#42

NTM-001 – Evidence-Based and Modeling-Supported Development of a Novel Alternative to Opioids for Moderately Severe Acute Post-Operative Pain; A Literature Review Related to Safety and Efficacy Studies of Continuous IV Infusion of Ketorolac Tromethamine and the Proposed Dosing Regimen of NTM-001

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Neumentum™ A Better Way In Pain Management

PURPOSE

NTM-001 (Neumentum, Inc.) is an innovative product consisting of a new formulation of ketorolac tromethamine in a pre-mixed bag for continuous IV infusion.

Target Indication for development) of NTM-001

NTM-001 is in development for the short-term management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting, for up to 24 hours.

Novel Formulation

The proposed formulation of NTM-001 (**Table 1**) is alcohol-free (vs. about 10% alcohol contained in currently available injectable formulations) aiming to reduce potential local irritation for the purpose of continuous infusion. It contains 1.0 mg/mL of ketorolac tromethamine, USP in saline solution (~0.9% NaCl) adjusted to a pH of ~7.4.

TABLE 1. COMPARISON OF KETOROLAC TROMETHAMINE FORMULATIONS

Formulation	Generic ketorolac tromethamine injection	Proposed Neumentum Formulation (NTM-001)
Ketorolac Tromethamine	15 mg/mL or 30 mg/mL	1.0 mg/mL
Sodium Chloride	6.68 mg/mL or 4.35 mg/mL	8.8 mg/mL
Citric Acid *	1 mg/mL (or 0)	n.a. (0)
Alcohol	100 mg/mL (10%)	n.a. (0)
pH adjustment with NaOH or HCl	6.9 – 7.9	approx.7.4
Container	Glass 1 mL vials or pre-filled syringes	Polyolefin 75-200 mL Plastic Infusion Bag

*Some generic formulations may contain 0.1% citric acid

NTM-001 is readily available for infusion and administered from pre-mixed polyolefin infusion bag via pre-programmed infusion pumps as in regular, daily hospital use.

Dosing Regimen supported by PK/PD Modeling and confirmed by Human Data

The development of NTM-001 and its dosing regimen (in adult patients without specific risk factors for NSAID use: 3.5 mg loading dose administered within 60 seconds, followed by a continuous infusion of 3.5 mg/h for 24h) has been strongly supported by PK/PD modeling. As in line with the generic IV ketorolac bolus reference label, a 50% dose reduction has been considered with NTM-001 for patient populations at special risk for NSAID use.

