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The Impact of Intraoperative Local Ketorolac on Opioid Use in the Management of Postoperative Pain in Thoracolumbar Spinal Fusions: A Retrospective Cohort Study

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ABSTRACT

Background: The United States is facing an opioid addiction epidemic with >63,600 deaths from drug overdoses in 2016 alone. Ketorolac is a nonsteroidal anti-inflammatory drug that has been shown to decrease postoperative pain in decompressive lumbar laminectomies. We sought to demonstrate that intraoperative intramuscular (IM) ketorolac is associated with decreased opioid use in the management of acute postoperative pain in thoracolumbar spinal fusions.

Methods: A retrospective review of consecutive patients undergoing open and minimally invasive (MIS) thoracolumbar fusions between 2017 and 2018. Ketorolac (30 mg) was injected into the paraspinal muscles adjacent to the operative site before closure. Patients were placed on a standard pain control regimen. All demographic and surgical data were assessed with univariate analysis to assess for differences between groups. Univariate analysis was used to identify significant covariates for the linear regressions with postoperative morphine equivalents, length of stay (LOS), and visual analog scale (VAS) for pain as dependent variables. A $P < .025$ was considered significant to account for multiple covariates.

Results: Two hundred twenty-five consecutive patients were included with 58 patients receiving intraoperative IM ketorolac. The average age of the ketorolac groups was 63.4 years (23–87 years) with an even distribution between genders. There was no significant difference in demographic or surgical data between the 2 cohorts. Postoperative opioid use, when corrected for LOS, showed no significance between cohorts, ketorolac 16.4 mg (95% confidence interval [CI]: 12.3–20.5) and nonketorolac 6.7 mg (95% CI: 14.1–19.4, $P = .8729$). Other than postoperative day zero VAS ($P = .05$), ketorolac was not a predictor of opioid use, LOS, or VAS.

Conclusion: The use of a single dose of intraoperative IM ketorolac did not decrease the overall opioid requirements or shorten the LOS following open or MIS lumbar fusions. However, we did demonstrate benefit in early pain control, which makes this promising for further investigation.

Level of Evidence: 3.

Clinical Relevance: This article promotes attention to the opioid crisis and the need for multimodal nonopioid based pain management in spine surgery.

Lumbar Spine

Keywords: lumbar fusion, postoperative pain control, ketorolac

INTRODUCTION

The United States is currently facing an opioid addiction epidemic with over 63,600 deaths from drug overdoses in 2016 alone.[1] The annual rate of drug overdose deaths from agents, including oxycodone and hydrocodone, has been steadily rising for the last 17 years.[1] Oxycodone and hydrocodone are both commonly used in the management of postoperative pain and are also currently the 2 drugs most commonly involved in overdose deaths.[2] Regardless of preoperative opioid use, surgery puts patients at increased risk of chronic opioid use.[2] One large scale study on lumbar fusion, patients showed postoperative chronic opioid use was associated with higher medical costs, worse outcomes, higher rates of new-onset psychiatric disorders, higher rates of failed back syndrome, and higher rates of additional lumbar surgery.[3]

Ketorolac (Toradol, Hoffman-La Roche, Inc, Nutley, NJ) is a nonsteroidal anti-inflammatory drug (NSAID) that has been investigated in the management of postoperative pain following spinal fusion and laminectomies.[4–9] Although there has been concern regarding the effects of NSAIDs on successful fusion, ketorolac had no significant

effect on rates of pseudarthrosis when used for less than 2 days following thoracolumbar fusion surgeries.[10] Both intravenous (IV) and intramuscular (IM) routes of administration have been shown to decrease the use of opioids in the postoperative period.[4,6–8,11] Specifically in decompressive lumbar laminectomy and fusion surgeries, adjunctive ketorolac showed a significant decrease in opioid consumption.[4,6,7] Previous studies suggest analgesic effects of ketorolac in the postoperative period may be dependent on dose and route of administration, and that IM ketorolac may be superior to IV.[12,13] Ketorolac was associated with a significantly shorter length of stay (LOS) following spine surgeries.[5,8,9]

Adjunctive ketorolac for postoperative pain is effective in subjective measures as well; it has been associated with lower postoperative pain scores compared with morphine alone,[4,8,11] and has even been shown to be more effective when used instead of morphine alone.[14] Opioid pain medications are associated with many undesirable side effects, including sedation, nausea, vomiting, and constipation. Presumably due to opioid-sparing effects, groups that received adjunctive ketorolac or ketorolac alone experienced fewer side effects.[5–7,9,15–17]

Based on the positive findings of the currently available literature, we sought to demonstrate that the use of intraoperative IM ketorolac is associated with decreased opioid use in the management of postoperative pain in thoracolumbar spinal fusions compared with patients who do not receive intraoperative ketorolac. Secondarily, we sought to show that the use of intraoperative IM ketorolac is associated with shorter postoperative hospital stays and lower average postoperative pain scores than those who did not receive intraoperative ketorolac.

