an increased amount of local anesthesia that is commonly used in those with natural red/auburn hair. We encourage ophthalmologists who use local anesthesia for their patients to include an assessment of their response to dental anesthesia. It is crucial to take a careful history to prevent intraoperative side effects due to movement if the patient is inadequately anesthetized. These individuals need to be identified who have had previously bad experiences with poor responses to local anesthesia. We recommend using twice the amount of topical anesthesia in these patients. Do not forget to ask about patients about their response to local anesthesia. Beware, redheads don't numb!

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