Office of Evidence Based Practice (EBP) – Critically Appraised Topic (CAT): ketorolac in gastric bypass patients and risk of bleeding

Specific Care Question

Does giving ketorolac to gastric bypass patients increase the risk of bleeding?

Recommendations from the XXXXX Team

Recommendations Based on Current Literature (Best Evidence) Only

No recommendation can be made for or against the use of ketorolac in pediatric bariatric surgery, based on the GRADE Evidence to Decision instrument[a] and the Summary of Findings Table[a]. The overall certainty in the evidence is very low[a]. The evidence does not demonstrate any differences of bleeding with or without the use of ketorolac.

When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.

Literature Summary

Background

In 2018 the percentage of obese children and adolescents aged 2 to 19 was 19.3%and the percent of severely obese children, and adolescents aged 2 to 18 was 6.1%(Fryar et al., 2020). As the need for bariatric surgeries increases in the pediatric population, anaesthesiologists find themselves reviewing alternatives for pain management due to the increase risk of respiratory depression and slowed bowel function in obese patients with use of narcotics (VanDercar et al., 1991). As narcotics are standard of care for pain control with adult patients undergoing bariatric surgeries, (Lujan et al., 2004; Paxton & Matthews, 2005), its use was adopted in pediatric bariatric surgical care. Patients recuperation from surgery is best managed with recovered airway reflexes, participation in respiratory therapies, ambulation, and bowel productivity, however, their pain must be controlled to complete these steps (Govindarajan et al., 2005). Using a non-opioid drug, for example, not only provides analgesia but minimizes the risk of side effects (Hariri et al., 2019). One non-opioid drug of interest is ketorolac as it shows benefit in managing post-operative pain without the undesirable side effects from opioids such as nausea, vomiting, constipation, and respiratory depression (Cassinelli et al., 2008; Garimella & Cellini, 2013; Stephens et al., 2015). However, debate continues regarding the use of ketorolac due to its side effect of gastrointestinal bleeding (Hariri et al., 2019).

This review will summarize identified literature to answer the specific care question on the use of ketorolac for pain management in bariatric surgeries and the increased risk for bleeding in the pediatric population.

Study Characteristics

The search for suitable studies was completed on July 12, 2021. C. Taylor, MD, and T. Glenski, MD, MSHA reviewed the nine titles and/or abstracts found in the search and identified[b] six single studies believed to answer the question. After an in-depth review of the identified studies[b], three were determined to answer the question. Three cohort studies (Bakhos et al., 2009; Hariri et al., 2019; Klein et al., 2012) answer the question of the use of ketorolac in bariatric patients and the impact of gastrointestinal bleeding.

Summary by Outcome

Risk of Post-operative Bleeding

Three studies (Bakhos et al., 2009; Hariri et al., 2019; Klein et al., 2012) measured incidence of gastrointestinal bleeding with the administration of ketorolac intra- or post-operatively with a bariatric surgery procedure (N = 1,849). Hariri et al. (2019) measured incidence of bleeding in bariatric surgical patients receiving ketorolac plus opioids post-operatively versus bariatric surgical patients receiving opioids only (n = 1,555). For the outcome of post-operation bleeding comparing the use of ketorolac plus opioid versus opioids only, the findings reported there was no difference, OR = *0*.44, 95% CI [0.17, 1.19], p = .11. Two studies (Bakhos et al., 2009; Klein et al., 2012) measured the incidence of bleeding in bariatric surgical patients post-operatively after receiving ketorolac versus no ketorolac (n = 294). For the outcome of post-operation bleeding with use of ketorolac versus no ketorolac, there was no difference, OR = 1.42, 95% CI [.65, 3.13], p = .38 (see Figure 2 & *Table 1*).

Certainty Of The Evidence For Risk of Bleeding. The certainty of the body of evidence was very low based on four factors[a]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have serious inconsistency due to moderate heterogeneity, I^2 = 57%and serious imprecision secondary to low number of events.

Identification of Studies

Search Strategy and Results (see Figure 1)

("Gastric Bypass"[Mesh] OR gastric bypass) AND ("Ketorolac"[Mesh] OR "Ketorolac Tromethamine"[Mesh] OR ketorolac)

Records identified through database searching *n* = 9

Additional records identified through other sources *n* = 0

Studies Included in this Review

Citation	Study Type
Bakhos et al., (2009)	Cohort
Hariri et al., (2019)	Cohort
Klein et al., (2012)	Cohort

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Feld et al., (2003)	Wrong outcome
Govindarajan et al., (2005)	Wrong outcome
Madan et al., (2005)	Wrong outcome

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings table(s) for this analysis.