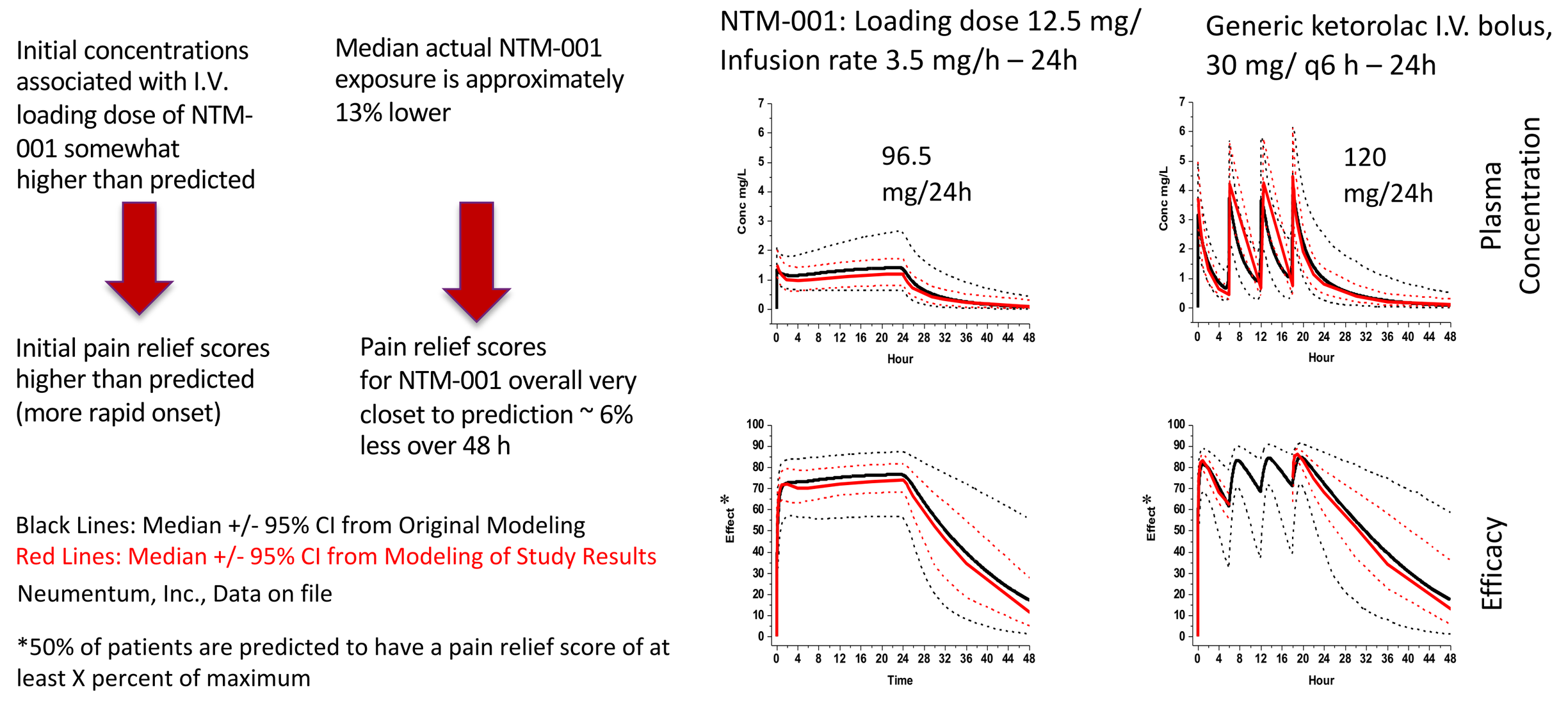
TABLE 2. COMPARISON OF KETOROLAC TROMETHAMINE FORMULATIONS

Formulation	Generic ketorolac tromethamine injection†	Proposed Neumentum Formulation (NTM-001)
Treatment Duration up to	5 days	24 hours
24 hr Dosing (patients < 65 yr/age, ≥ 50 kg body weight, normal renal function)†	30 mg IM/IV injection every 6 hours; not to exceed 120 mg/day	Loading dose: 12.5 mg IV from NTM-001 infusion solution. Maintenance dose: 3.5 mg/hr as a continuous infusion x 24 hours. (total maximum dose 96.5 mg/24 hr)

†A 50% reduced dosing regimen is proposed for risk patient populations (≥65 years old, renally impaired and/or less than 50 kg (110 lb) body weight), in line with the current label and in patients with moderate hepatic impairment.

Predictions of PK/PD modeling have been recently confirmed by results of a first-in-man randomized, controlled PK study of NTM-001 vs a ketorolac bolus q6h regimen in cohorts of healthy young and older (>/=65y of age) adults with no and with different degrees of renal impairment (Steigerwald et al, PAINWEEK 2019, abstracts 39 and 40)

FIGURE 1. PK RESULTS VS. MODELING IN A COHORT OF HEALTHY YOUNG VOLUNTEERS


Initial concentrations associated with I.V. loading dose of NTM-001 somewhat higher than predicted
Median actual NTM-001 exposure is approximately 13% lower
NTM-001: Loading dose 12.5 mg/ Infusion rate 3.5 mg/h – 24h
Generic ketorolac I.V. bolus, 30 mg/ q6 h – 24h
96.5 mg/24h
120 mg/24h
Conc mg/L
Hour
Plasma Concentration
Initial pain relief scores higher than predicted (more rapid onset)
Pain relief scores for NTM-001 overall very closet to prediction ~ 6% less over 48 h
Effect*
Time
Efficacy
Black Lines: Median +/- 95% CI from Original Modeling
Red Lines: Median +/- 95% CI from Modeling of Study Results
Neumentum, Inc., Data on file
*50% of patients are predicted to have a pain relief score of at least X percent of maximum

Published literature describing use of infusions of diluted IV ketorolac tromethamine also strongly supports the regimen of a loading dose followed by continuous infusion for safe and effective post-operative analgesia. We performed a systematic review of available literature related to trials that evaluated the efficacy and/or safety of continuous infusion ketorolac tromethamine for a period of 24 – 48 hours with a focus on adult patients.