METHODS

Our study was performed following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for cohort studies. After receiving institutional review board approval and a waiver of consent were obtained, we retrospectively reviewed the electronic medical records of consecutive patients who underwent open and minimally invasive (MIS) thoracolumbar transforaminal interbody fusion by 2 neurosurgeons from March 2017 through April 2018. The inclusion criteria were patients over 18 years of age, presenting for elective open or MIS thoracolumbar posterior instrumented interbody fusion. The exclusion criteria were emergent surgery, surgery for neoplastic process or infection, patients with documented allergy to NSAIDs or opioids, patients with greater than a 10-day LOS, and patients requiring more than 1 operation during the same hospital stay. We collected data on patient demographics, including age at the time of surgery, gender, body mass index, and preoperative daily opioid use. Preoperative opioid use was determined by querying MI Automated Prescription System for any opioid medication filled in within 6 months before the surgery date. The surgical data collected included the number of involved spinal levels, open/MIS, length of surgery, intraoperative IM ketorolac use, and intraoperative analgesic use. The perioperative data collected included the preoperative and postoperative visual analog scale (VAS) score for pain daily until discharge, LOS, daily opioid use converted to morphine milligram equivalents (MMEs)[18] for 72 hours postoperatively, and antispasmodic use.

Analgesic Regimen

Before closure, 30 mg of ketorolac was injected in the musculocutaneous tissue adjacent to the operative bed.

Then postoperatively all patients were treated with a standard analgesic regimen. The regimen included an oral opioid, antispasmodic, and an IV opioid for breakthrough severe pain. All patients who were on opioids before surgery were placed on their preoperative doses of medication then increased as needed. All immediate-release opioids were orders "as needed"; no patients had scheduled immediate release pain medication.

Statistical Methods

The statistical analysis with univariate analysis was used to determine significant covariates. Linear regressions with significant covariates as the independent variables and postoperative morphine equivalents, LOS and VAS for pain as the dependent variables were used to determine the predictors of the dependent variables. For LOS, MIS versus open surgery, the number of fusion levels, and age were significant. For 24-hour postoperative MME and postoperative MME corrected by LOS, number of fusion levels, age, and preoperative opioid use were significant. Ketorolac use was included in all predictive modeling.

Table 1. Demographics for ketorolac and nonketorolac cohorts.

	Ketorolac (n = 58)	Nonketorolac (n = 167)	*P* Value
Age, mean (range), y	63.4 (23–87)	62.9 (17–89)	.7294
Gender, n (%)			
Male	29 (50)	87 (52.3)	.7832
Female	29 (50)	80 (47.7)	
BMI, mean (range)	29.6 (16–44)	30.7 (17–61)	.2385
Preoperative opioid use, n (%)	24 (41)	63 (37.7)	.6413
Number of spinal levels, median (range)	2 (1–4)	2 (1–9)	.5491
Number of laminectomy levels, median (range)	1 (0–3)	2 (0–6)	.6197
Length of surgery, mean (range), min	170 (43–480)	158 (47–625)	.3377
Minimally invasive, n (%)	49 (84)	142 (85)	.9202
Postoperative AKI, n (%)	3 (8.6)	11 (6.6)	.7008

Abbreviations: AKI, acute kidney injury; BMI, body mass index.

Additional subgroup analysis of postoperative VAS by day was performed with significant covariates. A $P < .025$ was considered statically significant for the linear regressions to account for multiple covariates. To analyze the statistical power of outcome parameters, we used a beta of 0.8 and an alpha of 0.05. All statistics were completed with JMP (Version 14.2; SAS Institute, Inc, Cary, NC).

