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ORIGINAL RESEARCH

Budget Impact and Cost-Effectiveness of Intravenous Meloxicam to Treat Moderate–Severe Postoperative Pain

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ABSTRACT

Introduction: This study assesses the budget impact and cost-effectiveness of intravenous meloxicam (MIV) to treat moderate–severe acute postoperative pain in adults.

Methods: A two-part Markov cohort model captured the pharmacoeconomic impact of MIV versus non-opioid intravenous analgesics (acetaminophen, ibuprofen, ketorolac) among a hypothetical adult cohort undergoing selected inpatient procedures and experiencing moderate–severe acute postoperative pain: Part 1 (postoperative hour 0 to discharge, cycled hourly), health states were defined by pain level. Pain transition rates, adverse event probabilities, and concomitant opioid utilization were derived from a network meta-analysis. Part 2 (discharge to week 52, cycled weekly), health states were defined by the presence/absence of pain-related readmission and opioid use disorder as determined by literature-based inputs relating to pain control outcomes. Healthcare utilization and direct medical costs were derived from an administrative claims database analysis. Primary outcomes were the incremental cost per member per month (PMPM) and cost per quality-adjusted life year (QALY) gained. Scenario, univariate, and probabilistic sensitivity analyses were conducted. The model assumed a private payer perspective in the USA (no discounting, 2019 US$).

Results: Modeled outcomes indicated MIV was associated with lower accumulated postoperative pain, fewer adverse events, and less opioid utilization for most procedures and comparators, with longer-term outcomes also generally favoring MIV. The budget impact of MIV was − $0.028 PMPM. From a cost-effectiveness perspective, MIV had lower costs and better outcomes for all comparisons except against ketorolac in orthopedic procedures where the former was cost-effective but not cost saving ($95,925/QALY). Scenario and sensitivity analyses indicated that modeled outcomes were robust to alternative inputs and underlying input uncertainty. Differences in direct medical costs were driven by reduced costs

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attributable to length of stay and opioid-related adverse drug events.
Conclusion: MIV was associated with modeled clinical and economic benefits compared to commonly used non-opioid intravenous analgesics.

Keywords: Budget impact; Cost-effectiveness; Meloxicam IV; Opioid; Postoperative pain

Key Summary Points

Why carry out this study?

Opioids are widely used as the only therapy to manage postoperative pain and yet the majority of patients report inadequate postoperative pain control.

High postoperative opioid utilization has been demonstrated to contribute greatly to the opioid abuse epidemic which results in a substantial economic burden for the healthcare system and society.

This study assesses the budget impact and cost-effectiveness of intravenous meloxicam (MIV) to treat moderate–severe acute postoperative pain in adults.

What was learned from the study?

Modeled outcomes indicated MIV was associated with lower accumulated postoperative pain, fewer adverse events, and less opioid utilization for most procedures and comparators, which in turn was associated with MIV being cost-effective.

INTRODUCTION

More than 100 million operations are performed annually in the USA [1]. Yet, despite initiatives to improve analgesic effectiveness and safety through diversified pharmacotherapy and reduced opioid utilization, approximately 70% of patients receive opioid agonist monotherapy to treat pain postoperatively [1, 2]. Notwithstanding the highest per capita postoperative opioid utilization globally [3], more than 80% of patients in the USA report inadequate postoperative pain control and up to 75% report severe pain—a figure that has remained constant for the last two decades [2, 4–6]. Inadequate pain control in this context has dual deleterious effects. First, patients are at increased risk for poor outcomes associated with the continued pain itself including longer hospital length of stay (LOS), more unplanned 30-day readmissions and emergency department (ED) visits, and conversion to chronic pain disorders [7, 8]. Second, high postoperative opioid utilization has produced commensurately high rates of opioid-related adverse drug events [3, 9]. High postoperative opioid utilization has also contributed greatly to the opioid abuse epidemic, which is associated with approximately 70,000 opioid-related overdose deaths annually (190 per day) [3, 9]. The annual economic burden of opioid abuse alone has been estimated at $86 billion in 2018-adjusted US dollars [10].

