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Original Article

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Opioid Prescribing for Kidney Stone Formers Undergoing Stone Removal

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Abstract

Background: Kidney stone formers may have episodes of severe pain and be at increased risk of narcotic use. Alabama has a high rate of opioid use. Within, we examine differences in opioid prescribing for kidney stone formers requiring stone removal procedures.

Methods: A retrospective review was conducted from June 2013 to July 2019. Twenty-five patients with recurrent cystine stones were randomly matched by age, gender, and procedure to 25 recurrent non-cystine and 25 first-time non-cystine stone formers. Patients underwent ureteroscopic stone removal and percutaneous nephrolithotomy. Opioids prescribed were identified through medical record review and the prescription drug monitoring program (PDMP) database. Morphine milligram equivalents (MMEs) standardized opioid utilization.

Results: Opioids prescribed at discharge significantly decreased (mean MME ± SD), 216.8 ± 125.9 for 2013 - 2016 and 124.2 ± 106.1 for 2017 - 2019 ($P < 0.001$) corresponding to implementation of an institutional opioid stewardship program. Opioids prescribed within 180 days of stone removal were similar amongst all three cohorts, mean 3,377.6 MME/patient. Over this 6-year time period, there was no difference in total amount of opioids prescribed for each cohort, mean 27,987.8 MME. The majority of prescriptions (56.4%) and MME prescribed (91.9 %) were from pain management and primary care providers.

Conclusions: MME prescribed for stone removal in an environment of high utilization has not declined and is not influenced by stone disease complexity. An opioid stewardship program was associated with decreased opioids prescribed by the surgeons conducting stone removal but had a negligible overall influence. The latter is driven by other care providers.

Keywords: Opioids; Opioid epidemic; Kidney stone disease; Ureteroscopy; Percutaneous nephrolithotomy

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Introduction

The United States opioid epidemic is a complex problem, negatively impacting the quality of life of those afflicted and increasing their risk of death [1]. Physician opioid prescribing practices have been implicated in the propagation of this epidemic [2, 3]. In 2018, 97.5 opioid prescriptions per 100 persons were dispensed in Alabama, nearly twice the national rate. This made Alabama the highest prescribing state for the eighth straight year, in spite of a 29% decline in opioid prescriptions over that period [4]. Rose and colleagues found that within 5 years of an initial opioid prescription, 3.6% of those receiving the prescription had begun using heroin [3]. In fact, any use of prescription opioids may increase the risk of chronic opioid use [5], frequently leading to opioid misuse or abuse. Morley and associates found a one in four chance of opioid misuse and a one in five chance of opioid abuse amongst those prescribed opioids over a 1-year period [6].

The acute severe pain that individuals experience with kidney stones results in the administration of analgesic regimens, many including opioids [7]. This increases the risk of opioid exposure in this cohort. In a cross-sectional analysis of National Medical Expenditure Panel Surveys, Pais and Sites reported that kidney stone formers are five times more likely to receive an opioid prescription than non-stone formers [8]. Furthermore, stone removing procedures may be an avenue to chronic opioid use. Tam and associates found that of opioid naive patients who were prescribed an opioid after stone removal with ureteroscopy, one in 16 went on to chronic opioid utilization [9].

Our institution's geographical location, Alabama, is associated with high albeit decreasing rates of opioid prescription. Additionally, a center-wide opioid stewardship program was instituted in 2017 with goals of combating the opioid epidemic. The Department of Urology adapted this stewardship's guidelines and there are no differences in postoperative management of patients who receive the same treatment. Thus, we hypoth-

esized that patients undergoing stone removing procedures at our center would likewise have decreasing opioid prescription patterns. Accordingly, we aimed to determine: 1) changes in the rate of opioid prescriptions over time for kidney stone formers requiring stone removing procedures; 2) differences in opioid prescription among recurrent kidney stone formers and first-time stone formers; and 3) the provider specialties most likely to prescribe opioids following stone removing procedures. Among the recurrent kidney stone formers undergoing stone removing procedures, two cohorts were evaluated: patients with cystinuria, an autosomal recessive disorder marked by development of recurrent cystine kidney stones at an early age, typically requiring frequent stone removing procedures; and recurrent non-cystine stone formers.

