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Does administration of haloperidol or ketorolac decrease opioid administration for abdominal pain patients? A retrospective study

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Abstract

Background: Haloperidol and ketorolac have been recommended as therapies that may decrease opioid use for treatment of pain in emergency department patients. The objective of our study is to determine if administration of haloperidol or ketorolac is associated with lower use of i.v. opioids for patients with non-specific abdominal pain.

Methods: A retrospective cohort study of adults (Age 18–60) with non-specific abdominal pain presenting to an emergency department in a large healthcare system. Cases were identified using ICD-10 codes and variables were abstracted from electronic health records. The association between administration of haloperidol or ketorolac with 1) any i.v. opioid administration and 2) receiving >1 dose of i.v. opioids were measured using adjusted odds ratios (AOR) from nominal logistic regression. The model included potential confounders related to both opioid and ketorolac or haloperidol administration.

Results: Of 11,688 patients 4091 received one or more doses of an i.v. opioid, 240 received haloperidol and 1788 received ketorolac. The majority of patients were women (67%) and the median age was 32 years. Odds ratios were adjusted for variables associated with opioids, ketorolac or haloperidol use. Haloperidol was not associated with decreased i.v. opioid use (AOR for receiving iv opioids 2.0, 95% CI 1.5 to 2.6) or a lower odds of reciving >1 dose of (AOR 2.0, 95% CI 1.3 to 3.1). Ketorolac was associated with a modest decrease in i.v. opioid use (AOR 0.84 95% CI.0.76 to 0.94 for receiving iv opioids) and a modest decrease for receiving multiple dose of iv opioids (AOR0.79 95% CI 0.63 to 0.99).

Conclusions: Haloperidol was not associated with decreased i.v. opioid use. Ketorolac was associated with a modest decrease in i.v. opioid use. Providers should consider the use of

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Contributions

All authors conceived the study. Dr. Heard collected and analyzed the data and drafted the manuscript. All authors contributed to the final draft and reviewed the final draft.

Declaration of Competing Interest

No authors have a conflict of interest.

haloperidol and ketorolac as potentially beneficial in some cases, but there is a need for high quality studies before they can be recommended as standard therapy.

1. Introduction

The use of opioids for treatment of acute pain dates back centuries. Emergency department (ED) studies have shown that opioids are effective for abdominal pain and also have demonstrated short-term safety [1]. However, in recent studies the prescribing of opioids for minor pain conditions is associated with an increased risk of progression to long-term use [1,2]. Providers concerned about opioid overuse have advocated the use of alternative medications to decrease opioid use when treating pain in the ED [3]. Two of these alternatives are antipsychotics, such as haloperidol, and non-steroidal anti-inflammatory medications, such as ketorolac. However, the effectiveness of these therapies has not been well measured.

Haloperidol, a butyrophenone antipsychotic medication, has limited evidence for its efficacy in acute pain, and studies have focused on the use of oral antipsychotics as adjunctive therapies [4]. In fact, in a recent systematic review of butyrophenone antipsychotics for acute abdominal pain, the authors concluded “we cannot draw a conclusion on the efficacy or benefit of neuroleptanalgesia in the management of patients with [acute abdominal pain]” [5]. However, recent educational programs have also emphasized the role of haloperidol for chronic pain patients in the ED with little supporting evidence [6]. In 2017, the Colorado Chapter of the American College of Emergency Physicians issued opioid prescribing and treatment guidelines that recommend haloperidol as an alternative to opioids for the treatment of abdominal pain [7]. The citation supporting this recommendation is a randomized controlled trial study of post-operative patients. The guidelines do not cite any emergency department focused studies for treatment of abdominal pain.

Ketorolac, a non-steroidal anti-inflammatory available for intravenous (i.v.) administration, is commonly used for the treatment of musculoskeletal pain, headaches, and renal colic in the ED. As with haloperidol, ketorolac is included in recent treatment guidelines as an alternative to opioids [7].

Abdominal pain is one of the most common types of pain treated in the emergency department. While some causes of abdominal pain are life threatening, the majority are self-limited, and often the provider will not identify a specific cause of the symptom (non-specific abdominal pain). Patients who are discharged with from the ED with nonspecific abdominal pain represent a group that the provider has identified as low-risk and who require only symptomatic care which could include opioids or alternatives to opioids. Given these characteristics, we selected non-specific abdominal pain as our study population.