Multimodal analgesia involves the administration of opioid and non-opioid agents that act on different sites, resulting in a synergistic impact on pain reduction [11, 12]. Where not contraindicated, multimodal analgesia may help mitigate opioid-related risks and is recommended by key clinical authorities such as the American Pain Society, the American Society of Anesthesiologists, and the American Society of Regional Anesthesia, and Pain Medicine among others [11, 12]. In multimodal pain management, the non-opioid component can comprise IV acetaminophen and IV non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and ketorolac, which are associated with less opioid use, fewer opioid-related adverse drug events, shorter LOS, better pain control, and lower direct medical costs [13–15]. However, the low cost of opioids and the gastrointestinal and cardio-nephrotoxic adverse events (AEs) associated with some non-opioid analgesics have contributed to the limited use of non-opioid IV analgesics to treat moderate–severe pain [16].

Intravenous meloxicam (MIV) has been approved by the US Food and Drug Administration to manage moderate-to-severe pain in adults, alone or in combination with non-NSAID analgesics. It has demonstrated efficacy in randomized controlled clinical trials of adults with moderate–severe pain following dental surgery [17], abdominal hysterectomy [18], bunionectomy [19, 20], abdominoplasty [21], and other major procedures [22, 23]. Whether these benefits impact healthcare resource utilization and associated costs has been unclear. Hence, an economic model was developed to assess the budget impact and cost-effectiveness of MIV for the treatment of adults with moderate–severe acute postoperative pain from a US private payer perspective (i.e., private insurance companies).

METHODS

Using established best practices [24, 25], we developed a pharmacoeconomic model to evaluate the budget impact and cost-effectiveness of MIV, when used to treat moderate–severe postoperative pain. MIV is only currently available in the USA; therefore, the model was conducted from a US third-party private payer perspective. No discounting was applied because of the short time horizon (52 weeks). All costs are in 2019 US dollars (USD).

Ethics Statement

This study relied on information obtained from the literature. There were no human subjects involved, and therefore this study was not subject to considerations of committee approval, informed consent, etc.

Target Population

The target population was defined as privately insured adults (i.e., age 18 years or more) treated for moderate–severe acute postoperative pain after undergoing one of the following procedures: major abdominal surgery (defined as open procedures requiring a transverse abdominal incision, excluding hysterectomy), open abdominal hysterectomy, bunionectomy, or unilateral joint replacement (knee, ankle, or shoulder). These procedures were chosen because they had been included in the MIV clinical trial program.

Model Structure

A Markov cohort model was developed to assess outcomes over proximate and longer-term periods (Fig. 1). The model simulated the progression of patient cohorts over time for each comparator and procedure individually. This approach was chosen given the need to model repeating mutually exclusive health states [26]. In the proximate period (postoperative hour 0 to discharge from the initial surgical encounter), health states were defined by pain level, with each state constituting one level of the 11-level pain intensity numeric rating scale (PINRS). The PINRS (0 = no pain to 10 the worst pain imaginable) is an objective, validated measure of postoperative pain that has been employed in previous similar economic analyses [27–29]. The duration of the initial inpatient state (part 1) was determined by the typical recovery period for the given surgical procedure [30] (Table S1 in the Supplementary Material). After the initial surgical discharge, we modeled the disposition of cohorts among health states characterized primarily by the presence or absence of a hospital readmission. That is, cohorts could either be in a state where they were in a readmission, a state where they were not in a readmission, or death. After readmission in part 2, cohorts transition to no readmission, but can potentially be readmitted again. The duration of model part 2 was equal to 1 year minus the duration of part 1.

Setting and Comparators

All procedures were conducted in an inpatient hospital setting where cohorts experiencing moderate–severe acute pain after one of the aforementioned procedures received (with or without concomitant opioids) one of the