Materials and Methods

Institutional Review Board exemption (IRB-300003232) was obtained to conduct this study and this study was conducted in compliance with the ethical standards of our institution on human subjects as well as with the Helsinki Declaration. A retrospective review of patients undergoing stone removing procedures from June 2013 to July 2019 was conducted, including patients with recurrent cystine stones, non-cystine recurrent stones, and non-cystine first-time stones. A maximum number (25) of patients with cystine stones were included. Our institution manages the care of one of the largest cohorts of those with cystinuria in the USA. Patients included in the recurrent cohorts either had a history of kidney stones prior to their stone removal procedure, or recurrence of stones after their procedure. The subjects were matched for age, gender, and type of procedure to reduce confounding. Only two procedures were included, ureteroscopic stone removal (URS) and percutaneous nephrolithotomy (PCNL). Initial treatment of kidney stones requiring removal is typically URS. Those with complex anatomy or a stone burden greater than 2 cm are treated with PCNL. Patients undergoing shock wave lithotripsy and open, laparoscopic, or robotic-assisted surgery were excluded as these were not performed in the cystinuric group during this time interval. Patients were cared for by surgeons across the Department of Urology, consisting of 11 operating surgeons at the time of data collection.

Demographic data captured included age, gender, race, body mass index (BMI), marital status, and the ZIP code of residence. Medical comorbidities including obesity, diabetes, hypertension, chronic kidney disease, lipid disorders, other endocrine disorders, and coronary artery disease were also captured. One patient diagnosed as having neuropathic pain was excluded due to a perceived elevated baseline pain level and pain sensitivity.

Intraoperative and inpatient opioid utilization was assessed by review of institutional medical records. Outpatient opioid prescriptions were measured by querying the prescription drug monitoring program (PDMP). The PDMP is a national database in which 49 states participate. It provides the name of opioid, total dose per filled prescription, and number of discrete prescribing providers. Dose standardization was accomplished through conversion to morphine milligram equivalents (MMEs) using a table provided by the Centers for Disease Control and Prevention [10]. Providers were categorized based on specialty. Primary care providers included family medicine and internal medicine providers.

Comparisons between group means were performed using analysis of variance, followed by the Tukey-Kramer multiple comparisons test when a statistically significant result was found. Comparisons of categorical variables were performed using the Chi-square test or Fisher's exact test when the assumptions for the Chi-square test were not tenable. Exploratory comparisons between group means accounting for the opioid-naive patients and the non-opioid patients were performed using analysis of covariance. Two time periods for analyses of opioid discharge prescription amounts, total opioid utilization, average prescription MME, and total number of opioid prescriptions were used: 2013 - 2016 and 2017 - 2019. Changes in the means within each stone group and then overall were compared using the paired *t*-test. Due to large variability in a few of the MME variables, nonparametric tests corresponding to the above analyses, including the Kruskal-Wallis test and the Wilcoxon signed-rank test, were also performed; results obtained from these were similar to those obtained from the parametric tests. Statistical tests were two-sided and statistical significance was defined as $P < 0.05$. Statistical tests were performed using SAS (version 9.4; SAS Institute, Cary, NC). Each cohort contained a patient with extremely high opioid utilization, over 470,000 MME over the 6-year period. Statistical analyses were performed with and without these high opioid utilization patients. Both sets of analyses yielded similar results. Results presented are from analyses that included these high opioid utilization patients.

Results

The demographic characteristics of the three cohorts (n = 25 in each cohort, 56% were men) are profiled in Table 1 and there were no significant differences except that more medical comorbidities were noted in the recurrent kidney stone forming cohort ($P = 0.003$). As expected, the cystinuric and recurrent cohorts had a greater number of total procedures and stone removing procedures compared to the first-time cohort ($P = 0.006$). A number of the first-time stone formers underwent more than one stone removing procedure during the study period. Several patients underwent non-urologic procedures during this interval at the UAB Medical Center and this was evenly distributed across all three cohorts.

