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The effect of ketorolac on posterior minimally invasive transforaminal lumbar interbody fusion: an interim analysis from a randomized, double-blinded, placebo-controlled trial

Chad F. Claus, DO[a,*], Evan Lytle, DO[a], Michael Lawless, DO[a], Doris Tong, MD[a], Diana Sigler, RPh[b], Lucas Garmo, BS[a], Dejan Slavnic, DO[a], Jacob Jasinski, DO[a], Robert W. McCabe, DO[a], Ascher Kaufmann, MD[a], Gustavo Anton, DO[a], Elise Yoon, DO[a], Ammar Alsalahi, MD[a], Karl Kado, MD[c], Peter Bono, DO[a], Daniel A. Carr, DO[a], Prashant Kelkar, DO[a], Clifford Houseman, DO[a], Boyd Richards, DO[a], Teck M. Soo, MD[a]

[a] *Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine, Southfield, MI, USA*

[b] *Department of Pharmacy, Ascension Providence Hospital, Southfield, MI, USA*

[c] *Division of Neuroradiology, Department of Radiology, Ascension Providence Hospital, Michigan State University, College of Human Medicine, Southfield, MI, USA*

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Abstract

BACKGROUND CONTEXT: Postoperative pain control following posterior lumbar fusion continues to be challenging and often requires high doses of opioids for pain relief. The use of ketorolac in spinal fusion is limited due to the risk of pseudarthrosis. However, recent literature suggests it may not affect fusion rates with short-term use and low doses.

PURPOSE: We sought to demonstrate noninferiority regarding fusion rates in patients who received ketorolac after undergoing minimally invasive (MIS) posterior lumbar interbody fusion. Additionally, we sought to demonstrate ketorolac's opioid-sparing effect on analgesia in the immediate postoperative period.

STUDY DESIGN/SETTING: This is a prospective, randomized, double-blinded, placebo-controlled trial. We are reporting our interim analysis.

PATIENT SAMPLE: Adults with degenerative spinal conditions eligible to undergo a one to three-level MIS transforaminal lumbar interbody fusion (TLIF).

OUTCOME MEASURES: Six-month and 1-year radiographic fusion as determined by Suk criteria, postoperative opioid consumption as measured by intravenous milligram morphine equivalent, length of stay, and drug-related complications. Self-reported and functional measures include validated visual analog scale, short-form 12, and Oswestry Disability Index.

METHODS: A double-blinded, randomized placebo-controlled, noninferiority trial of patients undergoing 1- to 3-level MIS TLIF was performed with bone morphogenetic protein (BMP). Patients were randomized to receive a 48-hour scheduled treatment of either intravenous ketorolac (15 mg every 6 hours) or saline in addition to a standardized pain regimen. The primary outcome was fusion. Secondary outcomes included 48-hour and total postoperative opioid use demonstrated as milligram morphine equivalence, pain scores, length of stay (LOS), and quality-of-life

FDA device/drug status: Not applicable.

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*Corresponding author. Division of Neurosurgery, Ascension Providence Hospital, Michigan State University, College of Human Medicine, 16001 W Nine Mile Rd, Southfield, MI 48075, USA.

E-mail address: chadfclaus@gmail.com (C.F. Claus).

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outcomes. Univariate analyses were performed. The present study provides results from a planned interim analysis.

RESULTS: Two hundred and forty-six patients were analyzed per protocol. Patient characteristics were comparable between the groups. There was no significant difference in 1-year fusion rates between the two treatments (p=.53). The difference in proportion of solid fusion between the ketorolac and placebo groups did not reach inferiority (p=.072, 95% confidence interval, -.07 to .21). There was a significant reduction in total/48-hour mean opioid consumption (p<.001) and LOS (p=.001) for the ketorolac group while demonstrating equivalent mean pain scores in 48 hours postoperative (p=.20). There was no significant difference in rates of perioperative complications.

CONCLUSIONS: Short-term use of low-dose ketorolac in patients who have undergone MIS TLIF with BMP demonstrated noninferior fusion rates. Ketorolac safely demonstrated a significant reduction in postoperative opioid use and LOS while maintaining equivalent postoperative pain control.

Keywords: Ketorolac; Lumbar fusion; Minimally invasive surgery; NSAIDs; Opioids; Patient-reported outcomes; Pseudarthrosis; Transforaminal lumbar interbody fusion