METHODS

A PubMed literature search (2018) identified 100 potential references using the terms "ketorolac continuous infusion." Routes of administration included IV, SC, and IM for durations of generally 24 or 48 hours to treat postoperative pain. After sorting for relevance, 39 references were reviewed and evaluated with particular attention to potential toxicities involving gastrointestinal, cardiovascular, and renal systems as well as dosing regimens used or adjusted for elderly patients and/or those with other special risk factors for NSAID use. Of particular interest was whether the continuous infusion was preceded by a single bolus injection of ketorolac tromethamine as a loading dose to achieve therapeutic concentrations as quickly as possible.

The final review included 23 adult studies, 2 pediatric studies, and 2 review articles of previous continuous infusion studies in adults or in pediatric patients. Additional literature is quoted to point out specific aspects linked to the rationale for selection of the loading dose for NTM-001.

One study concentrated on cardiovascular safety following coronary artery bypass graft (CABG) surgery (Howard et al., 2016), and another study focused on renal safety in patients undergoing laparoscopic donor nephrectomy (LDN) or percutaneous nephrolithotomy (PNL) (Grimsby et al., 2012). Another study evaluated the pharmacokinetics of continuous SC infusion of ketorolac for 24 hours (Burdick et al., 2017).

Evidence on ketorolac postoperative continuous infusions lasting 24 to 48+ hours was studied in:

- 23 primary published papers involving adults (N = 3191)
- 2 primary published papers in children (N = 122)
- Overall total of 3313 subjects

The results in adult patients are summarized in this poster.

RESULTS

TABLE 3. TABULAR SUMMARY OF KETOROLAC CONTINUOUS INFUSION STUDIES

Ref.	N (total)	Mean Age (Yr)	Age ± SD (Yr)	Infusion Route	Max Bolus (mg)	Max Infusion Rate (mg/hr)	Total Daily Dose (max) (mg)	Infusion Duration (hr)	Effective (?)	Code
Howard (2018)	--									A
Burdick (2017)	12	32	±11	sc	0	5	120	24	--	B
Schwinghammer (2017)	191	65	±9	iv	30	3.6	120	48	V	
Howard (2016)	178	59	±8	iv	ǂ	3.6	90	24	NR	C
Grimsby (2012)	135	43	--	iv	0	3.6	86	24	V	D
Russo (2012)	80	38	±4	iv	0	3.75	90	24	V	
Jo (2011)	52	2	±1	iv	7.5	1.25	38	48	V	E
Becchi (2008)	70	71	±11	iv	0	2.4	58	48	V	
Pieri (2002)	585	65	±12	iv	0	3.75	90	48	V	
Barilaro (2001)	60	57	±10	iv	0	0.8	19	24	N	
Campbell (2000)	72	35	±7	sc	10.5	1.75	52.5	24-26	N	
Perttunen (1999)	30	41	--	iv	10	3.75	100	48	V	
Giannotti (1998)	300	58	±15	iv	30	3.75	120	24	V	
Kostamovaara (1998)	85	65	--	iv	30	5.8	120	16	V	
Shelbourne (1998)	313	--	--	iv	0	5	120	25	V	
Chiaretti (1997)	52	4	±5	iv	18	3.15	87	22	V	E
Forrest (1997)	--	≥1								F
O'Hara (1997)	191	43	±10	iv	30	2.5	140	24	V	G
Beatti (1997)	130	64	±13	iv	30	5	150	24	V	
Testa (1996)	36	--	--	iv	30	1.25	114	30	V	G
Etches (1995)	174	65	±1	iv	30	5	150	24	V	
Blackburn (1995)	60	42	--	iv	25	4	120	24	V	
Perlin (1994)	21	24	±5.4	iv	30	5	150	≤5 days	V	
Ready (1994)	207	44	±12	iv	30	5	150	24	V	
Varrassi (1994)	95	53	±1	iv	30	2	78	24	V	
Burns (1991)	63	47	--	im	6.25	2.5	65	48	V	
Kenny (1990)	60	--	--	im	12	3	84	24	V	
Gillies (1987)	61	50	±13	Im	24	3	96	24	V	