There was no difference in opioid use between the groups during their hospitalization for the stone removing procedures (Table 2). In addition, there were no differences in this parameter between the two time periods with regard to in-hospital utilization (Table 2). The amount of opioids prescribed at discharge decreased over time. Using the metric for comparing the two periods as described in the Methods section, from 2013 to 2016, a mean of 216.7 ± 135.9 MME per patient discharge was prescribed, in contrast to 124.2 ± 106.1 MME per patient discharge from 2017 to 2019 ($P = 0.002$) (Table 2). Opioid amounts prescribed at discharge and within 180 days of the procedure were similar for all three groups (Table 3). The total amount of opioids prescribed over 6-year period was

Table 1. Means With Standard Deviations for Demographic Characteristics, Comorbidities, and Surgical Procedures of the Three Cohorts

Patient characteristic	Total (n = 75)	Cystinuric stone formers (n = 25)	Non-cystine recurrent stone formers (n = 25)	Non-cystine first-time stone formers (n = 25)	P-value
Gender					1.0
Male	42 (56%)	14 (56%)	14 (56%)	14 (56%)	
Female	33 (44%)	11 (44%)	11 (44%)	11 (44%)	
Age (years)	35.4 ± 15.4	34.7 ± 16.7	35.6 ± 14.5	35.8 ± 15.4	0.97
BMI (kg/m^2)	30.6 ± 8.6	30.9 ± 9.4	30.5 ± 8.3	30.4 ± 8.5	0.98
Race[a]					0.70
White	60 (81.1%)	21 (84%)	21 (84%)	18 (75%)	
Non-white	14 (18.9%)	4 (16%)	4 (16%)	6 (25%)	
Married	32 (42.7%)	11 (44%)	8 (32%)	13 (52%)	0.40
Not married	43 (57.3%)	14 (56%)	17 (68%)	12 (48%)	
Zip code adjusted income (US dollars)	49,524.3 ± 19,935.3	54,016.0 ± 23,694.8	47,187.2 ± 18,835.1	47,455.8 ± 16,856.1	0.41
Ureteroscopic stone removal	59 (78.7%)	21 (84%)	18 (72%)	20 (80%)	0.57
Percutaneous nephrolithotomy	16 (31.3%)	4 (16%)	7 (28%)	5 (20%)	
Medical comorbidities (number)	3.7 ± 3.7	2.4 ± 2.3	5.6 ± 4.9	2.9 ± 2.4	0.003
Hypertension	16 (21.3%)	2 (8%)	8 (32%)	6 (24%)	0.11
Diabetes mellitus	8 (10.7%)	0 (0%)	5 (20%)	3 (12%)	0.09
Obesity	35 (46.7%)	13 (52%)	11 (44%)	11 (44%)	0.81
Chronic kidney disease	5 (6.7%)	2 (8%)	1 (4%)	2 (8%)	1.0
Other endocrine disorders	4 (5.3%)	1 (4%)	3 (12%)	0 (0%)	0.32
Stroke	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0
Number of UAB stone removing procedures	3.7 ± 3.4	4.0 ± 3.8	4.9 ± 3.6	2.0 ± 1.6	0.006
Number of UAB non-urology procedures	0.2 ± 0.5	0.2 ± 0.4	0.1 ± 0.4	0.3 ± 0.7	0.28

[a]Race data available for 24/25 for first-time stone formers. BMI: body mass index.

Table 2. Means and Standard Deviations for UAB Hospital and Discharge Opioid Utilization

	Total (n = 75)	Cystinuric stone formers (n = 25)	Non-cystine recurrent stone formers (n = 25)	Non-cystine first-time stone formers (n = 25)	P-value
UAB hospital opioid utilization (MME/stay)					
Intraoperative MME[a]	17.6 ± 7.3	19.7 ± 6.2	15.9 ± 8.6	17.0 ± 6.9	0.25
Inpatient MME	47.9 ± 85.6	42.1 ± 90.9	56.6 ± 83.6	45.0 ± 84.9	0.82
UAB opioid discharge prescription amounts (MME/patient/discharge)					
2013 - 2016	216.7 ± 135.9	236.4 ± 158.4	190 ± 139.9	230.6 ± 111.1	
2017 - 2019	124.2 ± 106.1	162.8 ± 131.3	109.2 ± 81.5	100.2 ± 92.3	
P-value	0.002	0.24	0.10	0.010	

[a]Data available for n = 61 total; n = 21 for cystinuric stone formers and first-time stone formers, n = 19 for recurrent stone formers. MME: morphine milligram equivalent.