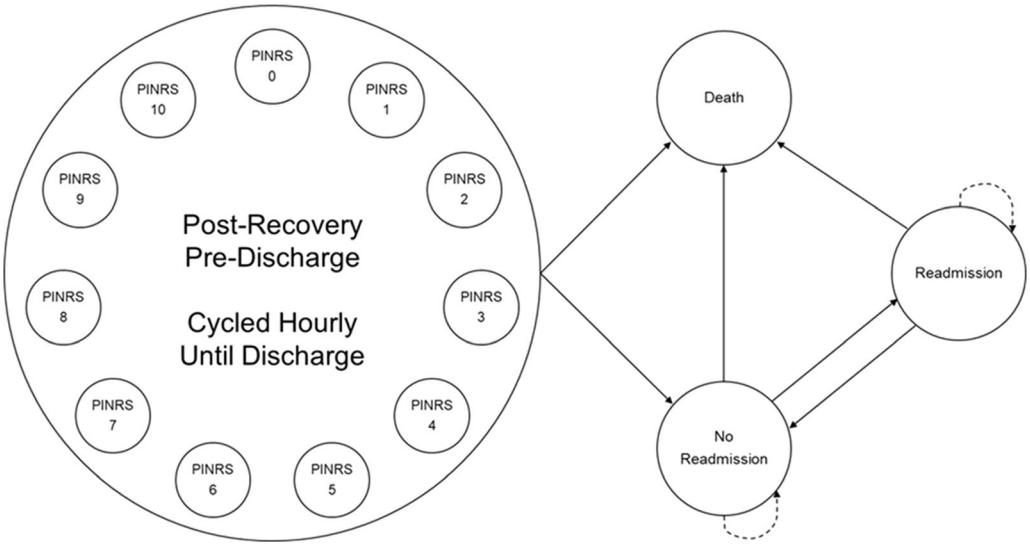

Fig. 1 Markov model structure. In the post-recovery, pre-discharge stage cohorts could transition among any of the PINRS states or remain in the same state. Following the initial discharge, cohorts transition between no readmission and readmission states or can transition to an absorbing state (i.e., death)

following IV non-opioid analgesics: MIV, acetaminophen, ibuprofen, and ketorolac.

Model Inputs

Model inputs are presented in the Supplementary Material (Table S1), which includes the base case values, minimum and maximum variability for univariate sensitivity analysis, the probability distribution used for probabilistic sensitivity analysis, and the sources of the data. Values were derived from three main sources: a network meta-analysis (NMA) [31], an original administrative claims database analysis [30], and the peer-reviewed literature.

Regarding the NMA, we previously [31] conducted a systematic literature review and subsequent NMA of randomized clinical trials (years 2000–2019, adult human subjects) of IV non-opioids (ketorolac, ibuprofen, acetaminophen) used to treat moderate–severe pain following the four procedure groups listed previously (prospectively registered in PROSPERO [CRD42019117360]). Having chosen a Bayesian approach to better account for uncertainties among the constituent trials [32, 33], we assessed the following outcomes for up to 72 h postoperatively: sum of pain intensity difference, total morphine milligram equivalents (MME) used, and opioid-related adverse drug event frequency. These outcomes from the NMA formed the basis of the modeled clinical effects in part 1 of the economic model. The sum of pain intensity difference outcomes given at different time points in the NMA was used to form a continuous trendline from postoperative hour 0 to discharge. The cohorts' initial pain score (i.e., initial state) was determined by the mean postoperative PINRS for the given procedure from the NMA. Cohorts then transitioned hourly among PINRS-defined health states depending on to the sum of pain intensity difference trendline until discharge.

As noted in the originally published report [31], PINRS was not measured in the orthopedic procedures in the MIV clinical trial program [34]. The present economic evaluation—which is primarily driven by modeling of postoperative pain scores—applies surrogate PINRS outcomes from the phase 3 MIV clinical trial for bunionectomy procedures [19]. This was considered a reasonable assumption given previous research indicating similar standardized effect sizes between bunionectomy and joint arthroplasty [35]. All other parameters for the

modeled orthopedic procedure cohort (e.g., adverse events, morphine and opioid consumption, etc.) were derived directly from the MIV clinical trial of orthopedic procedures [36].

Analgesic utilization across different procedures was based on the claims analysis and expert opinion (Table S2 in the Supplementary Material) [30]. All medication costs were wholesale acquisition costs taken from IBM Micromedex/REDBOOK (2019) [36]. The wholesale acquisition cost for meloxicam IV was $94.00 per 30 mg dose. Intravenous drug administration costs were extracted from the literature [37]. For each procedure, LOS and associated procedure costs were derived by conducting an original administrative claims database analysis using Marketscan Commercial Database (2014–2017) [30]. Utility values represented the quality of life experienced in each health state. In part 1 of the model, a lower value (i.e., worse quality of life) was attributed to the health states where cohorts had not reached a less than 50% pain score improvement (i.e., utility value = 0.495; mean of moderate and severe pain values) [38] and a higher value was attributed to health states where cohorts reached at least 50% pain score improvement (i.e., utility value = 0.74) [38]. The utility value at the postoperative discharge served as the baseline utility for part 2 of the model. Disutility values were applied throughout to downwardly adjust utility when patients experienced postoperative pain after discharge (i.e., disutility value = − 0.02 for one cycle) [39], opioid-related adverse drug events or AEs (i.e., disutility value = − 0.0014 for one cycle) [40], opioid use disorder (i.e., disutility value = − 0.064) [41], or opioid-associated death (i.e., utility value = 0). All utility values were identified through searching the Tufts CEA Registry, which is a compendium of utility values and outcomes from cost-effectiveness studies that is searchable by topic and keyword [42]. Other inputs including cost of aggregate grade 3 or 4 AE, cost impact of opioid-related adverse drug event on 30-day readmission [6], probability [43], and cost of opioid use disorder and cost of opioid use disorder conversion [44] were derived from the literature (Table S1 in the Supplementary Material).

