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Exploratory Study on Association of Single-Nucleotide Polymorphisms with Hydromorphone Analgesia in Emergency Department

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Abstract

Objectives—To provide information on distribution of important single-nucleotide polymorphisms (SNPs) and evaluate their associations with clinical response to intravenous hydromorphone in Emergency Department.

Methods—A prospective exploratory study was performed. A convenience sample of adult Emergency Department patients with acute pain deemed to require intravenous opioids received 1 mg of intravenous hydromorphone. Primary outcome was pain score (numerical rating scale, NRS) reduction between baseline and 30 minutes after medication administration. Secondary outcomes were pain relief, patient satisfaction with analgesia, desire for more analgesics, and side effects (nausea, vomiting, and pruritis). SNPs in OPRM1 gene (opioid receptor, A118G), ABCB1 gene (opioid transporter, C3435T), COMT gene (pain sensitivity, G1947A), and UGT2B7 gene (opioid metabolism, -G840A) were tested. We used Kruskal-Wallis test to compare the primary outcome and Chi-square (or Fisher test) to compare the secondary outcomes among patients carrying different SNPs.

Results—1438 patients were screened and 163 patients were enrolled in the study. The mean age was 39 years. 63% were female, 58% were Hispanic, and 67% pain located in abdomen. The median pain NRS reduction at 30 min was 5 (interquartile range 3 to 8). There was no difference in pain NRS reduction among patients carrying different SNPs. Secondary outcome analysis revealed statistically significant associations between patient satisfaction with treatment and OPRM1, and between nausea and UGT2B7.

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Conclusions—This exploratory study did not show a significant difference in pain NRS reduction among patients carrying different SNPs. Patient satisfaction with analgesia and nausea were statistically significantly associated with OPRM1 and UGT2B7, respectively.

Keywords

single-nucleotide polymorphism; hydromorphone; Emergency Department

INTRODUCTION

Oligoanalgesia, or inadequate pain treatment, is a common problem in the Emergency Department [1]. This is partially due to the wide inter-individual variation in response to analgesics. Studies have shown that several factors, such as age, gender, race, and co-morbidity, could influence individual's response to opioids. Recent pharmacogenomic investigations have demonstrated that genetic factors could also modulate clinical response to opioids[2, 3].

The primary target site for opioids is the μ -opioid receptor (OPRM1). The bioavailability of opioids is influenced by a transmembrane P-glycoprotein (ABCB1) and its hepatic metabolism enzyme UDP-glucuronosyltransferase 2B7 (UGT2B7). Studies done on post-operative and cancer patients have revealed that single-nucleotide polymorphisms (SNPs) in the genes encoding for these proteins were associated with response to opioid treatment[4, 5]. In addition, it has been shown that genetic variability in the gene encoding for catechol-O-methyltransferase enzyme (COMT, which is involved in pain perception) could contribute to the individual differences in pain sensitivity and response to morphine [6]. However, none of the pain genetic study has been performed in the Emergency Department, where pain is the most common presentation and opioids are the mainstay treatment for moderate and severe pain [7].

Adequate pain relief requires personalized pain treatment. Identifying the association between individual genetic background and clinical response to opioid treatment will provide evidence for pharmacogenomic-directed personalized pain management. This exploratory study was designed to provide preliminary information on the distribution of candidate SNPs in Emergency Department population. This information could provide a basis for a future study to test the hypothesis that genetic variations influence individual response to hydromorphone treatment in Emergency Department.

METHODS

Study Design

Participants in a previous prospective study designed primarily to investigate patient's total body weight and clinical response to hydromorphone treatment in Emergency Department were eligible for inclusion after providing additional consent for genetic testing [8]. The study was approved by institutional review board and registered with ClinicalTrials.gov (Identifier NCT01675778).