Table 3. Means and Standard Deviations for Number of Discrete Providers and MMEs From PDMP (Provider/MME/Patient)

	Total (n = 75)	Cystinuric stone formers (n = 25)	Non-cystine recurrent stone formers (n = 25)	Non-cystine first-time stone formers (n = 25)	P-value
Discrete providers	7.9 ± 7.3	8.7 ± 8.1	7.8 ± 7.2	7.2 ± 6.7	0.76
Non-UAB providers	7.2 ± 7.2	7.8 ± 8.0	7.2 ± 7.1	6.4 ± 6.6	0.79
MMEs exposure within 180 days of stone removal procedure	3,377.6 ± 11,932.7	3,117.8 ± 10,238.3	3,406.3 ± 12,009.3	3,608.7 ± 13,779.0	0.99
Total opioid exposure over 6 years	27,987.8 ± 97,891.2[a]	29,951.8 ± 99,647.3[b]	30,116.7 ± 102,718.4[c]	23,894.8 ± 95,077.6[d]	0.97[e]

Total opioid exposure over 6 years including high opioid utilizing individuals (> 470,000 MME over 6 years) found in each cohort. Total opioid exposure over 6 years excluding high opioid utilizing individuals: [a]8,699.0 ± 23,400.7; [b]10,623.1 ± 24,803.1 ; [c]10,303.2 ± 27,726.7 ; [d]5,170.6 ± 16,938.1 ; [e]0.67. MMEs: morphine milligram equivalents; PDMP: prescription drug monitoring program.

Table 4. Mean and Standard Deviation for Provider Prescribing Habits by Specialty and Prescribing Provider Distribution From PDMP

Provider specialty	Total (n = 1,596 prescriptions from n = 75 patients)	Cystinuric stone formers (n = 660 prescriptions from n = 25 patients)	Non-cystine recurrent stone formers (n = 597 prescriptions from n = 25 patients)	Non-cystine first-time stone formers (n = 339 prescriptions from n = 25 patients)	P-value
Pain management					
MME	2,616.9 ± 2399.8	3,147.6 ± 2697.7	2,300.7 ± 2,166.4	576.7 ± 233.5	< 0.001[a, b]
Prescriptions	420 (26.3%)	169 (25.6%)	245 (41.0%)	6 (1.8%)	0.001
Urology					
MME	216.1 ± 173.7	230.6 ± 182.4	209.2 ± 180.3	184.6 ± 108.8	0.29
Prescriptions	295 (18.4%)	141 (21.4%)	114 (19.1%)	40 (11.8%)	0.001
Emergency medicine					
MME	138.1 ± 86.1	152.4 ± 87.8	132.5 ± 77.8	127 ± 90.9	0.38
Prescriptions	117 (7.3%)	43 (6.5%)	34 (5.7%)	40 (11.8%)	0.002
Primary care providers					
MME	1,623.0 ± 2,855.2	671.2 ± 796.2	1,248.9 ± 1,472.4	3,062.5 ± 4,217.0	< 0.001[b,c]
Prescriptions	510 (32.0%)	238 (36.1%)	91 (15.2%)	181 (53.4%)	< 0.001
Other surgical specialties					
MME	402.8 ± 1,078.2	164.8 ± 105.8	439.3 ± 413.1	426.7 ± 1528.7	0.59
Prescriptions	104 (6.5%)	18 (2.7%)	37 (6.2%)	49 (14.4%)	< 0.001
Other medical specialties					
MME	497.2 ± 666.9	186.3 ± 116.5	720.8 ± 814.3	238.7 ± 167.8	0.034a
Prescriptions	44 (2.8%)	13 (2.0%)	25 (4.2%)	6 (1.8%)	0.026
Dental					
MME	148.9 ± 68.0	138.8 ± 59.2	172.6 ± 72.0	103.2 ± 33.0	0.023[c]
Prescriptions	35 (2.2%)	4 (0.6%)	21 (3.5%)	10 (2.9%)	0.001
Unknown					
MME	274.6 ± 227.8	328.2 ± 292.3	218.5 ± 124.4	254.2 ± 168.4	0.15
Prescriptions	71 (4.4%)	34 (5.2%)	30 (5.1%)	7 (2.1%)	0.056