Introduction

Posterior lumbar fusion remains one of the most common spinal procedures performed today [1]. Postoperative pain control following posterior lumbar fusion continues to be challenging and often requires high doses of opioids for pain relief. However, opioid analgesia is associated with significant adverse effects such as nausea, vomiting, urinary retention, and respiratory depression. Additionally, patients remain at high risk for continued postoperative opioid use [2]. Studies have demonstrated the use of opioids for acute postoperative pain as an unintended gateway to long-term opioid addiction [3]. As the opioid epidemic continues throughout the United States, strategies to combat and limit opioid use following spinal surgery remain a tremendous public health priority. Ketorolac, a nonsteroidal anti-inflammatory (NSAID) with a well-described opioid-sparing effect, has been used as an effective analgesic for postoperative pain control [4–8]. Yet, historically, NSAID use has been avoided due to concerns related to intraoperative and postoperative bleeding, as well as platelet aggregation inhibition [9]. More importantly, ketorolac has been shown to decrease osteogenesis and inhibit spinal fusion in adults [10–16]. However, these adverse effects may be type-specific, dose, or duration-dependent [12–19]. A recent meta-analysis of retrospective studies demonstrated that ketorolac was associated with pseudarthrosis in adults only when administered for >2 days and/or at a dose of ≥120 mg/d [20]. To date, there has been no randomized controlled trial to evaluate the safety and efficacy of the use of ketorolac following posterior spinal fusion. As spine surgery practice adopts a more patient-centric approach involving patient-reported outcomes, treatment paradigms such as enhanced recovery after surgery (ERAS) protocols have, in large part, continued to limit the use of NSAIDs despite their ostensible benefit [21]. The option to include NSAIDs such as ketorolac in these protocols would prove valuable in the continuing improvement of such protocols. In this randomized, double-blind, noninferiority trial, we aimed to evaluate the early and long-term effects of ketorolac on patients undergoing minimally invasive (MIS) transforaminal lumbar interbody fusion (TLIF) with bone morphogenetic protein (BMP), namely its opioid-sparing effect on postoperative analgesia and effect on fusion, respectively.

Here, we describe the results of our interim 1-year analysis involving 292 patients.

Methods

This is a randomized, double-blind, placebo-controlled, noninferiority trial involving the use of ketorolac for postoperative analgesia for patients who have undergone elective, minimally invasive TLIF with BMP. The study is continuing enrollment. The interim analysis described here involved the first 292 patients enrolled and was conducted to assess ketorolac's safety and efficacy as our recruitment reaches its 50% benchmark. The trial's prespecified endpoints are planned to be reported at trial completion. The data cutoff for this interim analysis was July 2020.

Patients

Following Institutional Review Board approval, consecutive patients scheduled to undergo elective lumbar spinal fusion using a minimally invasive TLIF technique between October 2017 and July 2020 were screened for eligibility. Inclusion criteria were as follows: age 18 and above, elective posterior minimally invasive lumbar fusion, three or fewer levels, use of BMP for the interbody fusion, and consent to participate in the study. The exclusion criteria were: patients with a history of drug-seeking behavior or chemical addiction currently dependent requiring treatment or use, creatinine level greater than 1.5 mg/dL, history of coagulopathy, active tobacco smoker or history in the past 6 weeks, revision of fusion at operative level(s), history of autoimmune/rheumatological condition, oral-systemic steroid use for greater than or equal to 1 week in the last 1 month, auto/workers' compensation-related injury, traumatic pathology at operative level, infection at operative level(s), tumor at operative level(s), patients on

chemotherapeutic agents in the last 6 months, patients who have a history of allergy to ketorolac, history of liver impairment/failure, or uncontrolled cardiovascular disease. All patients included in the study gave written informed consent.

Study design, intervention, randomization, and blinding

This was a randomized, double-blinded, placebo-controlled, noninferiority trial drafted in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines. The study was carried out in secondary and tertiary care settings. The study was funded by the institution's research department and conducted according to the declaration of Helsinki [22], the NIH human subjects guidelines, and the International Conference on Harmonization E6 Guideline for Good Clinical Practice [23], and registered at http://www.clinicaltrials.gov (Identifier NCT03278691). CONSORT 2017 guidelines, including the noninferiority extension [24], were used in reporting. The complete study protocol was previously published [25].

This study implemented a two-arm parallel design without crossover with equal randomization per arm. On the day of surgery, patients were randomized with a centralized treatment allocation mechanism and block randomization to ensure the two arms achieve an equal proportion of patients over time.

All patients, treatment providers, investigators, and statisticians were blinded to the allocation. Blinding was achieved by concealment of allocation sequence to personnel involved in the enrollment, care, and evaluation of the patient. Each patient received a standardized general anesthesia protocol. Using a standardized surgical technique, the patients underwent a minimally invasive lumbar instrumented interbody fusion using a tubular retractor system for the facetectomy, discectomy, and interbody cage placement. The interbody cage was augmented with locally harvested autograft, cancellous chip allograft, and the minimally effective dose of rhBMP-2 (1.05 mg/level) [26]. The interbody fusion was further supported by percutaneous pedicle screw fixation. Postoperatively, each patient received a standardized analgesic regimen, in addition to their treatment allocation in which the treatment patients received 15 mg (1 mL) of intravenous ketorolac while the control patients received 1 mL of normal saline every 6 hours for 48 hours postoperative (see Supplementary Appendix). While in the hospital, the patients were evaluated daily at 4-hour intervals for any major adverse events, specifically gastrointestinal bleeding, postoperative wound or spinal hematoma, and acute kidney injury (AKI), as defined as an increase in Cr >50% from baseline. Strict trial monitoring and quality control were followed. A data safety monitoring board was established.