Study Setting and Participants

The study was conducted in Adult Emergency Department of an academic urban hospital, with approximately 75,000 annual visits. Inclusion criteria were patients 18 to 65 years of age, English or Spanish speaking, presenting to the ED with pain of less than or equal to 7 days' duration, and judged by the ED attending physician to require intravenous opioid analgesics. Exclusion criteria were inability or unwillingness to provide informed consent, previous allergic reaction to hydromorphone, systolic blood pressure less than 90 mmHg and room air oxygen saturation by pulse oximetry < 95% at baseline, alcohol or drug intoxication, drug seeking behavior as judged by the attending physician, use of other opioids or benzodiazepines within the past 24 hours, use of a monoamine oxidase inhibitor in the past 30 days, methadone use, history of COPD, sleep apnea, renal failure, liver disease, or chronic pain syndrome (sickle cell disease, peripheral neuropathy, diabetic neuropathy, or fibromyalgia), pregnancy or breast feeding, and previous enrollment in the same study.

Study Protocol

The study protocol was described in detail elsewhere [8]. Briefly, after collection of baseline information, pain intensity score, and vital signs, 1 mg intravenous hydromorphone was administered. Data including pain intensity, pain relief, satisfaction, side effects and adverse events were collected at 15 and 30 minutes after hydromorphone administration. Two milliliters of blood were obtained together with other clinical blood tests, or drawn later if the patient agreed. All data were recorded on a standardized data collection instrument.

Measurements

Pain intensity was measured on an 11-point verbally administered numeric rating scale (NRS), ranging from 0 equal to "no pain" to 10 equal to "worst possible pain". The NRS was recorded at baseline before hydromorphone administration, and at 15 and 30 minutes after administration.

Assessment of degree of pain relief, satisfaction with analgesia, desire for more analgesics, and side effects (nausea, vomiting, and pruritis), as well as basic demographics were documented as described before [8].

All DNA extraction and genotyping were performed at the Genomics Core facility at Albert Einstein College of Medicine. DNA was extracted from the whole blood samples with QIAamp DNA isolation kit (QIAGEN, Valencia, CA) and stored at -20°C until genotyping. SNP testing was carried out with Taqman assay (Applied Biosystems, Foster City, CA). Four SNPs were selected based on previous publications showing potential relationship with opioid response. They were A118G polymorphism of the OPRM1 gene (rs1799971), C3435T of the ABCB1 gene (rs1045642), G1947A of the COMT gene (rs4680), and -G840A of the UGT2B7 gene (rs7438135). Polymerase chain reaction was performed on an ABI PRISM 7900HT instrument (Applied Biosystems, Foster City, CA). Genotype discrimination was performed by SDS software, version 2.2.

Outcome Measures

The primary outcome was the change in NRS pain score from baseline to 30 minutes after hydromorphone administration, which was calculated as NRS at baseline minus NRS at 30 minutes. Secondary outcomes were pain relief, patient satisfaction with analgesia, desire for more analgesics, and side effects (nausea, vomiting, and pruritis).

Data Analysis

Data analysis was performed for exploratory purposes only, due to the reason that the sample size was initially calculated for the parent study. The relationships between pain intensity change and SNPs were assessed with Kruskal-Wallis test. The relationships between patient pain relief, satisfaction, desire for more analgesics, frequency of side effects and the genotypes were assessed with Chi square analysis (or Fisher test).

Statistical software STATA version 12.1 (Stata Corporation, College Station, TX) was used for data analysis.

RESULTS

We approached 1438 patients and 163 were finally included in the study (The final study population was similar to our previous study[8], except that 2 patients did not receive genetic tests and were excluded, whereas 2 patients without measured weight received genetic tests and were included in this study). All received 1mg intravenous hydromorphone, had NRS pain score recorded at baseline and 30 minutes, and provided blood samples for DNA analysis. None of them received additional opioid analgesics between baseline and 30 minutes. The mean age was 39 years. Sixty-three percent of the patients were female, 58% were Hispanic, and 25% were African American. Sixty-seven percent of patients had pain located in the abdomen. Three SNP testing results were undetermined (1 for COMT and 2 for UGT2B7).

