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Pharmacogenetics-guided analgesics in major abdominal surgery: Further benefits within an enhanced recovery protocol☆

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ABSTRACT

Objective: Effective, narcotic sparing analgesia is a major component of Enhanced Recovery Protocols (ERP), however the risk of poor analgesia and opioid related side effects (ORADE) remains an issue related to poor outcomes and satisfaction, and is strongly related to the risk of narcotic dependence after surgery. A variety of genes can impact narcotic and non-steroidal (NSAID) drug efficacy including: the CYP family (drug metabolism-narcotics and NSAID), or COMT/ABCB1/OPRM1 (functional receptor and transport activity for analgesia vs side effects). The purpose of this study was to perform the first assessment of the impact of a pharmacogenetics (PGx) guided selection of analgesics following major abdominal surgery within an ERP.

Methods: A consecutive series of open and laparoscopic colorectal resections or major ventral hernia repair (PGx group) had a guided analgesic protocol based upon assessment of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, COMT, OPRM1, and ABCB1 genes. Study patients were compared to a recent historical series of patients (H group) managed using our well validated ERP. The primary outcome measure was the Overall Benefit of Analgesia Score (OBAS). Pain scores were also assessed.

Results: The data demonstrated a similar mix of procedures and gender between groups and more than half of the PGx group had revised analgesia from the standard ERP. The PGx group demonstrated significantly lower OBAS scores ($p = 0.0.1$) from POD1 (3.8 vs 5.4) through POD 5 (3.0 vs 4.5) Analgesia was also superior for the PGx group from POD1 through POD 5 ($p = 0.04$).

Conclusion: Pharmacogenetics guidance resulted in frequent modifications of the analgesic program, resulting in excellent analgesia with a 50% reduction in narcotic consumption, and a reduced incidence of analgesic related side effects compared to our standard ERP. These data suggest further improvement in ERP resulting from a patient centric analgesic, reduced narcotic regimen which provides early and durable pain control with fewer narcotic related side effects.

1. Introduction

Effective, narcotic-sparing analgesia is a major component of every Enhanced Recovery Protocol (ERP), however, the risk of highly variable responses, poor analgesia and opioid-related side effects (ORADE) remains an issue related to poor outcomes and satisfaction, and is strongly related to the risk of narcotic dependence after surgery.[1,2] Individual analgesic efficacy and side effect profile is significantly impacted by genetic variations due to either inherited variants (*i.e.*, germ-line genetic variants) or acquired variants (*i.e.*, somatic mutation).[3] A variety of genes can impact narcotic and non-steroidal (NSAID) drug efficacy including the CYP family (drug metabolism-narcotics and NSAID), or COMT/ABCB1/OPRM1 (functional receptor and transport activity for analgesia vs side effects).[4] These germ-line variants of genes encode drug-metabolizing enzymes, drug transporters, drug targets, and human-leukocyte antigen (HLA) which can affect individual response to medications.[4] Somatic variants of genes are frequently

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associated with the development or progression of cancer, and affect the drug response of tumors that carry specific mutations, so called targeted therapy.[5] Because of the impact of genetic variants on medication responses, how to give the "right drug" at the "right dose" for the "right patient" is a major goal in the era of precision medicine.[6]

There is significant data to suggest that acute postoperative pain is poorly managed and the proposed solution has been to recommend a more liberal use of analgesics.[7,8] It is also recognized that the types of analgesic may play a significant role in adverse outcomes related to acute pain management, especially given data that despite unpredictable pharmacokinetics and analgesic properties of codeine, it is amongst the most commonly prescribed opioid for both short and long term analgesic programs.[9–11] Even more disconcerting was a recent report by Alam and colleagues who found that 7% of minor surgical procedures were prescribed narcotics for pain and 7% were still taking narcotics one year after their procedure.[12]

Despite the considerable data regarding the frequency of variations in the reported effectiveness in acute pain management, the significant risk of chronic narcotic consumption after acute pain management, and the growing body of data regarding the role of specific SNP's in specific genes related to narcotic activity, there remains limited data assessing the role of using a multi-gene panel for selection of an analgesic program. Therefore, we performed the first structured assessment of the potential benefit of altering our standard enhanced recovery analgesic program based on the patient centric findings from a multi-gene pharmacogenetic testing platform.