ǂoptional; NR=Not Reported
Codes: A=Review; B=PK; C=CV; D=Renal; E=Peds; F=Peds Review; G=PCA

TABLE 4. LITERATURE REVIEW OF KETOROLAC CONTINUOUS INFUSION FOR POSTOPERATIVE PAIN: SELECTED EXAMPLES - ARRANGED BY PUBLICATION DATE

Ref. / Indication/ Type of trial/	Subjects Treatment arms/Cohorts Analgesic co-medications	Ketorolac •Loading dose (mg) •Infusion (rate) •Infusion duration (hr)	Outcomes measures/Results: Efficacy/ Effectiveness	Outcomes measures/Results: Tolerability/ Safety
Schwinghammer (2017) Unilateral total knee arthroplasty (TKA) Retrospective, open-label, single center study (2011-2013)	Adults (N=191) Mean age= 65.3 ± 8.8 years (ketorolac group, n=116) 2 cohorts: ketorolac continuous infusion (n=116) vs. standard opioid protocol (n=75) PRN opioids in ketorolac group (i.v. morphine or hydromorphone q2h) PRN tramadol and NSAIDs in opioid protocol group	30 mg i.v. bolus 3.6 mg/hr i.v. Day 1 total dose = 120 mg ketorolac Day 2 total dose = 90 mg ketorolac No dose reduction for ≥65 y.o 48 hr	Median pain scores lower in the ketorolac infusion group at 48 hr post-operatively (3.0 vs. 3.5; p=0.033) 89% opioid sparing in ketorolac group: 34±39 mg morphine equivalent doses vs 302±37 mg. (p<0.001) 30 hr reduced LOS	Less respiratory depression (5.2% vs. 25.3%, p<0.001) Less naloxone (0% vs 8%, p=0.002) used in ketorolac group vs opioid group Other AEs similar.
Howard (2016) Postoperative isolated coronary artery bypass graft (CABG) surgery Cohort study	Adults (N=178) Mean age= 59 ± 8 years (ketorolac group)* •Ketorolac continuous infusion (n=89) vs. •no ketorolac (n=89)** optional concomitant analgesics	3.6 mg/hr i.v. (0.09 mg/L) Total daily dose = 90 mg i.v. ketorolac 24 hr	Primary outcome = mortality (hospital mortality + 30 day all-cause mortality) Secondary outcomes = risk of MI, bleeding, ↓ Hb, ↓ platelets Results = no increased risk of mortality, MI, or bleeding events in ketorolac infusion patients vs. controls	
Russo (2012) Major gynecological surgery RCT	Adults (N=80 women) Mean age = 38.4 ± 4.2 years (ketorolac infusion Group) Infusion vs. bolus arm Morphine 0.02 mg/kg/hr in both groups	None 3.75 mg/hr i.v. infusion (2 ml/h); comparison to i.v. ketorolac q8 hr Total daily dose = 90 mg i.v. ketorolac 24 hr	Better pain relief in bolus ketorolac group than in i.v. infusion group (without initial bolus)	None
Pieri (2002) Major abdominal surgery Observational study	Adults (N=585) Mean age = 65 ± 11.7 years 369M / 216 F 1 arm Tramadol 12.5 mg/hr i.v. Infusion combined with ketorolac	None (bolus 100 mg i.v. tramadol before end of surgery) 3.75 mg/hr i.v (2 ml/hr x 1.88 mg/mL) Total daily dose = 90 mg i.v. ketorolac. 48 hr	Effective pain control: • rest pain ≤3; • movement pain = 3-4.	Nausea (23%) Vomiting (8.5%)

*NOTE: ketorolac patients had lower Society of Thoracic Surgeons (STS) scores at entry than controls p=0.003); **NOTE: fewer ketorolac patients had on-pump surgeries (29%) vs. controls (79%; p=0.01) Retrospective single-center, five-year chart review (2008- 2012)

The following points summarize the literature review:

1. In adults, effective analgesia was reported in 21 studies with infusion rates of 1.3 to 5.8 mg/hr (median = 3.6 mg/hr). Two reports indicated that ketorolac infusion did not produce effective analgesia following infusion rates of 0.8 mg/hr or 1.75 mg/hr.