The median baseline pain NRS was 10 (interquartile range 8 to 10). The median pain NRS reduction was 5 (interquartile range 3 to 8). The genotype distribution in each SNP is shown in Figure 1. There was no statistically significant difference in pain NRS reduction among patients carrying different SNPs in the genes tested (Figure 1). In the secondary outcome analysis, there were statistically significant differences in patient satisfaction with analgesia among patients carrying different OPRM1 SNP, and in nausea among patients with different UGT2B7 SNP (Table 1).

DISCUSSION

This was an exploratory study designed to provide information on the distribution of candidate SNPs in our Emergency Department population and to conduct a preliminary investigation of the association between SNPs and clinical response to hydromorphone treatment. We did not observe a statistically significant difference in pain NRS reduction among patients with different SNPs tested. Our secondary outcome analysis suggested that these SNPs might be associated with patient satisfaction and the side effects from hydromorphone treatment.

Intravenous opioids are the mainstay treatment for moderate and severe pain in the Emergency Department. Previous studies have suggested that there was wide inter-individual variation in the clinical response to opioid treatment. Many factors, such as age, gender, race/ethnicity, psychological factors, and genetic polymorphisms, have been suggested to play a role in opioid responses. Each factor may only account for a small proportion of variation in the treatment response. The possibility of a small contribution of genetic variants to the clinical response may still exist, but may be masked by a wide variation in patient clinical response due to other factors.

Most previous pain genetic studies have reported positive associations between the SNPs tested and clinical response to treatment [4–6]. However, previous opioid genetic studies were mostly performed in patients who received morphine. The lack of association between pain NRS reduction and SNPs tested in the current study may be due to differences in hydromorphone and morphine analgesia pathways.

In this exploratory study, this lack of association between SNPs and clinical response may relate in part to the small sample size and inability to adjust for other factors contributing to variability of opioid response. We believe that future studies with larger sample size and consideration of multiple influencing factors are warranted. In addition, the selection of SNPs in the current study was based on prior data on opioid pharmacodynamics and pharmacokinetics. Genome-wide association studies have identified other genetic variants which might be responsible for pain treatment response [9, 10].

The secondary analysis revealed a statistically significant difference in satisfaction with analgesia among patients carrying different OPRM1 SNP, and in nausea in patients with different UGT2B7 SNP. Whether the results were related to a clinically significant effect or type I error from multiple comparisons warrants further study.

LIMITATIONS

This study enrolled patients with acute pain from heterogeneous causes. These heterogeneous causes may involve different pain activation and transmission pathways that may not respond equally to the same opioid. This heterogeneity may interfere with detection of small response differences due to genetic variants. However, the purpose of the current exploratory study was to provide the preliminary information on the distribution of candidate gene polymorphisms in this Emergency Department population. This sample of patients is likely to be representative of the heterogeneity of pain etiologies that occurs in Emergency Department patients.

The current study was an exploratory study. The outcome analyses were limited by the small sample size. The study included only a small proportion of trauma patients, and excluded pediatric and geriatric patients. This sample had a large proportion of Hispanic and Black patients. The results may not be generalizable to populations with other racial and ethnic composition.

CONCLUSIONS

This exploratory study provided the basis for future studies to test the association between candidate SNPs and the clinical response to hydromorphone treatment in the Emergency Department. This study did not demonstrate a significant association between SNPs tested and clinical response to hydromorphone. Sample size limitation, heterogeneity of pain etiology, and confounding factors may all have contributed to this result. However, this study provided useful information for future study design. Further study with a larger sample size is warranted.

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Highlights

Oligoanalgesia is a common problem in the Emergency Department.

We performed an exploratory pain genetic study in the Emergency Department.

No difference in pain score reductions among patients carrying different genes.

Patient satisfaction and nausea were associated with OPRM1 and UGT2B7, respectively.

Figure 1. Pain NRS change by different SNP groups

The horizontal line within each rectangle indicates the median (50th percentile). The upper and lower limits of each rectangle represent the 25th and 75th percentiles. The upper and lower ticks outside the rectangle represent the most extreme data points.

