Autonomic Neuroscience: Basic and Clinical 202 (2017) 102–107

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

Exploring the multifactorial nature of postoperative nausea and vomiting in women following surgery for breast cancer

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ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form 25 September 2016
Accepted 26 September 2016

Keywords:
Nausea
Vomiting
PONV
Genetics
Neurotransmitters
Breast cancer surgery

ABSTRACT

Background: Postoperative nausea and vomiting (PONV) are two of the most frequent and distressing complications following surgical procedures, with as many as 80% of patients considered to be at risk. Despite recognition of well-established risk factors and the subsequent use of clinical guidelines, 20–30% of women do not respond to antiemetic protocols, indicating that there may be a genetic risk.
Objective: The purpose of this pilot study was to describe the incidence and explore the risk factors associated with PONV after surgery in women diagnosed with early stage breast cancer.
Methods: A prospective cohort design was employed to measure PONV in women recruited prior to surgery. DNA was extracted from saliva samples collected prior to discharge. Polymorphisms for seven candidate genes with a known role in one of the neural pathways associated with PONV were included in this study; serotonin receptor (HTR3A), serotonin transport (SLC6A4), tryptophan (TPH), dopamine receptors (DRD2/ANKK and DRD3), catechol-*O*-methyltransferase (COMT) and histamine (H1).
Results: Twenty-nine (29.8%) women experienced nausea and 10 (11%) experienced nausea and vomiting while in the PACU despite administration of multiple antiemetic medications. Women who experienced PONV had higher levels of pain and received more opioids than those women who did not experienced PONV. Odds ratios demonstrated that alleles for the COMT, DRD3, and TPH genes were associated with decreased PONV.
Conclusion: The understanding of the multifactorial nature of PONV and the recognition of genetic risk will ultimately lead to the development of personalized interventions to manage these frequent and often debilitating symptoms.

Contents

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http://dx.doi.org/10.1016/j.autneu.2016.09.017
1566-0702/

1. Introduction

In 2016 it is estimated that over 240,000 women in the United States will be diagnosed with breast cancer (www.cancer.org). Surgery is the primary treatment for women with early stage breast cancer, and as many as 80% of these women will experience postoperative nausea and vomiting (PONV) (Gan et al., 2014). PONV can lead to aspiration, wound dehiscence, bleeding, hematoma, dehydration, electrolyte imbalance, exhaustion, delayed mobilization, recovery and ability to begin oral medications. (Miaskowski, 2009; Jolley, 2001). PONV is one of the strongest predictors of prolonged hospital stay and unanticipated admission for outpatient surgery patients accounting for millions of dollars of health care costs annually (Gan et al., 2014; Janicki and Sugino, 2014; Marla and Stallard, 2009). The use of opioids for postoperative pain has long been recognized as a primary predictor of PONV, and other known predictors include female gender, a negative smoking history and previous experience of PONV or motion sickness (Apfel et al., 2008; Meng and Quinlan, 2006; Murphy et al., 2006; Wesmiller et al., 2013; White et al., 2008). Type and duration of anesthesia, and medications used during the surgical procedures are also known be associated with PONV (Gan et al., 2014; Janicki et al., 2011). Additionally, in patients with breast cancer, preoperative psychological factors including distress increase the severity of PONV (Montgomery et al., 2010; Wesmiller et al., 2016). Certainly the use of 5-HT_3 antagonists, and more recently the neurokinin 1 receptor antagonists have improved the management of PONV, but despite progress based upon evidence from voluminous clinical trials examining the efficacy of antiemetic regimes, 25–30% of postoperative patients continue to suffer from vomiting, and to a greater extent, nausea. Nausea is less well understood, and yet is considered by patients to be far more of a problem because of its debilitating nature.

Growing evidence, including our own, suggests that the gap in the ability to control nausea and vomiting may be explained by genomic variability (Fasching et al., 2008; Laugsand et al., 2011; Wesmiller et al., 2014). Because the first choice of antiemetic medications are serotonin receptor antagonists (Gan et al., 2014), we first focused on the genes of the serotonin pathway and the CYP450 family (hepatic enzymes responsible for the metabolism of these medications). We found that individuals characterized as *CYP2D6* poor metabolizers experience increased PONV (Wesmiller et al., 2013). We also found that variability in the promoter region of the serotonin transport gene was associated with increased nausea and vomiting in women with breast cancer after surgery yet prior to initiation of adjuvant chemotherapy (Wesmiller et al., 2014). Other single nucleotide polymorphisms (SNPs) in the serotonin receptor genes *HTR3A* and *HTR3B* gene have been identified which independently influenced the incidence of PONV (Laugsand et al., 2011; Ma et al., 2013; Reuffert et al., 2009). Because droperidol and metoclopramide are dopamine antagonists that have a history of successfully preventing PONV, variability in dopamine receptors is also a logical target to study.