Outcome assessment

Our prior protocol mandated that all patients were evaluated at 6-month and 1-year postoperative follow-up visits for the primary fusion outcome by a combination of clinical symptoms and radiographic images, and for secondary outcomes by standardized and validated questionnaires. We evaluated radiographic fusion independently at each interspace. Fusion was determined by two blinded independent neuroradiologists using a combination of static and dynamic anterior-posterior and lateral x-rays (XRs). The Suk diagnostic criteria were used to establish fusion [27,28]. In symptomatic patients with inconclusive or positive XR images, computed tomography (CT) was then used to evaluate fusion using the Christensen criteria and guide clinical management [28]. Those patients assessed at 1 year who were determined to have nonunion had additional follow-up to further evaluate fusion status up to 2 years following their surgery date. The COVID-19 pandemic presented a unique challenge in collecting timely radiographic follow-up. To minimize "lost to follow-up" due to the impact of COVID-19, the follow-up period was extended to 2 years for all patients whose 6-month follow-up dates were supposed to occur after March 2020.

Secondary outcomes included 48-hour and total opioid use during hospitalization recorded as intravenous milligram morphine equivalence (MME), length of stay, pain intensity measured through the visual analog scale (VAS), and patient-reported outcomes (PROs). Pain was assessed every 6 hours following surgery until the discontinuation of the study medication/placebo. PROs were collected via the 12-item short-form, Oswestry Disability Index, at baseline and postoperative intervals (6-months, 1-year, and 2-year).

Statistical analysis

Using clinically and statistically important differences in fusion rate, a noninferiority margin was determined as -0.15. Noninferiority was considered to have been demonstrated if the lower bound of the 95% confidence interval (CI) for the difference in fusion rate exceeded -0.15. The sample size of 300 fusion levels per arm was estimated to be sufficient (with a two-sided 95% CI and 95% power) to detect inferiority.

The comparability of the two groups baseline characteristics (age, sex, body-mass index, diabetes mellitus, specific lumbar level, number of operative levels, total dose of Fentanyl during surgery, duration of surgery, estimated blood loss, and opioid tolerance [as defined as any use of opioids for 14 or more days in the 3 months immediately preceding the lumbar fusion]) was evaluated by univariate analyses. The primary outcome, fusion, was analyzed by univariate analysis. Parametric quantitative data were compared using t test, whereas nonparametric quantitative data were compared using the Mann-Whitney U test. A p value <.05 was considered significant. Outcomes were analyzed per protocol.

Results

Participants

A total of 994 patients were assessed for eligibility, with 292 patients randomized to receive either ketorolac or placebo after meeting eligibility and consented to participate (Fig. 1). A total of 140 patients were assigned to the ketorolac group, of which ten did not receive the assigned treatment (Fig. 1). The placebo group comprised 152 patients, of which 14 did not receive the assigned treatment. Eleven patients in each group withdrew their consent after randomization. At the time of this interim analysis, 165 patients and 194 fusion levels were assessed for the primary outcome at 1-year. The per-protocol analysis for secondary outcomes included 246 patients (119 in the ketorolac group and 127 in the placebo group) (Fig. 1).

The baseline characteristics of the patients are shown in Table 1. There were no significant differences between the two treatment groups in any preoperative or perioperative variables (Table 2).

Fusion

A total of 247 levels and 194 levels were assessed for the primary outcome at 6-months and 1-year, respectively.

Table 1
Patient demographics

N=246	Ketorolac(n=119)	Control(n=127)	p value
Age	61.0±10.8	61.4±11.3	.63
Sex (male)	55 (46.2)	56 (44.1)	.74
BMI	31.0±6.0	31.2±6.3	.77
Diabetes mellitus	18 (15.1)	25 (19.7)	.35
Opioid tolerant*	48 (40.3)	50 (39.4)	.88
Disposition	—	—	.79
Home	106 (89.1)	113 (89.0)	—
SAR	11 (9.2)	13 (10.2)	—
IPR	2 (1.7)	1 (0.8)	—

Continuous data presented as mean±SD. Categorical data presented as n (%). p<.05 considered significant. BMI, body mass index; SAR, subacute rehabilitation; IPR, inpatient rehabilitation.

* Opioid tolerant defined as any opioid use for ≥14 days in the last 3 months.