RESULTS

A total of 225 consecutive patients underwent open and MIS transforaminal interbody fusion and satisfied the inclusion criteria (Table 1). Fifty-eight patients received IM ketorolac with an average age of 63.4 years (23–87 years) and an even distribution between genders. One-hundred sixty-seven patients were in the nonketorolac cohort with a mean age of 62.9 years (17–89 years) and 80 (47.7%) female patients. There was no significant difference between the groups in any of the collected demographics (Table 1). Postoperative opioid use (in MME) was similar between the cohorts at 39.5 mg (95% CI: 28.2–50.8) and 38.3 mg (95% CI: 31.7–44.9, $P = .8562$) for ketorolac and control, respectively. When MME was corrected for LOS, no significance between cohorts with the ketorolac group using 16.4 mg (95% CI: 12.3–20.5) and the control group 6.7 mg (95% CI: 14.1–19.4, $P = .8729$) was seen. There was no statistical difference between the 2 cohorts in opioid use on any postoperative day except postoperative day 2, which was 12.0 mg (95% CI: 7.7–16.3) for the ketorolac cohort and 19.3 (95% CI: 14.0–24.7, $P = .0327$) for the control cohort (Table 2). There was a difference in postoperative pain on day 3 with the ketorolac group having a mean VAS of 5.0 (95% CI: 4.5–5.6) compared with control of 5.8 (95% CI: 5.5–6.2, $P = .023$). Postoperative day 0 VAS mean was also trending toward significance: VAS of 6.64 (95% CI: 6.2–7.1) and 7.07 (95% CI: 6.8–7.31, $P = .0744$) for the ketorolac and control cohorts, respectively. This trend was lost by postoperative day 1 (Table 2). Patients who had preoperative opioid use reported statistically higher pain scores during days 0 to 2 ($P < .005$).

Table 2. Dependent variables through POD 3.

	Ketorolac	Nonketorolac	*P* Value
Postoperative MME, mean (SD)			
POD 0	11.7 (9.9–13.9)	11.0 (9.7–12.2)	.5148
POD 1	15.4 (11.3–19.4)	17.3 (14.0–20.5)	.4707
POD 2	12.0 (7.7–16.3)	19.3 (14.0–24.7)	.0327
POD 3	13.4 (2.8–23.9)	21.7 (11.4–32.1)	.2271
Total	39.5 (28.2–50.8)	38.3 (31.7–44.9)	.8562
Corrected for LOS total	16.4 (12.3–20.5)	16.7 (14.1–19.4)	.8729
VAS for pain, mean (SD)			
Preoperative	3.4 (2.6–4.2)	3.4 (2.9–3.9)	.9046
POD 0	6.6 (6.2–7.0)	7.1 (6.8–7.3)	.0744
POD 1	5.7 (5.4–6.1)	6.0 (5.7–6.2)	.2707
POD 2	5.5 (5.1–5.9)	5.6 (5.3–5.9)	.6410
POD 3	5.0 (4.5–5.7)	5.8 (5.5–6.2)	.0234
LOS, mean (SD), d	2.79 (2.3–3.3)	2.70 (2.4–3.0)	.6926

Abbreviations: LOS, length of stay; MME, morphine milligram equivalent; POD, postoperative day; VAS, visual analog scale.

In determining if local IM ketorolac is a predictor for the LOS, postoperative opioid use, or postoperative pain control, it was noted that for other than postoperative day 0 ($P = .057$) VAS, ketorolac had no significant impact. The patient's age (–0.49 [95% CI: –0.680 to –0.310], $P = < .0001$) and preoperative opioid use 4.85 (95% CI: 2.34–7.37, $P = .0002$) were the greatest predictors total postoperative MME corrected for LOS (Table 3). There was an inverse relationship between age and postoperative opioid use with older patients requiring less medication than young patients (Table 3). Age was also a significant predictor for LOS (0.03 [95% CI: 0.012–0.047], $P = .0013$) (Table 3). Lastly, preoperative opioid use and IM local ketorolac were

Table 3. Linear regression with significant covariates.[a]

	Estimate	SE	*P* Value	95% CI	
Predictors of postoperative opioid use corrected for length of stay					
Age at time of surgery	−0.49	0.09	<.0001	−0.68	−0.31
Preoperative opioid use	4.85	1.28	.00	2.34	7.37
Ketorolac	−0.04	1.40	.77	−3.16	2.35
Predictors of length of stay					
Age at time of surgery	0.029	0.009	.001	0.012	0.047
Ketorolac	0.061	0.134	.648	−0.203	0.326
Predictors of pain on postoperative day 0					
Ketorolac	−0.229	0.120	.057	−0.466	0.007
Preoperative opioid use	0.390	0.107	.000	0.180	0.600