[a]A significant difference between cystinuric and recurrent stone formers. [b]A significant difference between cystinuric and first-time stone formers. [c]A difference between recurrent and first-time stone formers. MME: morphine milligram equivalent; PDMP: prescription drug monitoring program.

also similar for all three cohorts (Table 3). Overall, the opioids utilized during the stone removing procedure, in the immediate peri-operative period, and those prescribed at discharge, comprised 0.8% of those prescribed by providers from outside our institution across all three groups. The number of discrete opioid providers for each group during this 6-year interval was similar (Table 3).

The number of total MMEs prescribed was not associated with age (P = 0.9), gender (P = 0.06) or race (P = 0.5). There were no significant associations between gender and racial differences in the amount of opioids prescribed at discharge. Cystinuric patients comprised six of the 13 patients with more than 10,000 prescription MMEs over this 6-year period, with recurrent and first-time stone formers comprising five and two, respectively. Across all three cohorts, there were no statistically significant differences in the date (year) for the index (initial) surgical procedure. Mean times observed for cystinuric, recurrent, and first-time stone formers were 39.7 ± 23.3, 32.5 ± 22.1, and 27.0 ± 20.8 months, respectively; there were not significant differences between these. Opioid naive patients (n = 30) were prescribed fewer opioids compared to non-opioid naive patients (n = 45) over the 6-year period overall (MME = 1,295 ± 2,611 vs. 45,783 ± 123,702), but this did not reach statistical significance (P = 0.06).

Table 4 provides a distribution of MME prescribed based on patient cohort and provider specialties. For MME prescribed, there are significant differences across the three cohorts for the following specialties: pain management (P < 0.001), primary care providers (P < 0.001), other medical specialties (P = 0.034), and dental (P = 0.023). For the number of prescriptions, there are significant differences across the three cohorts for all specialties except for those classified as unknown. Of note, the highest amount of MME prescribed for first-time stone formers was from primary care providers, and

the highest amount for both recurrent cohorts originated from pain management specialists. A collective analysis of all three cohorts demonstrated that the majority of prescriptions (930 of 1,596, 58.3%) and most MME (mean 2,071.8 ± 2,703.5) originated from pain management and primary care providers; in contrast, urology and the other specialties comprised a smaller amount of the number of prescriptions (666 of 1,596, 41.7%) and fewer MME (mean 252.8 ± 490.1). The difference in the MMEs did not reach statistical significance (P = 0.065).

There were no differences observed in total opioid utilization per year, average prescription MME, or number of opioid prescriptions per year between the two time periods of 2013 - 2016 and 2017 - 2019, as shown in Table 5.

Discussion

The opioid crisis in the USA has led to opioid dependence and opioid related overdose deaths [11]. Patients with kidney stones may experience severe acute pain and some have chronic pain. Opioids have historically been used for management of patients with kidney stone-related pain. Kidney stone removing procedures may be the initial opioid exposure for these patients. Tam et al reported that of 27,740 patients undergoing ureteroscopic kidney stone removal, currently the most common operation for nephrolithiasis in USA, 51.2% were opioid naive, with 6.2% developing persistent opioid use after the initial procedure [9]. Kang et al found similar results in a cohort of 208 patients undergoing URS, as 7% continued to use opioids following their procedure [12]. This has prompted many groups to develop opioid stewardship programs using a variety of approaches including enhanced recovery after surgery protocols to eliminate or limit the prescribing of opioids after URS [13-15]. Similarly, an opioid stewardship program was undertaken at our institution which was associated with a significant decrease in opioids prescribed at the time of discharge following stone removing procedures. The amount of opioids prescribed was within those recommended by an expert multidisciplinary panel which included urologists [11].