Analysis and Outcomes

Base Case Analysis

The base case analysis included a 52-week analytical horizon and considered only part 1 of the model (i.e., the inpatient component), but part 2 of the model (i.e., post discharge) was included as an exploratory secondary analysis. The base case model was evaluated from a payer perspective and included only utilization and associated direct medical costs attributable to analgesic drug administration, procedure and associated LOS, AEs, opioid-related adverse drug events, pharmacy, and unplanned readmissions. In the exploratory secondary analysis, costs attributable to subsequent opioid dependence, misuse, and abuse were estimated. Outcomes were not discounted because of the short time horizon (at most 1 year) [45], and included total direct medical cost and direct medical cost per patient.

The budget impact in the base case model was evaluated assuming 100% uptake by MIV and an annual member volume of 100,000,000 members. In addition, an annual rate of 20,000 procedures (abdominal = 10%, hysterectomy = 10%, bunionectomy = 20%, orthopedic = 60%) was assumed on the basis of the relative prevalence of these procedures derived from the claims analysis [30].

The primary outcomes for the budget impact and cost-effectiveness analyses were incremental cost per member per month and incremental cost per quality-adjusted life year gained, respectively. Additionally, clinical outcomes such as proportion of patients with at least 50% pain intensity difference 0–24 h, at least one opioid-related adverse drug event, at least one AE, 30-day readmission, incident opioid addiction (exploratory analysis), and total MMEs consumed were also estimated. Total costs (medical and pharmacy) were estimated as the sum of costs for base procedure and additional LOS, AEs (non-opioid-related adverse drug events and opioid-related adverse drug events), analgesics (IV non-opioid and rescue), analgesic administration, 30-day readmissions, and opioid use disorder risk (exploratory analysis).

All costs were reported in 2019 USD. Where necessary, input costs were adjusted to 2019

USD using the medical care component of the Consumer Price Index provided by the US Bureau of Labor Statistics (seasonally adjusted, all urban consumers) [46].

Scenario Analysis

At the time base case analysis was conducted, pain scores for orthopedic procedures in the base analysis were estimated from MIV trials for bunionectomy. Hence, a scenario analysis was run to analyze the budget impact (cost analysis) using model inputs derived from the results of the more recent phase 3b study assessing the safety and efficacy of perioperative MIV for moderate-to-severe pain management in total knee arthroplasty [47]. In this study, MIV was administered preoperatively, and pain was assessed post surgically at set time points as opposed to phase III studies, where MIV was administered post surgically upon a patient achieving a pain score of 4 or greater. Specifically, the following data were used as inputs in the model: pain intensity differences (0–24 and 0–48 h), MME utilized, subjects with at least one serious AE, and mean length of hospital stay. For this scenario analysis, pain intensity differences (0–24 and 0–48 h) were estimated using the patient level data from the trial for the MIV and placebo arms by two approaches: using only observed pain intensity scores and by assuming a pain intensity score for the missing time point.

Sensitivity Analysis

The robustness of the model assumptions was tested by conducting univariate and probabilistic sensitivity analyses. Where standard deviations were not available clinical variables were varied by ± 15%. Cost variables were varied by ± 50% to account for inherent variability as costs were derived from multiple data sources including claims analysis or literature, consistent with other studies [48]. For probabilistic sensitivity analyses a normal distribution was used for pain scores, differences in MME utilized, and LOS; a beta distribution for probabilities and utilities; and gamma distribution for costs.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Base Case Outcomes

Overall, MIV was associated with similar or better clinical outcomes (Tables 1 and S3–S6 in the Supplementary Material) and lower direct medical costs (Tables 2 and S7–S10 in the Supplementary Material) across procedures and comparators (except vs ibuprofen for bunionectomy and vs ketorolac for orthopedic procedures). The difference in direct medical costs was driven largely by reduced costs attributed to length of stay and opioid-related adverse drug events associated with MIV.