2. Methods

2.1. Study description and participants

We evaluated a consecutive series of patients undergoing open or laparoscopic colorectal and major ventral hernia surgery at University Hospitals of Cleveland, Case Medical Center from March 2015 thru February 2016 who received pharmacogenetic testing via buccal swab prior to surgery (PGx group) and compared them to a historical group (H Group) of patients undergoing the same operations, but managed within our standard enhanced recovery protocol. Prior to initiating study activities, all participants signed a consent form. The study protocol and consent form was approved by the Case Western Reserve University Institutional Review Board.

2.2. Pharmacogenetic testing

Buccal epithelial samples were collected using cheek swabs at the clinical sites and shipped to AltheaDx (San Diego, CA) for pharmacogenetic testing using the NeuroIDgenetix Test. Genomic DNA (gDNA) was extracted using the QIAGEN DSP DNA Midi Kit (QIAGEN, Valencia, CA, USA). The NeuroIDgenetix pain panel analyzes 9 genes, including *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4/CYP3A5, ABCB1, COMT*, and *OPRM1*. Methods used for detection were: TaqMan OpenArray Genotyping and CYP2D6 copy number variation determination. In addition to screening for genetic variants in pharmacokinetic and pharmacodynamic genes that could impact therapeutic response, AltheaDx's proprietary IDgenetix® algorithm screens for metabolic interactions caused by concomitant prescriptions, over the counter (OTC) and herbal medications and environmental factors (foods, alcohol, tobacco, *etc.*) that may significantly alter the metabolism of the pain medications. The genotyping results are provided on the NeuroIDgenetix report along with a list of medications classified as "Use as Directed" (UAD) or "Use with Caution and/or Increased Monitoring" (UWC). Medications listed in the UWC column have pharmacologic actions or metabolism influenced by genetic variants detected in the patient, or drug interactions detected within the current drug regimen. The medications listed in the UAD column can be administered according to the manufacturer's standard prescribing information since no genetic variants or metabolic interactions were identified that would suggest a need for increased caution or dose adjustment.

2.3. Postoperative care

The enhanced recovery protocols have been published previously.[13,14] Our standard analgesic program included: narcotic-sparing oral analgesic administration of ibuprofen, acetaminophen, and gabapentin; intravenous patient controlled intravenous narcotic analgesia using either morphine or fentanyl based on surgeon preference for 12–48 h; and oral supplementation with oxycodone as needed. The nursing service provided adjunctive pain management using a standard 1–10 visual analogue pain score. The Overall Benefit of Analgesia Score (OBAS) was used to assess the combined impact on analgesia, patient satisfaction, and the impact of drug associated side effects.[15] The H Group had OBAS scores recorded by research teams not involved in direct patient care. No patients received an epidural or TAP block for analgesia. Based upon the test results for specific genes, we altered the analgesic selection to avoid any medications potentially impacted by a genetic variant. Analgesic selections for the PGx group were determined by the senior investigator (AJS) to maintain consistency. No attempt was made to assess the magnitude of a specific genetic variant on the performance of any agent.

2.4. Data collection and statistical analysis

OBAS, pain assessments and prescription drug use information were collected pre-operatively and after the surgical procedure was conducted on a daily basis until discharge. Pain scores were collected on the OBAS form asking patients to rate their current pain on a scale between 0 = minimal pain to 4 = maximum imaginable pain. The primary efficacy end-point, overall OBAS score, was compared between the PGx group and the H group from Post-Op Day 1 (POD1) through POD5. A comparison between the two study arms was performed by both *t*-test and the Wilcoxon's test. In addition, a mixed model repeated measures (MMRM) analysis using an AR(1) covariance structure was performed using all available data from day of surgery to discharge. A 2-sided p value < 0.05 favoring the PGx arm was regarded as a statistically significant benefit. Postoperative opioid use was assessed for subjects in both the PGx and H groups. Opioid administration was documented during postoperative hospitalization, totaled and converted to oral morphine equivalents using standardized conversion ratios.[46]

3. Results

We evaluated 63 consecutive patients undergoing open or laparoscopic colorectal and major ventral hernia surgery in the PGx group and compared them to 47 patients from our historical control population (H group). Among the 63 enrolled Experimental Subjects, 13 subjects were excluded due to cancelled surgeries, insufficient specimen, or withdrew from study which left 50 evaluable patients. The mean length of stay was 5 days for both the PGx and H groups. The study populations were similar and included 50 PGx patients (mean age 64.5 yrs; female/male ratio 64%/35%; colon/hernia: 44/5) and 47 H patients (mean age 60.6 yrs; female/male ratio 47%/53%; colon/hernia: 42/5). One patient in each cohort had