Abbreviation: CI, confidence interval.
[a]A *P* value of <.025 was considered significant to account for multiple covariates.

predictors of postoperative day 0 VAS with preoperative opioid use resulting in mildly increased postoperative pain 0.390 (95% CI: 0.1795–0.6003, $P = .0003$) and ketorolac –0.229 (95% CI: –0.447 to 0.007, $P = .05$) mildly decreasing pain (Table 3). There was not a significant difference in the rate of postoperative acute kidney injury between the cohorts with 3 (5.17%) events in the ketorolac group and 11 (6.6%) in the nonketorolac group ($P = .7008$). Patients in neither group required revision surgery due to hematoma formation.

DISCUSSION

According to the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2017, 11.4 million people over the age of 12 years old misused opioid medication.[19] Of the 11.4 million, 10.5 million misused prescription opioid-based pain relievers with hydrocodone and oxycodone were the most abused.[19] The growth was most notable in the spinal surgery age group (>26 years). The reduction of opioid use, to help alleviate the growing opioid epidemic, is challenging for surgeons because opioids are a powerful tool for managing immediate postoperative pain, but carry the risk of long-term abuse.[2,3] The SAMHSA 2017 report also highlighted 37% of patients who abused prescription opioids obtained from health care professionals.[19]

In order to address this issue, we sought to demonstrate that the use of intraoperative IM ketorolac is associated with decreased opioid use in the management of postoperative pain in thoracolumbar spinal fusions. Secondarily, we sought to show the use of intraoperative IM ketorolac is associated with shorter postoperative hospital stays and lower average postoperative pain scores.

Locally applied NSAIDs have shown to be successful at treating musculoskeletal pain.[20] In a recent meta-analysis, Derry et al.[20] reviewed 61 studies, which included 5311 patients in a randomized control trial and found formulations of topical diclofenac, ibuprofen, ketoprofen, piroxicam, and indomethacin demonstrated significantly higher rates of clinical success, as defined as more participants with at least 50% pain relief, than matching topical placebo.[20] They also noted the various formulations had minimal local skin irritation, which was not significantly different from placebos.[20] The benefit is also seen in the treatment of postoperative pain. Murdoch et al.[21] used locally administered intraperitoneal (IP) ketorolac and compared its effectiveness with IV ketorolac and control during laparoscopic cholecystectomy. They demonstrated IP ketorolac was superior to the control at reducing fentanyl consumption (mean difference, 29 μg [95% CI: 2–56], $P = .04$) and as effective as IV (mean difference, 16 μg [95% CI: 12–43], $P = .27$), which parallels similar studies.[12,13,21] Thiel et al.[22] systematically reviewed the use of topical NSAIDs in the treatment of corneal abrasions and found NSAIDs to be effective at treating pain and also the use of topical NSAIDs does not appear to complicate wound healing.[22] We theorized that a locally injected NSAID would function similarly to a topically applied NSAID. Although we found a single dose of 30 mg of intraoperative local IM ketorolac was ineffective at reducing the total opioid use or decreasing the LOS, we were able to see a trending reduction in postoperative pain in the first 24-hour period. This reduction was not maintained on subsequent postoperative days. The loss in pain reduction is likely due to the pharmacokinetics of ketorolac, which has an elimination half-life of 4 to 6 hours.[23] This would suggest a single dose is not sufficient to affect long-term opioid use. Further administration of ketorolac would have likely resulted in continued pain reduction and potentially the desired effect of overall opioid use.

The majority of the limitations to the study are related to the retrospective nature of the study design. Due to this fact, we were limited in the allocation of the patients to the treatment and nontreatment groups, which resulted in only 56 patients receiving ketorolac. Also, because this was not a randomized control trial with a rigorous treatment protocol, it suffered from significant

variations in those patients included (both in surgical treatment and postoperative pain control).

Going forward, we would like to conduct a randomized control trial with more patients, dosed over consecutive days to determine if the use of locally administered IM ketorolac can elicit a reduction in opioid use in spinal fusions. With a larger cohort and the robust protocol, a randomized controlled trial affords the ability to resolve many of the limitations of this study and better address the question.

CONCLUSION

The use of a single dose of 30 mg locally injected IM ketorolac did not decrease the overall opioid requirements or shorten the LOS following open or MIS transforaminal lumbar fusions. However, we were able to show some benefit in early pain control, which makes this promising for further investigation.

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