In the base case budget impact analysis, assuming 100,000,000 member volume in a given year with an annual rate of 20,000 procedures (abdominal = 10%, hysterectomy = 10%, bunionectomy = 20%, Orthopedic = 60%) and 100% replacement with MIV, the total annual direct medical cost was $656 million for the MIV group versus $687 million for the aggregated comparator group. The incremental cost per member per month cost associated with implementing MIV in such a plan was estimated as − $0.028 (Table 2).

For all procedures and relative to all comparators (except orthopedic–ketorolac), total costs associated with MIV were lower than the comparator and total quality-adjusted life year gains associated with MIV were higher than the comparator (i.e., MIV was the dominant treatment strategy). For orthopedic procedures, MIV produced 0.002 more quality-adjusted life years versus ketorolac, but at an incremental cost of $228.88. The resulting incremental cost-effectiveness ratio was $95,925/quality-adjusted life year gained (Table 3). Pairwise economic comparisons (direct medical costs) can be found in Table S7 (abdominal procedures), Table S8 (bunionectomy), Table S9 (hysterectomy), and

Table 1 Modeled clinical outcomes across procedures and comparators

	MIV vs acetaminophen (%)	MIV vs ibuprofen (%)	MIV vs ketorolac (%)
Abdominal			
≥ 50% pain intensity difference 0–24 h	5.64	7.72	8.32
Patients with ≥ 1 grade 3/4 AE	− 2.73	− 1.40	− 0.40
Patients with opioid-related adverse drug event	− 1.90	− 3.32	− 2.46
Patients with 30-day readmission	− 0.75	− 1.31	− 0.97
Patients with incident opioid addiction	− 0.17	− 0.21	− 0.20
MMEs consumed	− 19.0	− 26.0	− 28.0
Bunionectomy			
≥ 50% pain intensity difference 0–24 h	2.29	− 0.38	4.20
Patients with ≥ 1 grade 3/4 AE	− 2.73	− 1.40	− 0.40
Patients with opioid-related adverse drug event	− 0.19	0.04	− 0.23
Patients with 30-day readmission	− 0.08	0.02	− 0.12
Patients with incident opioid addiction	− 0.03	-0.03	− 0.03
MMEs consumed	− 6.0	1.0	− 11.0
Hysterectomy			
≥ 50% pain intensity difference 0–24 h	3.86	3.56	7.72
Patients with ≥ 1 grade 3/4 AE	− 2.73	− 1.40	− 0.40
Patients with opioid-related adverse drug event	− 3.05	− 2.55	− 4.50
Patients with 30-day readmission	− 1.21	− 1.01	− 1.78
Patients with incident opioid addiction	− 0.27	− 0.24	− 0.26
MMEs consumed	− 13.0	− 12.0	− 26.0
Orthopedic			
≥ 50% pain intensity difference 0–24 h	9.17	7.26	− 0.76
Patients with ≥ 1 grade 3/4 AE	− 2.73	− 1.40	− 0.40
Patients with ORADE opioid-related adverse drug event	− 4.25	− 4.19	0.31
Patients with 30-day readmission	− 1.68	− 1.65	0.12
Patients with incident opioid addiction	− 0.49	− 0.61	− 0.57
MMEs consumed	− 24.0	− 19.0	2.0

AE adverse event, *MIV* meloxicam intravenous, *MME* morphine milligram equivalent

Table 2 Outcomes of the budget impact analysis

	Without MIV	With MIV	Difference
Total annual cost	$686,074,185	$655,945,419	− $30,128,765
Pharmacy only	$5,569,906	$6,062,916,419	$493,010
Medical only	$680,504,279	$649,882,503	− $30,621,776
Incremental cost per member per month	− $0.028		

MIV meloxicam intravenous

Table S10 (orthopedic procedures) in the Supplementary Material.

Scenario Analysis

Regardless of the methodology used to estimate pain intensity difference, MIV showed a greater reduction in pain intensity difference versus placebo. When the results from the phase 3b trial were applied, the incremental cost per member per month increased to − $0.021 from − $0.028 in the base case analysis. The use of varied pain intensity difference scores did not impact the results significantly.