- **a.** Bolus doses of ketorolac (mean = 16.5 mg, median = 18 mg) were used in 18 of the 22 studies reporting favorable analgesia.
- **b.** Bolus doses were not used in either of the two studies reporting ineffective analgesia.

In non-infusion trials, bolus doses of 10/15/30 mg IV ketorolac provide adequate levels of analgesia for acute pain in the emergency room (Motov et al., 2017) without significant differences in efficacy:

- Motov et al conducted a randomized, double-blind trial to assess the analgesic efficacy of 3 doses of intravenous ketorolac (10, 15, and 30mg)
- in patients aged 18 to 65 years and presenting to the ED
- with moderate to severe acute pain, defined by a numeric rating scale score ≥ 5.
- 240 subjects (80 in each dose group) were enrolled
- At 30 minutes, substantial pain reduction was demonstrated without any differences between the groups. No relevant differences in use of rescue medication were observed.

FIGURE 2. IMPUTED PAIN SCORES FOR THE 10-, 15-, AND 30-MG KETOROLAC DOSE GROUPS OVER TIME (ADAPTED FROM MOTOV ET AL. 2017, SCHEMATIC

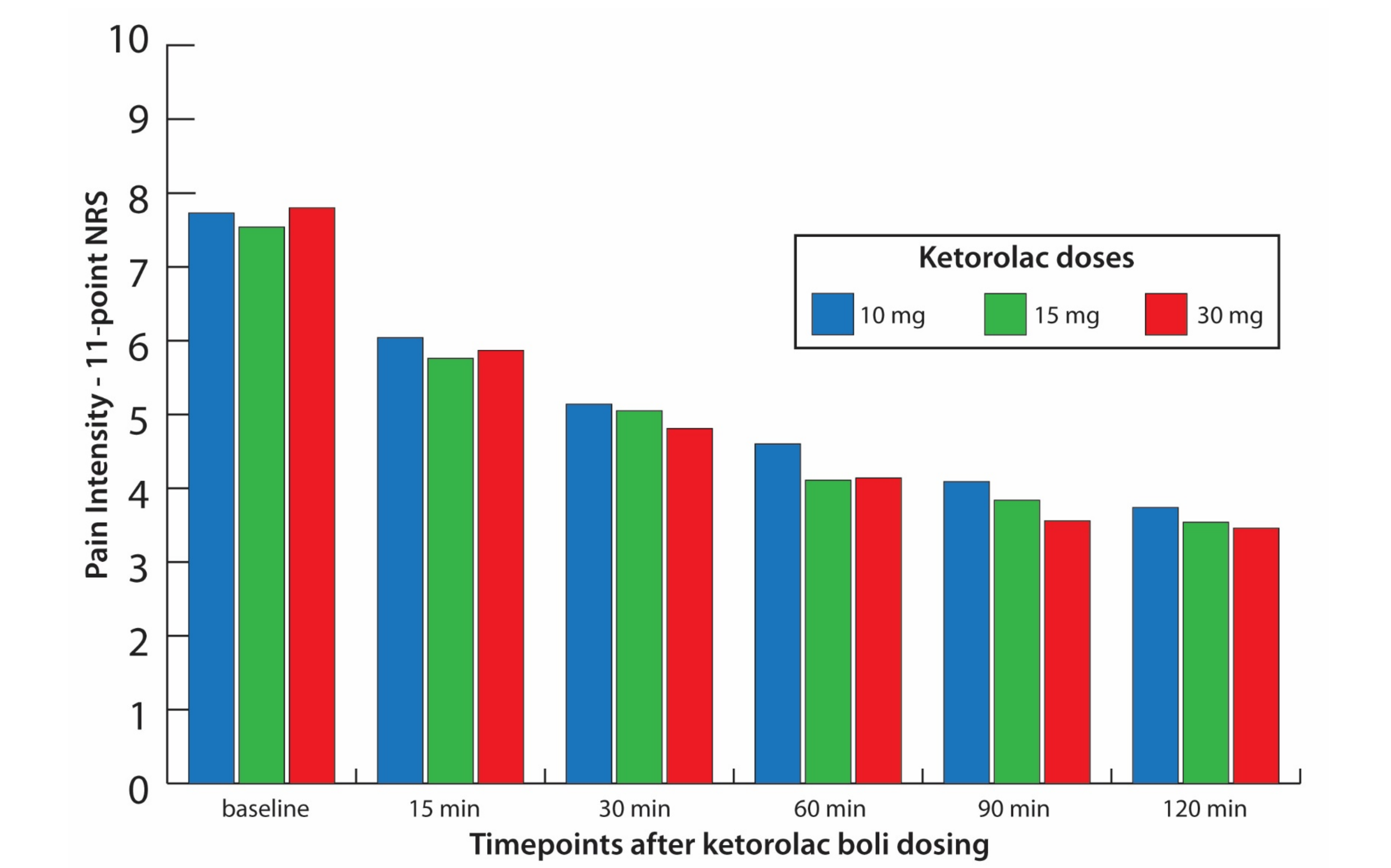
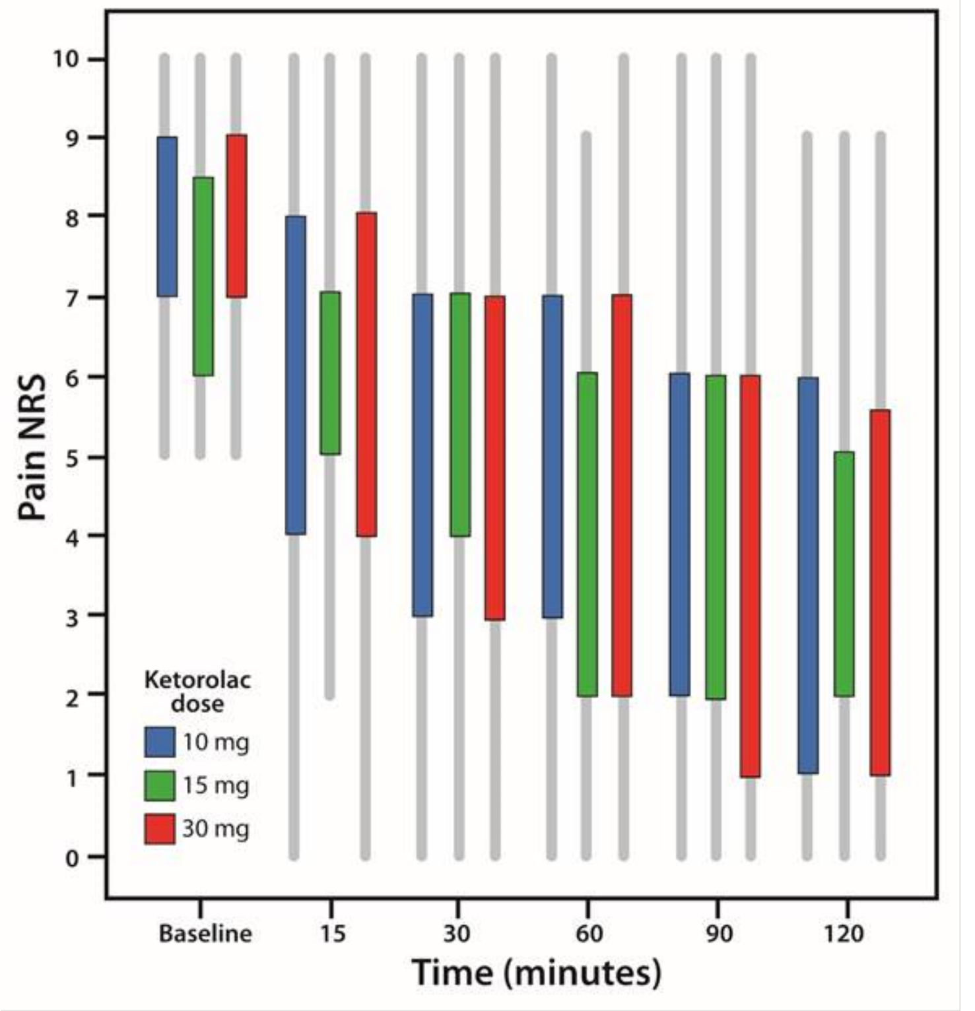