The objectives of our study are to determine if administration of haloperidol or ketorolac is associated with lower use of i.v. opioids. We hypothesized ED administration of parenteral ketorolac or haloperidol will be associated with less i.v. opioid use during the ED visit.

2. Methods

2.1. Design

This is a retrospective cohort study. The study was reviewed by our local Institutional Review Board and deemed not human research as only de-identified records were used.

2.2. Setting

The study was conducted using data from a hospital system located in the Rocky Mountain Region. The system includes 18 sites within one health care system - an urban academic medical center, four community hospitals and 13 freestanding EDs. The total volume for the system is approximately 300,000 ED visits per year.

2.3. Subjects

As the objective of this study was to evaluate the use of these medications when only symptomatic care was warranted, we identified low-risk patients with non-specific abdominal pain who were discharged from the ED. We included adults aged 18–60 years of age with a diagnosis of nonspecific abdominal pain (ICD-10 code R10.x) and with no ED visits in the previous 6 months (to focus on patients without surgical disease, chronic abdominal pain, or other pain syndrome). We included all patients evaluated between Jan 1, 2016 to June 30, 2017.

2.4. Variables

Our primary outcome variables were administration of any i.v. opioid and administration of >1 dose of i.v. opioids. Our primary predictor variables were the administration of i.v. or i.m. haloperidol or i.v. or i.m. ketorolac. Covariates were collapsed into the categories as noted below to improve model stability. The covariates of interest were age, gender, race (collapsed into Caucasian, Black, other or unknown), ethnicity (collapsed into Hispanic or non-Hispanic), English as a primary language, payer type (collapsed into Commercial, Medicaid, Medicare, None), the use of imaging and triage category as measured by Emergency Severity Index (ESI). To improve model stability, ESI categories were collapsed into ESI 1 or 2; ESI 3; or ESI 4 or 5 and none recorded). Of note, our ED process allows rapid discharge of very low acuity patients after provider evaluation. These patients do not have ESI recorded by nursing staff. Therefore we grouped patients with no recorded ESI with those assigned 4 or 5 (the lowest acuity). ESI 1 and 2 were grouped due to small numbers of patients with ESI 1 (Highest acuity).

Our primary outcome was the administration of any dose of i.v. opioid; our secondary outcome was the administration of >1 dose of i.v. opioids in patients who received haloperidol or ketorolac vs. those who did not receive haloperidol or ketorolac.

2.4.1. Data collection—Variables were abstracted from an electronic health record (EPIC; Madison, WI) into an Excel (Microsoft; Redmond, WA) spreadsheet. All variables were captured in the record as structured fields; we did not search free text.

2.4.2. Sample size—We estimated that a sample of 2845 subjects would provide 80% power to detect a 5% decrease in the proportion of subjects treated with i.v. opioids assuming that 10% of subjects received opioids and 10% of subjects received haloperidol or ketorolac.

2.5. Analysis

Descriptive statistics are used to present patients' demographic data. Bivariate associations were measured using X^2 (discrete variables) and Wilcoxon Rank Sum (continuous variables). Unadjusted associations were measured with relative risks (RR) and 95% confidence intervals. Adjusted odds ratios were calculated using nominal logistic regression including covariates associated with both the predictor and outcome variable at the $p < 0.05$ levels in the bivariate analysis. All analyses were performed using JMP Pro 13.2 (SAS Institute; Carey, NC). Odds ratios are reported with 95% confidence intervals.

3. Results

A total of 11,688 patients were identified in the cohort. Of these 4091 received i.v. opioid (opioid group) and 7597 did not (no opioid group) (Tables 1a and 1b). In an unadjusted analysis, haloperidol was associated with an increased rate of i.v. opioid administration (RR 1.4 95% CI 1.2 to 1.6) while ketorolac was not associated with i.v. opioid administration (RR 1.1 95% CI 0.99 to 1.1).

Haloperidol, ketorolac and opioid administration were associated with race, payer type, and ESI; ketorolac and opioid administration were also associated with age, ethnicity and gender; ketorolac administration was also associated with English as a primary language. Imaging was more frequent in patients who received i.v. opioids and less frequent in patients who received haloperidol or ketorolac. In models adjusted for variables associated with 1) i.v. opioids and haloperidol and 2) i.v. opioids and ketorolac, patients treated with haloperidol were more likely to receive i.v. opioids in the emergency department than those who did not receive haloperidol (AOR 2.0, 95% CI 1.5 to 2.6) and patients treated with ketorolac were less likely to receive i.v. opioids than those who did not receive ketorolac (AOR 0.84, 95% CI.0.76 to 0.94).