Sensitivity Analysis

Univariate sensitivity analysis indicated that modeled outcomes were robust to alternative inputs and underlying input uncertainty. Figure 2 shows the top variables that resulted in maximum variability in difference in total costs for each procedure with MIV vs acetaminophen, ibuprofen, and ketorolac. Overall, the univariate sensitivity analysis indicated that modeled outcomes were robust to alternative inputs, underlying input uncertainty, and did not change the direction of cost difference between MIV and comparators. Generally, the variables that resulted in maximum variability included baseline inpatient cost for procedures, MME utilization threshold (Table S1 in the Supplementary Material), baseline LOS, probability of moderate opioid-related adverse drug event, and readmission after opioid-related adverse drug event.

The probabilistic sensitivity analysis included 10,000 bootstrapped Monte Carlo iterations for all procedures and comparators. On the basis of the results of the probabilistic sensitivity analysis, MIV remained cost saving in greater than 95% of the simulations (i.e., it had a 95% probability of being cost saving).

DISCUSSION

This model estimated the budget impact and cost-effectiveness of MIV, indicated for the treatment of moderate–severe pain in adults. Overall, MIV demonstrated clinical benefits and was found to be cost saving compared with IV formulations of acetaminophen, ibuprofen, and ketorolac across all procedures (abdominal, bunionectomy, hysterectomy, and orthopedic) except against ketorolac for orthopedic procedures. This budget impact analysis indicated that implementing MIV was associated with savings per patient per month. Furthermore, MIV was dominant versus other comparators in cost-effectiveness analysis across procedures except ketorolac for orthopedic procedures. The clinical benefits and cost savings associated with MIV were mostly associated with reduced length of stay and readmissions attributable to opioid-related adverse drug events. The sensitivity analysis demonstrated the robustness of the model and modeled outcomes to underlying structural and input uncertainty.

A study by Jahr et al. evaluating the effect of MIV and ketorolac on platelet function showed that, while ketorolac was associated with significantly longer closure times, MIV did not have any significant effect on sample closure

Table 3 Clinical and economic outcomes of the cost-effectiveness analysis by procedure and comparator

	MIV vs acetaminophen	MIV vs ibuprofen	MIV vs ketorolac
Abdominal			
Facility stay	(524.59)	(918.86)	(680.31)
Base procedure	–	–	–
Additional LOS	(524.59)	(918.86)	(680.31)
AEs	(420.69)	(677.68)	(490.61)
Non-opioid-related adverse drug events	(47.78)	(24.50)	(7.00)
Opioid-related adverse drug events	(372.91)	(653.18)	(483.61)
Analgesics	(269.13)	79.01	81.35
IV non-opioid analgesic	(264.00)	88.00	88.00
Rescue analgesic	(5.13)	(8.99)	(6.65)
Analgesic administration	(371.28)	(415.83)	(388.88)
30-day readmissions	(132.35)	(231.81)	(171.63)
Total (base case)	(1718.03)	(2165.18)	(1650.08)
Total (base case + opioid use disorder risk)	(1732.42)	(2183.59)	(1666.96)
Quality-adjusted life years	0.007	0.010	0.009
Incremental cost per quality-adjusted life year gained	Dominant	Dominant	Dominant
Bunionectomy			
Facility stay	(24.91)	5.40	(30.22)
Base procedure	–	–	–
Additional LOS	(24.91)	5.40	(30.22)
AEs	(74.33)	(18.75)	(41.49)
Non-opioid-related adverse drug events	(47.78)	(24.50)	(7.00)
Opioid-related adverse drug events	(26.56)	5.75	(34.49)
Analgesics	(66.32)	22.07	21.47
IV non-opioid analgesic	(66.00)	22.00	22.00
Rescue analgesic	(0.32)	0.07	(0.53)
Analgesic administration	(167.23)	(153.57)	(174.53)
30-day readmissions	(20.06)	4.35	(32.12)
Total (base case)	(352.85)	(140.50)	(256.89)
Total (base case + opioid use disorder risk)	(355.04)	(143.33)	(263.15)
Quality-adjusted life years	0.003	0.001	0.003
Incremental cost per quality-adjusted life year gained	Dominant	Dominant	Dominant
Hysterectomy			