In spite of a reduction in the opioids prescribed at the time of discharge after the stone removing procedure, the total amount of opioids prescribed did not decline over time. In addition, the total amount of opioids prescribed did not differ between cohorts, and was not associated with age, gender, or race. The total amount of opioids prescribed to opioid naive patients was less but did not meet conventional limits of statistical significance. Cumulatively, these results suggest that little progress has been made in reducing opioid prescribing to kidney stone patients undergoing stone removing procedures at a tertiary medical center.

Our results also demonstrate that urologists performing kidney stone removing procedures in a high opioid prescribing state constitute a small fraction of total opioids prescribed (MME) to patients, 0.8% from our urologists and 2.2% from those providing urologic care at other centers. Over 90% of prescribers were pain specialists and primary care providers. It is possible that such prescribing patterns could also be encountered for patients undergoing other surgical procedures, making

Table 5. Mean and Standard Deviation for Total Opioid Utilization by Year, Average Prescription MME, and Average Number of Opioid Prescriptions by Year, All From PDMP

	Cystinuric stone formers (n = 25)	Non-cystine recurrent stone formers (n = 25)	Non-cystine first-time stone formers (n = 25)	Total (n = 75)
Total opioid utilization (MME/year/person)				
2013 - 2016	3,963.4 ± 13,010.0	5,014.5 ± 17,586.1	5,766.6 ± 25,919.8	4,914.8 ± 19,329.9
2017 - 2019	5,786.1 ± 19,400.3	4,241.1 ± 13,566.4	1,262.6 ± 3,799.2	3,858.5 ± 13,763.2
P-value	0.19	0.41	0.38	0.52
Average prescription MME (MME/prescription/time period)				
2013 - 2016	269.6 ± 647.6	342.7 ± 758.9	419.2 ± 1,483.8	343.8 ± 1,020.1
2017 - 2019	450.9 ± 1,040.9	337.7 ± 765.8	316.4 ± 793.3	368.3 ± 865.6
P-value	0.05	0.92	0.52	0.70
Total number of opioid prescriptions (prescription/year)				
2013 - 2016	4.1 ± 6.4	4.0 ± 6.6	2.2 ± 4.5	3.4 ± 5.9
2017 - 2019	4.7 ± 6.7	3.5 ± 6.3	2.5 ± 2.9	3.6 ± 5.6
P-value	0.52	0.49	0.78	0.80

MME: morphine milligram equivalent; PDMP: prescription drug monitoring program.

these findings relevant to other surgical specialists.

Methods to curb opioid prescribing are crucial, particularly in high utilization states such as Alabama. More effective central oversight strategies need to be developed to immediately warn providers of prior and ongoing opioid prescribing for patients with mechanisms to deter or stop such practices. Furthermore, enhanced communication among treating providers is crucial to improve this problem. The findings of this study suggest that institution-wide stewardship programs are necessary but not sufficient to control overall opioid prescribing.

This study has certain limitations including that it was retrospective. The results could have been influenced by the complexity of disease managed at a tertiary medical center and may not be seen in patients receiving care in other settings. We are also assuming that the patients are individually utilizing the opioids prescribed. Additionally, it was not feasible to adjust opioid consumption for potential confounders such as other procedures not performed at our institution. Outside of our discharge prescription, it is difficult to determine if opioids prescribed are related to the patient's stone disease or other conditions. Although we manage the care of one of the largest number of recurrent cystine stone cohorts in the nation, upon which patient matching was based, the overall number of patients included in this study was limited. PCNL is a more invasive procedure than URS, and although patients were matched by procedure in each group, this may be a source of heterogeneity within the groups. Finally, the study population is relatively young (mean age 35 years) which was driven by the young age of the recurrent cystine stone cohort.

Conclusions

Patients with different spectrums of stone disease undergoing stone removing procedures in a high opioid utilization state received a small fraction of opioid prescriptions from urologists performing the procedures. Most opioid prescriptions originated from primary care and pain management specialists and were unrelated to patients' initial stone removal procedures. These findings may be relevant to other surgical specialists and should prompt the development of stringent, real-time programs to limit opioid prescribing.

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Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

All authors contributed to the concept, data collection, analysis, and writing equally.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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