There was no significant difference between the two groups in the primary outcome; the proportion of radiographic nonunion was 9.3% in each treatment group at 1-year (Table 3). The difference in proportion for solid fusion between the ketorolac group and the placebo group was .026 (95% CI, -.010 to .15) and .072 (95% CI, -.07 to .21) at 6-months and 1-year, respectively, which did not cross the specified inferiority margin of -0.15 (Fig. 2). Of the radiographic nonunions, the ketorolac group observed 2 (1.7%) patients who

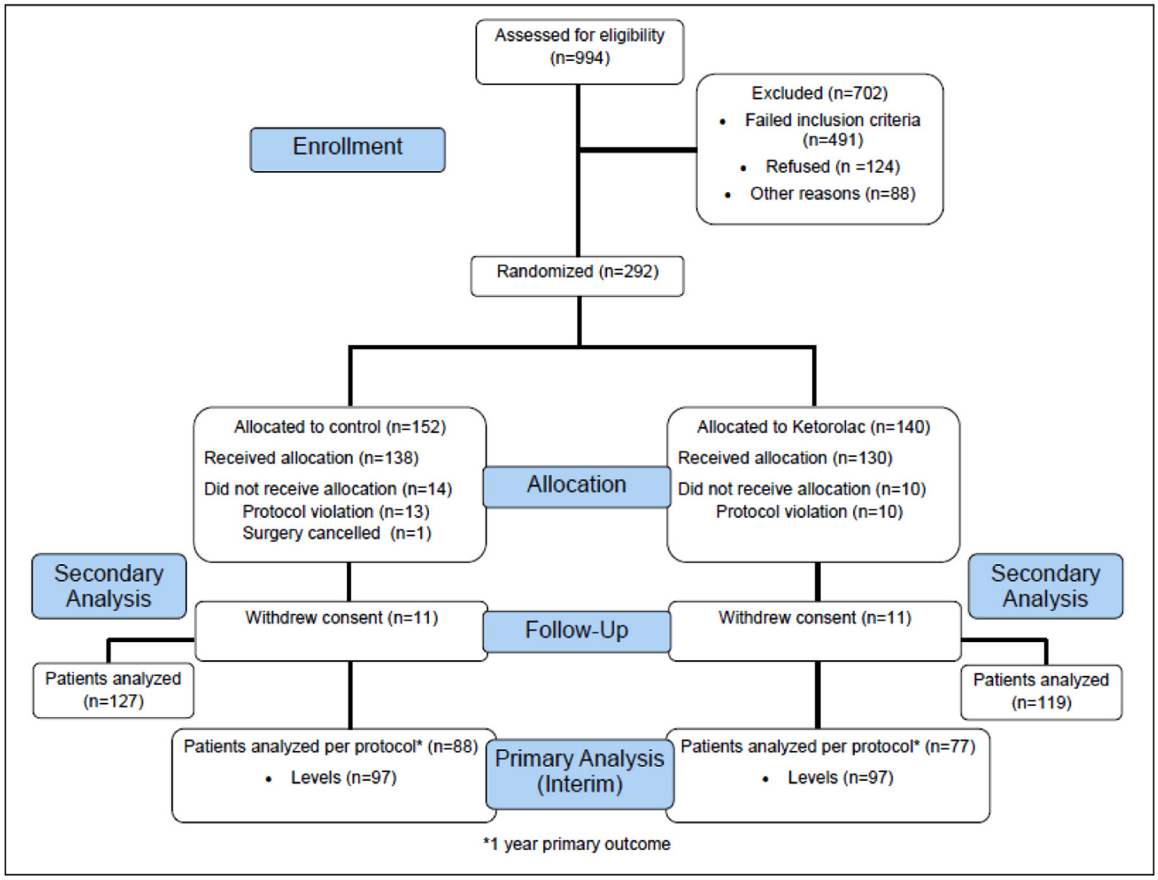

Fig. 1. CONSORT flow diagram of trial profile.

Table 2
Patient operative data

N=246	Ketorolac(n=119)	Control(n=127)	p value
Estimated blood loss (mL)	201.7±167.8	247.1±264.9	.11
Surgery time (min)	139.7±54.3	146.7±52.6	.31
Intraoperative opioids (mcg)	231.5±107.5	247.4±116.3	.27
Durotomy	8 (6.7)	7 (5.5)	.69
Number of operative levels	—	—	.21
One	89 (74.8)	84 (66.1)	—
Two	24 (20.2)	37 (29.1)	—
Three	6 (5.0)	6 (4.7)	—

Continuous data presented as mean±SD. Categorical data presented as n (%). p<.05 considered significant. mL, milliliters; min, minutes; mcg, micrograms of Fentanyl.

Table 3
Fusion outcomes

	Ketorolac	Control	Δ	95% CI	p value
6-Month (N=247)	n=119	n=128			.79
Solid fusion	58 (48.7)	59 (46.1)	2.6	-0.10 to 0.15	—
Probable fusion	49 (41.2)	58 (45.3)	-4.1	-0.17 to 0.08	—
Nonunion	12 (10.1)	11 (8.6)	1.5	-0.06 to 0.09	—
1-Year (N=194)	n=97	n=97			.53
Solid fusion	63 (64.9)	56 (57.7)	7.2	-0.07 to 0.21	—
Probable fusion	25 (25.8)	32 (33.0)	-7.2	-0.20 to 0.06	—
Nonunion	9 (9.3)	9 (9.3)	0	-0.08 to 0.08	—

6-month and 1-year fusion outcomes as evaluated by Suk criteria. Values presented as number of levels (%). p<.05 considered significant.