Table 3 continued

	MIV vs acetaminophen	MIV vs ibuprofen	MIV vs ketorolac
Facility stay	(898.11)	(750.07)	(1325.78)
Base procedure	–	–	–
Additional LOS	(898.11)	(750.07)	(1325.78)
AEs	(686.21)	(557.70)	(949.45)
Non-opioid-related adverse drug events	(47.78)	(24.50)	(7.00)
Opioid-related adverse drug events	(638.43)	(533.20)	(942.45)
Analgesics	(268.42)	84.31	81.47
IV non-opioid analgesic	(264.00)	88.00	88.00
Rescue analgesic	(4.42)	(3.69)	(6.53)
Analgesic administration	(387.32)	(362.04)	(460.32)
30-day readmissions	(212.98)	(177.87)	(314.40)
Total (base case)	(2453.04)	(1763.38)	(2968.49)
Total (base case + opioid use disorder risk)	(2476.19)	(1784.33)	(2991.27)
Quality-adjusted life years	0.008	0.006	0.010
Incremental cost per quality-adjusted life year gained	Dominant	Dominant	Dominant
Orthopedic			
Facility stay	(1341.33)	(1341.33)	(1341.33)
Base procedure	–	–	–
Additional LOS	(1341.33)	(1341.33)	(1341.33)
AEs	(1296.03)	(1296.03)	(1296.03)
Non-opioid-related adverse drug events	(47.78)	(47.78)	(47.78)
Opioid-related adverse drug events	(1248.26)	(1248.26)	(1248.26)
Analgesics	(154.20)	(154.20)	(154.20)
IV non-opioid analgesic	(151.80)	(151.80)	(151.80)
Rescue analgesic	(2.40)	(2.40)	(2.40)
Analgesic administration	(265.97)	(265.97)	(265.97)
30-day readmissions	(388.44)	(388.44)	(388.44)
Total (base case)	(3445.98)	(3445.98)	277.58
Total (base case + opioid use disorder risk)	(3488.21)	(3488.21)	228.88
Quality-adjusted life years	0.012	0.011	0.002
Incremental cost per quality-adjusted life year gained	Dominant	Dominant	$95,925

AE adverse event, *LOS* length of stay, *MIV* meloxicam intravenous, *MME* morphine milligram equivalent