Several human nausea and vomiting studies have focused on the popular dopamine receptor gene DRD2 Taq1 polymorphism finding that the *A2A2* genotype of the *DRD2* rs1800497 may be associated with an increased risk for vomiting but not nausea (Frey et al., 2016; Nakagawa et al., 2008). The COMT enzyme metabolizes catecholamines including dopamine, noradrenaline and adrenaline. The most studied polymorphism in the *COMT* gene is rs4680, also known as the Val158Met functional polymorphism, which has been associated with variability in the perception of pain and analgesic requirements (Rakvag et al., 2008). Several studies have reported a higher incidence of PONV in subjects that carried the AA genotype for A118G of the mu-opioid receptor gene (Chou et al., 2006a; Chou et al., 2006b; Lee et al., 2015; Sia et al., 2008; Zhou et al., 2012).

Given the association of anxiety and PONV (Montgomery et al., 2010), it is realistic to consider acetylcholine receptors as potential targets. In the only GWAS study reported on genetic association of PONV, acetylcholine receptor 3 subtype (*CHRM3*) was associated with PONV (Janicki et al., 2011). Though no research has been reported on histamine and PONV, pregnancy-induced nausea and vomiting has been successfully treated with antihistamines (Goecke et al., 2010). It is clear that PONV is related to multiple neuro-pathways in addition to physiologic and environmental factors, and it is also clear that some patients respond well to multiple drug antiemetic protocols and others do not. It is imperative to understand the potential of genomic variability in the mechanisms underlying PONV. Therefore, the purpose of this preliminary prospective study was to describe the variability of PONV in women undergoing surgery for early stage breast cancer, and explore risk factors that are associated with that variability, focusing on genes of the serotonin and dopamine pathways.

2. Methods

2.1. Subjects

This study, which was approved by the University of Pittsburgh Institutional Review Board, included 93 women, aged 18–80 years with a diagnosis of early stage breast cancer (stages 1, 2, or 3a) based on the tumor, nodes, metastasis classification of malignant tumors (Edge et al., 2010) with no clinical evidence of distant metastases and scheduled for surgery. Exclusion criteria included a previous history of neurologic conditions such as stroke, head injury, spinal cord injury, and intracerebral hemorrhage that could also contribute to nausea. Women scheduled for a surgical procedure that was expected to last longer than 4 h were also excluded, due to increased nausea from extended exposure to anesthesia (Gan, 2006).

2.2. Phenotype data

This study employed a prospective cohort design to investigate the association of genetic variation with the variability in the occurrence of PONV following breast cancer surgery. Study participants were recruited in the preoperative holding area of a large women's hospital that houses a nationally known comprehensive breast cancer program. After informed consent was obtained, preoperative phenotype data were collected including history of PONV, history of motion sickness, smoking history, age, race and preoperative antiemetic medications. Immediately following surgery, and while participants were in the Post-Anesthesia Care Unit (PACU), post-operative phenotype data including pain scores, nausea scores, frequency of vomiting, anxiety and all medications including anesthesia agents given during the surgical procedure were collected for all study participants. Pain and Nausea were measured on an 11 point verbal scale, with 0 representing no pain or no nausea, and a score of 10 representing the most pain or nausea ever experienced. Anxiety was measured by the Profile of Mood States Anxiety Tension Short Form (POMS-SF) (Wyrwich and Yu, 2011).

2.3. Genotype data

Polymorphisms for seven candidate genes with a known role in one of the neural pathways associated with PONV were included in this pilot study; serotonin receptor (*HTR3A*), serotonin transport (*SLC6A4*), tryptophan (*TPH*); a precursor to serotonin, dopamine receptors (*DRD2*/*ANKK* and *DRD3*), catechol-*O*-methyltransferase (*COMT*) and histamine (*H1*) (Horn et al., 2014). The polymorphisms included in the analysis are described in Table 1. For this study, primarily, the focus was on genes of the dopaminergic and serotonergic pathway.

Two milliliters of saliva were obtained from all participants using the Oragene DNA self-collection kit (DNA Genotek Inc.) before discharge from the hospital for genotype data collection. DNA was extracted utilizing the protocol and reagents from the manufacturer. TaqMan allele discrimination technology and commercially available assays (Thermo Fisher Scientific, Waltham, MA) or polymerase chain reaction with