Table 1

Secondary outcomes by different SNP groups.

Outcomes, N (%)	Total (N = 163)	OPRMI			ABCB1			UGT2B7			COMT		
		AA (N = 120)	AG (N = 39)	GG (N = 4)	CC (N = 25)	CT (N = 62)	TT (N = 76)	AA (N = 75)	AG (N = 75)	GG (N = 11)	AA (N = 27)	AG (N = 67)	GG (N = 68)
Pain relief													
None	5 (3)	5 (4)	0 (0)	0 (0)	0 (0)	2 (3)	3 (4)	4 (5)	1 (1)	0 (0)	0 (0)	3 (5)	2 (3)
Slight	23 (14)	15 (13)	7 (18)	1 (25)	3 (12)	10 (1)	10 (13)	13 (17)	8 (11)	2 (18)	5 (19)	8 (12)	10 (15)
Moderate	46 (28)	35 (29)	10 (26)	1 (25)	9 (36)	17 (27)	20 (26)	18 (24)	27 (36)	1 (9)	8 (30)	20 (30)	17 (25)
Lots	46 (28)	37 (31)	9 (23)	0 (0)	5 (20)	16 (26)	25 (33)	18 (24)	21 (28)	6 (55)	6 (22)	23 (34)	17 (25)
Complete	43 (26)	37 (23)	13 (33)	2 (50)	8 (32)	17 (27)	18 (24)	22 (29)	18 (24)	2 (18)	8 (30)	13 (19)	22 (32)
Satisfaction with analgesia													
Very dissatisfied	2 (1)	0 (0)	2 (5)	0 (0)	0 (0)	1 (2)	1 (1)	0 (0)	2 (3)	0 (0)	0 (0)	1 (2)	0 (0)
Dissatisfied	9 (6)	8 (7)	1 (3)	0 (0)	0 (0)	4 (7)	5 (7)	7 (10)	2 (3)	0 (0)	2 (7)	5 (8)	2 (3)
Uncertain	26 (16)	23 (20)	1 (3)	2 (50)	5 (21)	12 (20)	9 (12)	12 (16)	11 (15)	3 (27)	5 (19)	8 (12)	13 (20)
Satisfied	65 (40)	45 (38)	20 (51)	0 (0)	11 (46)	26 (43)	28 (37)	28 (38)	34 (46)	3 (27)	7 (26)	33 (49)	25 (38)
Very satisfied	59 (37)	42 (36)	15 (39)	2 (50)	8 (33)	18 (30)	33 (43)	27 (37)	25 (34)	5 (46)	13 (48)	20 (30)	26 (39)
Desire for more analgesics													
Yes	38 (24)	29 (24)	9 (23)	0 (0)	6 (24)	16 (26)	16 (21)	53 (71)	59 (79)	10 (100)	4 (15)	14 (21)	19 (28)
Side effects Nausea													
Yes	31 (19)	24 (20)	6 (15)	1 (25)	4 (16)	13 (21)	14 (18)	16 (21)	9 (12)	6 (55)	2 (7)	16 (24)	13 (19)
Vomiting													
Yes	4 (3)	3 (3)	1 (3)	0 (0)	1 (4)	1 (2)	2 (3)	2 (3)	1 (1)	1 (9)	1 (4)	2 (3)	1 (2)
Pruritis													

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Outcomes, N (%)	Total (N = 163)	OPRM1			ABCB1			UGT2B7			COMT		
		AA	AG	GG	CC	CT	TT	AA	AG	GG	AA	AG	GG
		(N = 120)	(N = 39)	(N = 4)	(N = 25)	(N = 62)	(N = 76)	(N = 75)	(N = 75)	(N = 11)	(N = 27)	(N = 67)	(N = 68)
Yes	12 (7)	7 (6)	5 (13)	0 (0)	1 (4)	3 (5)	8 (11)	7 (9)	4 (5)	1 (9)	4 (15)	3 (5)	5 (7)