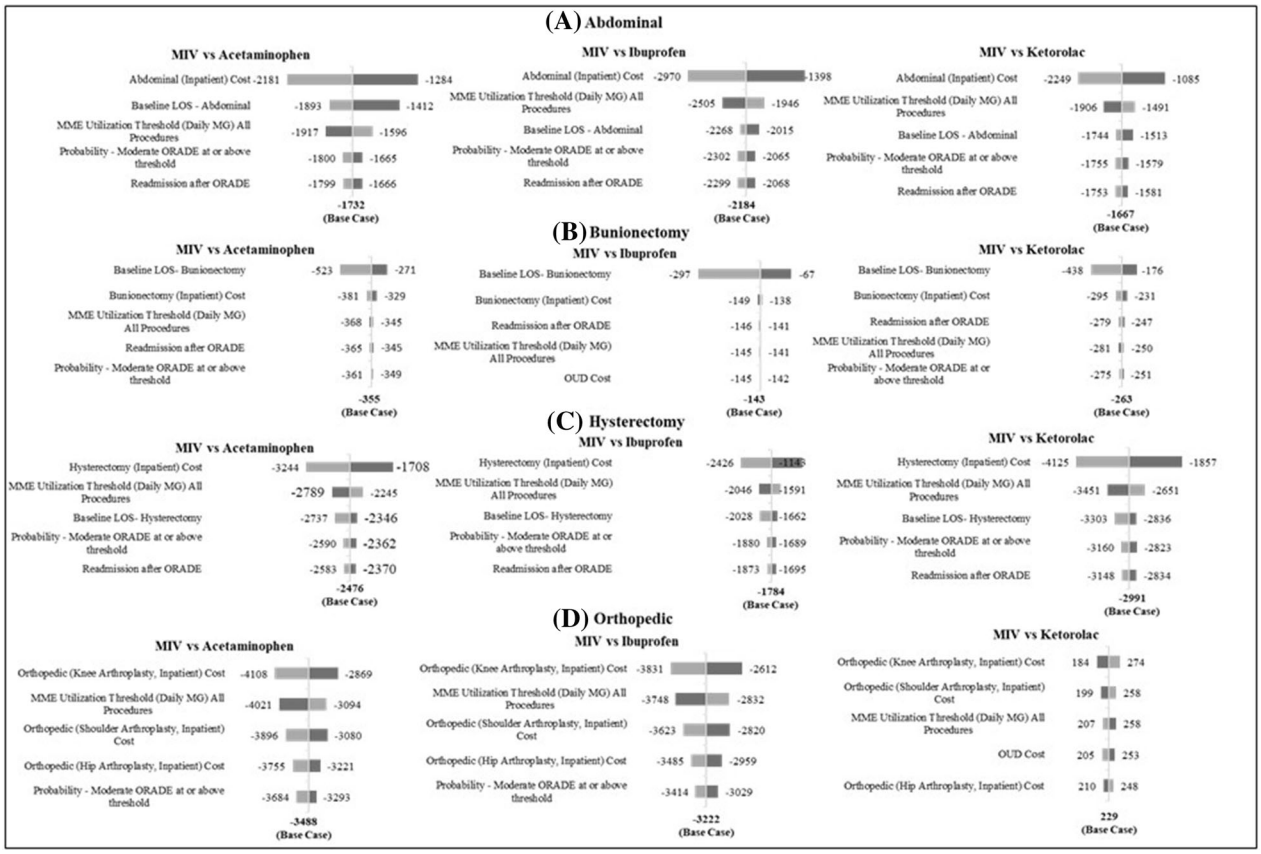

Fig. 2 Results of univariate sensitivity analysis: difference in total direct costs for MIV vs comparator

time at therapeutic or supratherapeutic exposure when compared with untreated controls [49]. As the sample closure time simulates the process of platelet adhesion and aggregation following a vascular injury, the findings from this study indicated that MIV may be associated with relatively lower risk for events related to platelet dysfunction. While our analysis did not specifically look at bleeding events, the modeled clinical outcomes showed that MIV was associated with lower risk of any AEs compared with ketorolac and other comparators. For orthopedic procedures, even though total costs were higher for MIV than ketorolac (difference $227), MIV was associated with higher quality-adjusted life year gains.

This model has important strengths. First, the model was constructed according to established best practices by ISPOR guidance on model development [24, 25]. Second, the model analyses were comprehensive, evaluating both clinical and economic outcomes associated with MIV, thus allowing assessment of both budget impact and cost-effectiveness of MIV. Third, the model was populated with the best available information including an extensive literature review, original NMA, and claims database analyses. For each procedure category, input parameters for resource utilization and associated costs that were derived from the claims database analysis are representative of a real-world treatment setting. A commercial/private claims database was chosen to align with a private payer perspective as the majority of the US population receives their health coverage through private health insurance plans. Despite a short time horizon of 1 year, the model evaluates longer-term implications of MIV by employing a two-stage approach. Fourth, this model generated a conservative estimate of the clinico-economic benefits of MIV by only considering direct medical costs. Fifth, the

probabilistic sensitivity analysis showed that MIV remained cost saving in greater than 95% of the simulations.

This model is also subject to a number of limitations. First, the model pertains only to patients undergoing the four procedure categories identified as those that were consistent with the procedures represented in the MIV clinical trial program. More real-world data for MIV across other procedure categories is needed and the model should be updated, and outcomes evaluated once other procedure data becomes available. Second, MIV clinical trial data, in the case of pain scores in the orthopedic procedures, were extrapolated in the base case analysis. However, a scenario analysis was conducted using the most recent MIV clinical trial data including pain scores for total knee arthroplasty and no major impact on findings from budget impact analysis was reported. Third, inputs from disparate sources were combined to produce the model. Fourth, the clinical benefit of opioid use reduction specifically in an MIV-treated population has not been directly assessed. Lastly, the outcomes of this model are not generalizable to all populations undergoing the modeled procedures. One reason is that the treatment patterns for patients undergoing procedures in the outpatient setting or covered by US public payer plans (i.e., primarily government programs such as Medicare, Medicaid, and CHIP which are plans for low-income individuals or families, the elderly, and other individuals that qualify for special subsidies) might be considerably different than those of the privately insured patients represented here. Also, the present model applied utilization distributions for acetaminophen, ibuprofen, and ketorolac to generate—for some outcomes—an aggregated comparator against MIV. This assumed higher utilization of ibuprofen versus acetaminophen and ketorolac. For some procedures and in some institutions the utilization might be different, which would impact the outcomes.

CONCLUSIONS

Cost-effective non-opioid alternatives are needed for the treatment of postoperative pain in the USA. This is a novel economic evaluation comparing the most common IV NSAID analgesics and acetaminophen in the USA. The results demonstrate that MIV is a cost-effective (and in some cases cost-saving) treatment alternative to the most common IV NSAID analgesics and acetaminophen used to treat moderate–severe postoperative pain. These benefits were primarily derived from modeled reductions in postoperative opioid use and associated reductions in opioid-related adverse drug events and hospital length of stay.

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Data Availability. The model described in this report was developed using information drawn from published studies that are referenced herein. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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