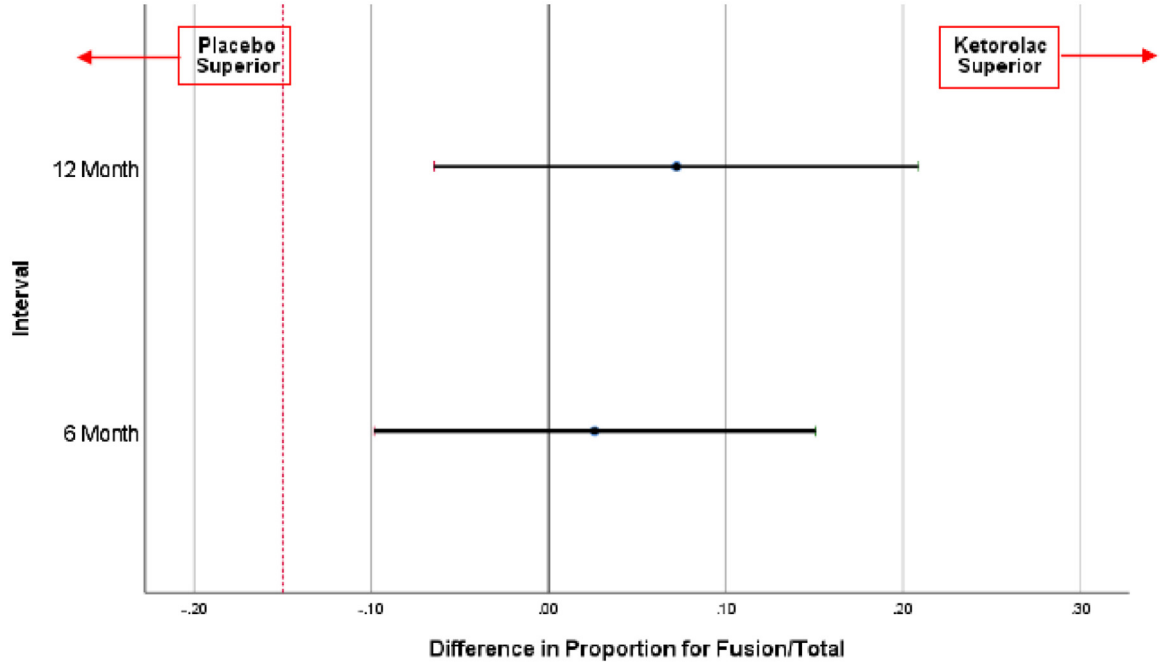

Fig. 2. Comparing solid fusion rates at 6 months and 1 year between the ketorolac and placebo groups. Red dashed line at -0.15 represents the noninferiority margin; the zone left of the noninferiority margin (red dashed line) represents the zone of inferiority. The horizontal black lines represent the confidence intervals (95%) of the difference in fusion rates between the two arms. The black dot in the middle of each horizontal line represents the difference in the fusion rates between the ketorolac vs. placebo group (black vertical line—no difference) for the 6-month and 1-year follow-up intervals.

Table 4
Secondary outcomes

N=246	Ketorolac (n=119)	Control(n=127)	Δ Mean	95% CI	p value
Total MME	52.5±39.5	84.7±55.4	-32.2	-44.3 to -20.2	**<.001**
48-hour MME	46.9±32.1	71.1±42.1	-24.2	-33.6 to -14.9	**<.001**
Postoperative VAS	6.0±1.4	6.2±1.5	-0.2	-0.6 to 0.1	.20
Length of Stay (d)	2.1±1.4	2.7±1.7	-0.7	-1.0 to -0.3	**.001**
Complications	—	—	—	—	—
Epidural hematoma	0	3 (2.4)	—	—	—
Wound hematoma	1 (0.8)	0	—	—	—
AKI	2 (1.7)	2 (1.6)	—	—	.95
Bleeding episode	0	0	—	—	—
Gastrointestinal	0	0	—	—	—
Surgical revisions	—	—	—	—	—
Pseudarthrosis	2 (1.7)	5 (3.9)	—	—	.52
Misplaced hardware	1 (0.8)	2 (1.6)	—	—	.60

Continuous data presented as mean±SD. Categorical data presented as n (%).
Total MME represents the total MME consumption during the entire hospitalization.
48-hour MME represents the total MME consumption within the first postoperative 48 hours.
Postoperative VAS represents the mean of all VAS collected over the first postoperative 48 hours.
p<.05 considered significant. Boldfaced p value indicates significance. MME, milligram morphine equivalence; VAS, visual analog scale; d, days; AKI, acute kidney injury.

demonstrated clinical pseudarthrosis requiring revision surgery (Table 4). Within the placebo arm, five (3.9%) patients demonstrated clinical pseudarthrosis requiring revision surgery.