As noted above, 4091 patients received one or more doses of i.v. opioid; 3487 received one dose, 546 received two doses, 54 received three doses, and four received 4 doses. Among patients who received at least one dose of i.v. opioid, we compared the odds of receiving >1 dose of i.v. opioid for patients treated with haloperidol or ketorolac versus those who did not receive these mediations. In a bivariate analysis, age, gender, payer type, imaging, and triage ESI were associated with receiving >1 dose of i.v. opioid. In a model adjusted for variables associated with both number of i.v. opioid doses and haloperidol or ketorolac administration, patients treated with haloperidol were more likely to receive 2 or more doses of i.v. opioids than those not receiving the haloperidol (AOR 2.0, 95% CI 1.3 to 3.1) while those receiving ketorolac were less likely to receive 2 or more i.v. doses of opioids (AOR 0.79, 95% CI 0.63 to 0.99).

4. Discussion

We found i.v. opioid use did not decrease when ED patients with non-specific abdominal pain were treated with haloperidol, but found a modest decrease in opioids when patients were treated with ketorolac. While the findings do not support haloperidol use and only modestly support ketorolac use to decrease opioid administration, we hope that this study will lead to higher quality studies to measure the value of these therapies. The current enthusiasm for their use is based more on avoiding i.v. opioids and anecdotal reports rather than scientific evidence of efficacy. Haloperidol and ketorolac are generally well tolerated, but both have adverse events that must be weighed against therapeutic benefit. We need high quality studies to determine the true risk of i.v. opioid administration in the ED and of the therapeutic benefit of ketorolac and haloperidol for pain.

Presently, there are no studies of haloperidol use in ED patients with non-specific abdominal pain. Benevides et al. evaluated the role of combination of haloperidol, dexamethasone, and ondansetron on nausea and pain intensity and morphine consumption after laparoscopic sleeve gastrectomy [8]. Other studies have found haloperidol is effective for the management of gastroparesis [9,10]. Droperidol, a closely related medication, has a morphine-sparing effect when co-administered with morphine via patient-controlled analgesia (PCA) for postoperative pain management [11], and epidural tramadol in combination with droperidol prolonged the duration of analgesia with better antiemetic properties [12]. However, the generalizability of these findings to ED patients is unclear. Ideally, a future study will specifically evaluate haloperidol for treatment of abdominal pain in a prospective, controlled manner.

Ketorolac is commonly used for the treatment of musculoskeletal pain, headaches and renal colic in the ED. A PubMed search on February 19, 2019 using the strategy “ketorolac abdominal pain AND (Clinical Trial[ptyp] AND Humans[Mesh])” identified one emergency department clinical trial that found ketorolac as effective as butorphanol for treatment of biliary colic [13]. However, there are no studies of ketorolac for non-specific abdominal pain. Given the small effect we observed, we look forward to further work evaluating the efficacy of ketorolac for nonspecific abdominal pain.

The efficacy and short-term safety of i.v. opioids for treatment of abdominal pain in the ED is well established [14]. While it is clear that opioids have been overused [1] and it appears there is some risk associated with even a short-term prescription of opioids [1,2], the association between opioids administered in the emergency department for treatment of acute pain and long term opioid use is not known. The current enthusiasm for non-opioid treatments for pain in the ED is likely a reaction to the current opioid abuse crisis. While protocols to decrease opioid use may be well intentioned and decrease opioid use in the ED [3], there should be clinical trials to support therapies recommended in guidelines. The use of haloperidol or ketorolac for treatment of non-specific abdominal pain does not have a strong scientific basis at this time.

5. Limitations

There are several limitations to the internal validity of this study. First, we did not assign patients to treatment and therefore there are likely baseline differences between the groups that may result in a biased measurement of association. For example, it is possible that patients with more perceived pain or distress might have been treated with haloperidol or ketorolac. While we adjusted for several characteristics, the inherent differences in the groups may have biased our findings toward increased opioid use. Second, we did not directly measure changes in pain scores but rather relied on secondary outcomes (the use of opioids and the number of doses) as a proxy for pain control. Finally, we did not compare total opioid dose using morphine equivalents and instead focused on repeat doses of opioids.