FIGURE 3. BOX-PLOTS FOR REPORTED PAIN NRS COMPARING DOSE GROUPS OVER TIME (ADAPTED FROM MOTOV ET AL., 2017)



According to the TORADOL Product Monograph (Roche, Canada 2015) "the greatest difference between large and small doses of TORADOL administered by either route is in the duration of analgesia."

2. In 10 adult studies, ketorolac infusion was reported to decrease opioid use by a range of 22 to 89% (mean = 42%; median = 37%).

3. Ketorolac plasma levels ranged from 0.4 to 2.2 µg/mL at 2 – 4 hr after an initial 10 mg IV bolus dose followed by 48 hr continuous IV infusion of ketorolac at 3.75 mg/hr. This is modestly lower than Cmax plasma levels of 2.2 – 3.0 µg/mL following a single 30 mg IM dose of ketorolac in healthy volunteers.

4. None of the reviewed 24 adult 24 – 48 hr continuous infusion references reported adverse GI, cardiovascular, or renal effects, nor clinically significant bleeding.

5. Many studies reported reductions in postoperative nausea and vomiting in ketorolac infusion compared to placebo groups when both were combined with rescue opioid analgesics. Reductions in postoperative nausea and vomiting may have been a consequence of reduced opioid consumption.

6. Beattie et al. (1997) reported nonfatal myocardial infarctions in 1 ketorolac subject and 2 placebo subjects following total hip or knee replacement; 21 subjects in this study had a history of previous myocardial infarctions. However, there were no differences in the number of ischemic episodes between ketorolac and placebo treatment groups, but ischemic episodes were shorter in subjects receiving ketorolac.

7. None of the studies reported dose reductions for elderly subjects or for those with renal, cardiovascular, or renal dysfunction as required by current IV/IM ketorolac labeling. However, as a caveat, most studies excluded subjects with severe renal, cardiovascular, GI, or renal disease.

CONCLUSION

- Published literature provides strong support for the efficacy of continuous infusion of ketorolac in adult postoperative patients for 24 to 48 hours following a variety of major surgical procedures.
- Our literature evaluation supports results from PK/PD modeling for NTM-001 that an initial loading dose is required to ensure a fast onset of analgesia following surgery.
- The variety of ketorolac loading dose regimens reflected in the analysis and further supportive evidence on bolus dosing suggest that loading doses lower than 30 mg are sufficient to reach effective plasma levels while avoiding unnecessary overexposure.
- Based on PK/PD modeling of different options for NTM-001 a loading dose of 12.5 mg has been selected as sufficiently effective, fast in onset, and safe for initiating analgesia in the postoperative setting.
- The infusion rate of 3.5 mg/hr proposed by modeling to maintain stable plasma levels and efficacy for 24 hours with NTM-001 is supported by literature (3.6 mg/h median).
- In line with published evidence, no increase but potentially a decrease of safety-related risks is anticipated with NTM-001 vs. a regular (30mg q6) IV ketorolac bolus regimen considering also lower overall (AUC/total daily dose) and peak (Cmax) exposure and a maximum duration of administration of 24 hours.

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Sources searched:

PubMed (www.ncbi.nlm.nih.gov/pubmed) search terms:

a."ketorolac infusion postoperative" = 116 hits, narrowed to 22 references examined for relevance (original search performed in 2013). b."ketorolac continuous infusion" = 100 hits, narrowed to 24 references examined for relevance (updated search performed in Feb. 2018). c.(ketorolac OR ibuprofen OR naproxen OR diclofenac OR indomethacin OR celecoxib OR parecoxib OR rofecoxib OR meloxicam) AND infusion AND (rest OR gap OR occupancy OR inhibition OR accommodation OR ulcers OR bleeding) = 699 hits; selected 17 with "infusion" in title; (updated search performed in Feb. 2018)

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