Opioid consumption

Total milligram intravenous morphine equivalence was recorded during the patients' entire hospitalization and the first 48-hours following surgery. Total mean MME (Δ=32.2, 95% CI, 20.2−44.3, p<.001) and 48-hour mean MME (Δ=24.2, 95% CI, 14.9−33.6, p<.001) was significantly reduced in the ketorolac group when compared with the placebo group (Table 4). Ketorolac patients achieved a significant reduction in mean MME consumption on postoperative day 0, 1, and 2 (Fig. 3).

Pain severity and length of stay

When compared with the controls in the first postoperative 48 hours, patients who received ketorolac did not have a significant reduction in their average pain scores during the first 48 hours postoperatively (Table 4); did not have a significant difference in their mean VAS over time as

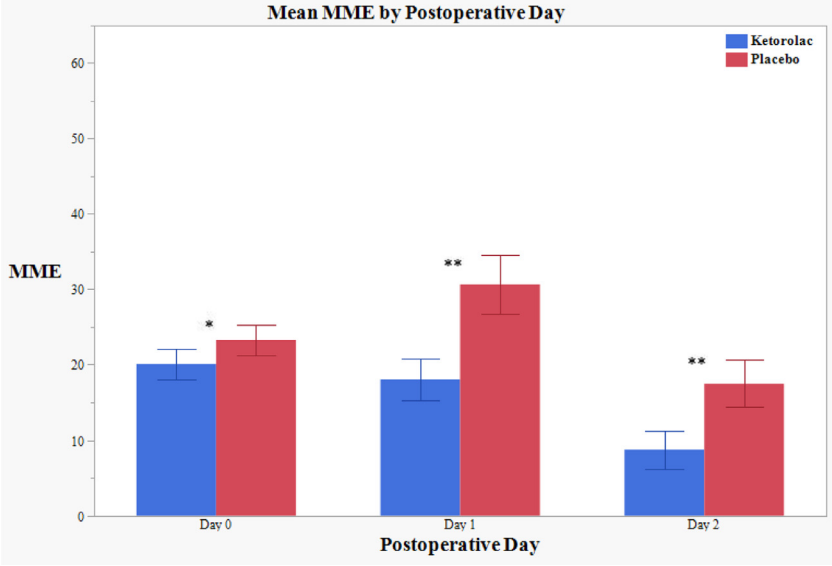

Fig. 3. Mean milligram morphine equivalents (MME) by postoperative day between the ketorolac group (blue) and the placebo group (red). * represents p value <.05. ** represents p value <.001. Error bars represent 95% confidence intervals.

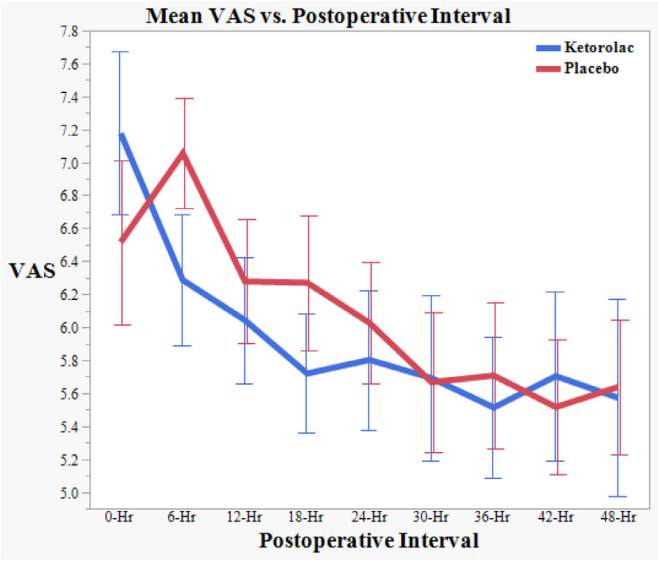

Fig. 4. Mean pain scores using the visual analog scale (VAS) at 6-hour intervals following surgery through 48 hours postoperatively. p value = .11. Error bars represent 95% confidence intervals.

collected every 6 hours (p=.11) (Fig. 4). Patients who received ketorolac had a significant reduction in length of stay (Δ=0.80 days, 95% CI, 0.19−1.17, p=.001)

Adverse events

There was no significant difference in drug-related adverse outcomes between the two groups. Adverse events were rare. Epidural hematoma that required surgical evacuation occurred in three patients (2.3%) in the placebo group and one (0.8%) superficial hematoma which did not extend subfascial was observed in the ketorolac group. AKI was observed in two patients (1.6%) in the placebo group and two patients (1.7%) in the ketorolac group. No patients in the ketorolac group experienced an epidural hematoma, major bleeding episode, or gastrointestinal complication (Table 4).