As our study only included patients with non-specific acute abdominal pain and no recent ED visits, the findings of our study should not be generalized to other patient populations such as patients with gastroparesis (where haloperidol has been found useful [9,10]) or chronic abdominal pain (where there is no systematic data). The external validity of our study may be further limited by regional differences in opioid, haloperidol or ketorolac use and by the presences of house staff at one of our institutions. While our study included an academic center, community hospitals and free standing EDs, medication use patterns may be different in other regions of the country.

6. Conclusions

In a large, retrospective study, ED use of haloperidol was not associated with a decrease in parenteral administration of opioids for patients with non-specific abdominal pain. Ketorolac provided a modest decrease in opioid use. Providers should consider the use of haloperidol and ketorolac as potentially beneficial in some cases, but there is a need for high quality studies before they can be recommended as standard therapy.

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Table 1a

Demographics.

	Haloperidol		No haloperidol	
	Opioid	**No Opioid**	**Opioid**	**No Opioid**
Total	116	124	3975	7473
Age, years median, (IQR)	35 (27 to 44)	31 (24 to 43)	35 (26–45)	30 (24–41)
Female, n (%)	79 (68.1%)	76 (61%)	2706 (68%)	4993 (67%)
Race, n (%)				
Caucasian	67 (57%)	56 (45%)	2700 (68%)	4646 (62%)
Black	25 (22%)	33 (27%)	357 (9%)	962 (13%)
Other/unknown	24 (21%)	35 (28%)	918 (23%)	1865 (25%)
Hispanic	16 (14%)	34 (27%)	912 (23%)	1770 (24%)
English primary language	109 (94%)	111 (89%)	3668 (92%)	6887 (92%)
Payer type				
Commercial, n (%)	41 (36%)	26 (21%)	1918 (48%)	3566 (48%)
Medicaid	51 (44%)	70 (56%)	1372 (35%)	2692 (36%)
Medicare	6 (5%)	4 (3%)	190 (5%)	207 (3%)
Self-pay	18 (16%)	24 (19%)	495 (12%)	1008 (13%)
Imaging performed	74 (64%)	49 (40%)	3293 (83%)	3812 (51%)
ESI, n (%)				
1 or 2	2 (2%)	4 (3%)	145 (4%)	131 (2%)
3	112 (97%)	116 (94%)	3726 (94%)	5873 (78%)
4 or 5	(0)%)	4 (3%)	76 (2%)	661 (9%)
Missing	2 (2%)	0 (0%)	28 (1%)	844 (11%)

IQR interquartile range.

Table 1b

	Ketorolac		No ketorolac	
	Opioid	**No opioid**	**Opioid**	**No opioid**
Total	653	1133	3438	6464
Age, median (IQR)	32 (25 to 41.5)	31 (24 to 40)	35 (26 to 46)	30 (24 to 41)
Female, n (%)	459 (70%)	794 (70%)	2326 (68%)	4274 (66%)
Race				
Caucasian	451 (69%)	796 (70%)	2316 (67)	3906 (60.4)
Black	49 (8%)	100 (9%)	333 (10%)	895 (14%)
Other	153 (23%)	237 (21%)	789 (23%)	1663 (26%)
Hispanic	156 (24%)	254 (22%)	772 (22%)	1550 (24%)
English primary language	610 (93%)	1066 (94%)	3167 (92%)	5932 (92%)
Payer type				
Commercial	320 (49%)	562 (50%)	1639 (48%)	3030 (47%)
Medicaid	230 (35%)	417 (37%)	1193 (35%)	2345 (36%)
Medicare	14 (2%)	30 (3%)	183 (5%)	181 (3%)
Self-pay	89 (14%)	124 (11%)	424 (12%)	908 (14%)
Imaging performed	583 (89%)	753 (66%)	2784 (81%)	3108 (48%)
ESI				
1 or 2	23 (4%)	10 (1%)	124 (4%)	125 (2%)
3	617 (94%)	1012 (89%)	3221 (94%)	4941 (76%)
4 or 5	11 (2%)	57 (5%)	65 (2%)	608 (9%)
Missing	2 (0.3%)	54 (5%)	28 (1%)	790 (12%)

IQR interquartile range.