Patient-reported outcomes

Change in patient-reported outcomes at 6-month and 1-year follow-up demonstrated no significant difference between the ketorolac and control groups (Table 5). Similarly, VAS scores and quality-of-life assessments demonstrated postoperative improvement without significant difference between groups at 6-month and 1-year.

Discussion

This randomized, placebo-controlled trial, analyzing the effect of ketorolac on 246 patients who underwent minimally invasive TLIF with BMP, demonstrated that short-term use of low-dose ketorolac led to a significant reduction in total MME during the hospitalization and the first 48-hour postoperative while maintaining equivalent pain control. We demonstrated comparable fusion rates between the two arms at 6-month and 1-year follow-up. We did not observe significant increased rates of ketorolac-related risks of major bleeding episodes, including epidural hematoma, AKI, or gastrointestinal complications.

NSAIDs remain one the most frequently used medications for the treatment of musculoskeletal pain. By inhibiting prostaglandin synthesis and leukotriene production to achieve anti-inflammatory properties, NSAIDs are highly effective analgesics [29,30]. Thus, the use of NSAIDs, such as ketorolac, has been widely successful in the treatment of postoperative pain following abdominal, gynecologic, and orthopedic surgical procedures [4,9,31]. However, its utilization in patients undergoing spinal fusion remains limited due to the heightened concern for pseudarthrosis [8,11,13,32]. More recently, questions have been raised regarding the effect of timing of NSAID administration and dose on fusion rates [12,13,15,16].

Table 5
Patient reported outcomes

	Ketorolac	Control	Δ Mean	95% CI	p value
6-Month (N=217)	n=100	n=117			
Δ ODI	-22.5±20.1	-22.5±22.3	-0.01	-5.7 to 5.7	.99
Δ SF-12 PCS	12.4±11.6	10.6±11.9	-1.76	-4.9 to 1.4	.28
Δ SF-12 MCS	3.0±10.6	2.6±12.0	-0.39	-3.5 to 2.7	.80
Δ SF-12 Sum	15.6±12.4	13.4±15.8	-2.20	-6.0 to 1.6	.25
Δ VAS	-4.4±3.6	-4.4±3.5	-0.01	-1.0 to 1.0	.99
1-Year (N=175)	n=90	n=85			
Δ ODI	-24.3±19.7	-20.3±22.0	3.99	-2.3 to 10.2	.21
Δ SF-12 PCS	12.7±12.0	11.8±12.8	-0.91	-4.7 to 2.8	.63
Δ SF-12 MCS	2.9±10.8	3.5±10.7	0.54	-2.7 to 3.8	.74
Δ SF-12 Sum	15.9±13.8	15.2±15.1	-0.70	-5.0 to 3.6	.75
Δ VAS	-4.8±3.5	-4.3±3.7	0.54	-0.5 to 1.6	.33

Continuous data presented as mean±SD. Categorical data presented as n (%). Δ represents change from baseline score; p<.05 considered significant. ODI, Oswestry Disability Index; SF-12, short form-12; PCS, physical component summary; MCS, mental component summary; VAS, visual analog pain scale.

Our study highlighted the opioid-sparing effect of ketorolac as an adjunct to postoperative opioid administration after MIS lumbar fusion surgery. Comparing ketorolac patients with controls, the total cumulative and first 48-hour postoperative opioid consumption were significantly less. Moreover, we demonstrated that the use of ketorolac not only significantly reduced opioid consumption but also maintained equivalent or maybe better postoperative pain scores. Ketorolac significantly reduced the length of stay compared with the placebo cohort which further supported an improved recovery profile in ketorolac patients. Both groups achieved similar improvements without any significant difference in all PRO measures over 6 months and 1 year, demonstrating long-term clinical equipoise.

The significant benefits of ketorolac on opioid consumption following lumber fusion remain overshadowed by the concerns over its potential effect on fusion rates. Many authors have reported significantly lower rates of fusion in those who received ketorolac following spinal fusions [8,10,32–36]. Glassman et al. reported a six times higher relative risk of nonunion in those who received ketorolac [32]. However, variability with regard to ketorolac dose, duration and route of administration, and the predominantly retrospective design of these studies failed to provide a conclusion with rigorous evidence [1,8,10,20,32,34,35,37]. Our interim analysis demonstrated a low radiographic incidence of nonunion in patients who received ketorolac with a rate comparable to the placebo group. Moreover, our rate of clinical pseudarthrosis (clinical presentation in conjunction with imaging findings) in patients who received ketorolac remained exceedingly low, with only 2 of the 119 patients evaluated at 1 year requiring revision surgery.

This study is the first to compare the effects of ketorolac on spinal fusion in combination with the use of BMP. BMP has been well described as a graft enhancer and graft substitute [38]. Its use has even been shown to overcome the inhibitory effects of nicotine and NSAIDs on bone formation in experimental animal models [39,40]. Thus, the use of BMP in combination with ketorolac may confound the true impact of ketorolac on fusion rates. Therefore, future studies are required to confirm similar noninhibitory effects of ketorolac in the absence of BMP use.

As with many other institutions, the COVID-19 pandemic presented unprecedented circumstances that forced unconventional practices in hospitals with diminishing resources. As elective procedures were placed on hold, recruitment and funds allocated to clinical trials were also placed on hold. Additionally, the pandemic created a difficult environment in which patients no longer felt safe to adhere to routine trial protocols such as in-clinic and radiographic follow-up. Such circumstances were discussed with the investigating team, all of which who felt it prudent and necessary to publish our investigation result in the interim, especially in light of the tremendous impact on opioid consumption. Opioid use for acute postoperative pain remains an ongoing challenge following spinal surgery. Thus, opioid-sparing analgesic techniques represent an opportunity to improve treatment protocols aimed at enhancing and optimizing the postoperative recovery process, such as ERAS. Multimodal analgesia strategies for pain control are often a key component of most ERAS programs [41], and the addition of an NSAID may offer superior analgesia [42]. However, major concerns of using NSAIDs in spine surgery regarding nonunion and bleeding remain prevalent [43]. Our interim data demonstrated that in patients who have undergone minimally invasive lumbar fusion, short-term, administration of low-dose ketorolac resulted in fusion rates comparable to the controls and well above the inferiority margin that was determined a priori.

Limitations

Although major sources of bias and confounding were addressed in this study through randomization and allocation concealment, a number of limitations remain that warrant discussion in the interpretation of this randomized controlled trial.

The COVID-19 pandemic has caused considerable barriers in maintaining consistent recruitment and follow-up. With a significant and unavoidable delay in obtaining our long-term fusion outcome, compounded by the ongoing opioid crisis, the authors felt compelled to share our significant results regarding ketorolac's opioid-sparing effect on postoperative analgesia after MIS lumbar fusion. Therefore, an important limitation is the interim nature of our analysis regarding the primary outcome. Even though the entire 95% CI of the fusion rate difference between the two arms was well above the noninferiority margin, the CIs at both 6-month and 1-year follow-up spanned more than 25%. With 50% of our enrollment outstanding, our long-term fusion outcome remains uncertain. Similarly, the lack of significant difference regarding adverse events and long-term patient-reported outcomes could be a function of the inadequate patient numbers at the time of interim analysis. One example is our relatively high observed incidence of epidural hematoma in the placebo group which is likely due to random error given the sample size required to show statistical significance.

Preoperative opioid usage has consistently been demonstrated as one of the strongest predictors of postoperative opioid dependence [44–48] and is also clearly associated with worse postoperative outcomes [49]. We followed our state's online prescription monitoring program (Michigan Automated Prescription System) and defined chronic opioid use as opioid use for ≥14 days in the last 3 months before surgery. However, as a validated definition of opioid tolerance has not been established, the possibility of selection bias remains. The determination of chronic opioid use before surgery heavily relies on patient self-reporting which introduced reporting bias. Furthermore, granular information regarding the quantity of opioids consumed was not collected and would have ideally provided additional

information into establishing the degree of opioid tolerance among participants.

CT has the strongest correlation with the assessment of fusion status [50]. Therefore, the use of CT would have been ideal for the assessment of our primary outcome. However, given the size of the study and the burden of radiation exposure with CT, XR was chosen as our method of evaluation. The 2014 AANS guidelines state a combination of static and lateral flexion/extension images is a valid and useful way of determining fusion in posterior lumbar fusions with instrumentation, as supported by Brodsky et al., who determined the correlation of fusion rates with such images using surgical exploration [51].

Finally, the nature of a randomized controlled trial with its highly selective patient population may lend certain challenges when generalized to the often-complex clinical situation. Examples would be our exclusion of smokers, our use of a standardized MIS TLIF technique and rhBMP-2. As discussed previously, the detrimental effect of ketorolac on spinal fusion may be overcome by the use of BMP. Therefore, our results may not be generalizable to patients undergoing MIS TLIF without BMP. Similarly, our use of a standardized MIS TLIF technique may render our result not generalizable to other fusion techniques. Further studies with different fusion techniques without the use of BMP are warranted. If our final results affirm our interim results, the next step would be to track long-term fusion results associated with the use of ketorolac in a large number of patients in registry studies.

Conclusion

Short-term use of low-dose ketorolac in patients who have undergone MIS TLIF with BMP significantly reduced postoperative opioid use and length of stay while maintaining equivalent postoperative pain control. The use of ketorolac was not associated with an increase in short-term perioperative adverse events. Our interim results suggested noninferior fusion rates with the use of ketorolac. However, confirmation of these results remains ongoing.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2021.08.011.

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