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[c]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[d]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

[d]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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Acronyms Used in this Document

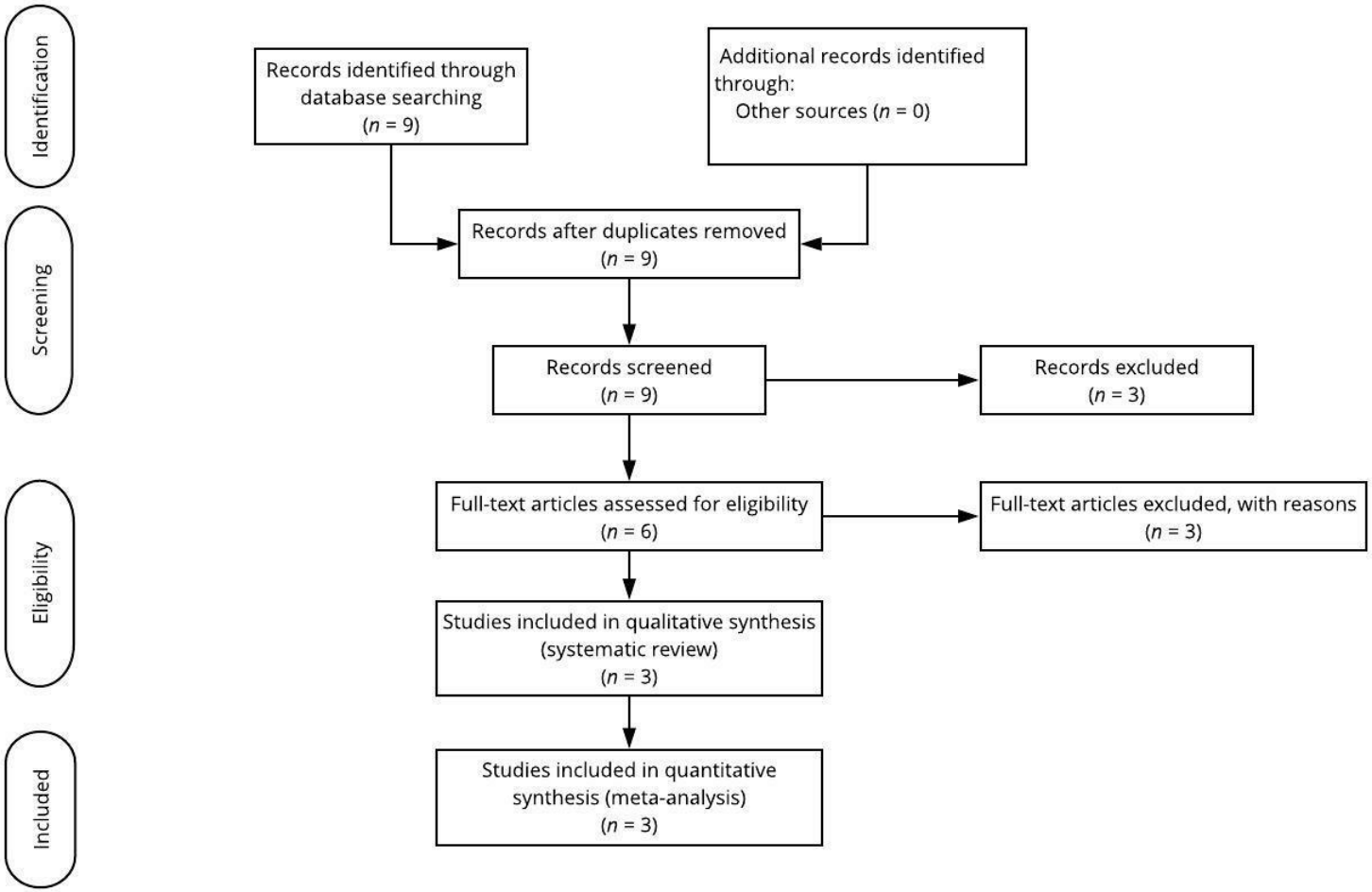
Acronym	Explanation
BMI	Body Mass Index
CAT	Critically Appraised Topic
CM	Children's Mercy
CPG	Clinical Practice Guideline
DVT	Deep vein thrombosis
EBP	Evidence Based Practice
GJ	Gastrostomy-Jejunostomy
IE	Internationale Enheder (Danish for International Units)
LMWH	Low-molecular weight heparin
NSAID	Non-steroidal anti-inflammatory drug
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RYGBP	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy

Statistical Acronyms Used in this Document

Statistical Acronym	Explanation
CI	Confidence Interval
I^2	Heterogeneity test
n	Number of cases in a subsample
N	Total number in sample
OR	Odds Ratio
P or p	Probability of success in a binary trial
SR	Systematic Review

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[d]



Summary of Findings Table

Table 1

Summary of Findings Table[c]: Ketorolac and bleeding

Question: Ketorolac compared to No Ketorolac for pain management
Setting: in patients undergoing bariatric surgery

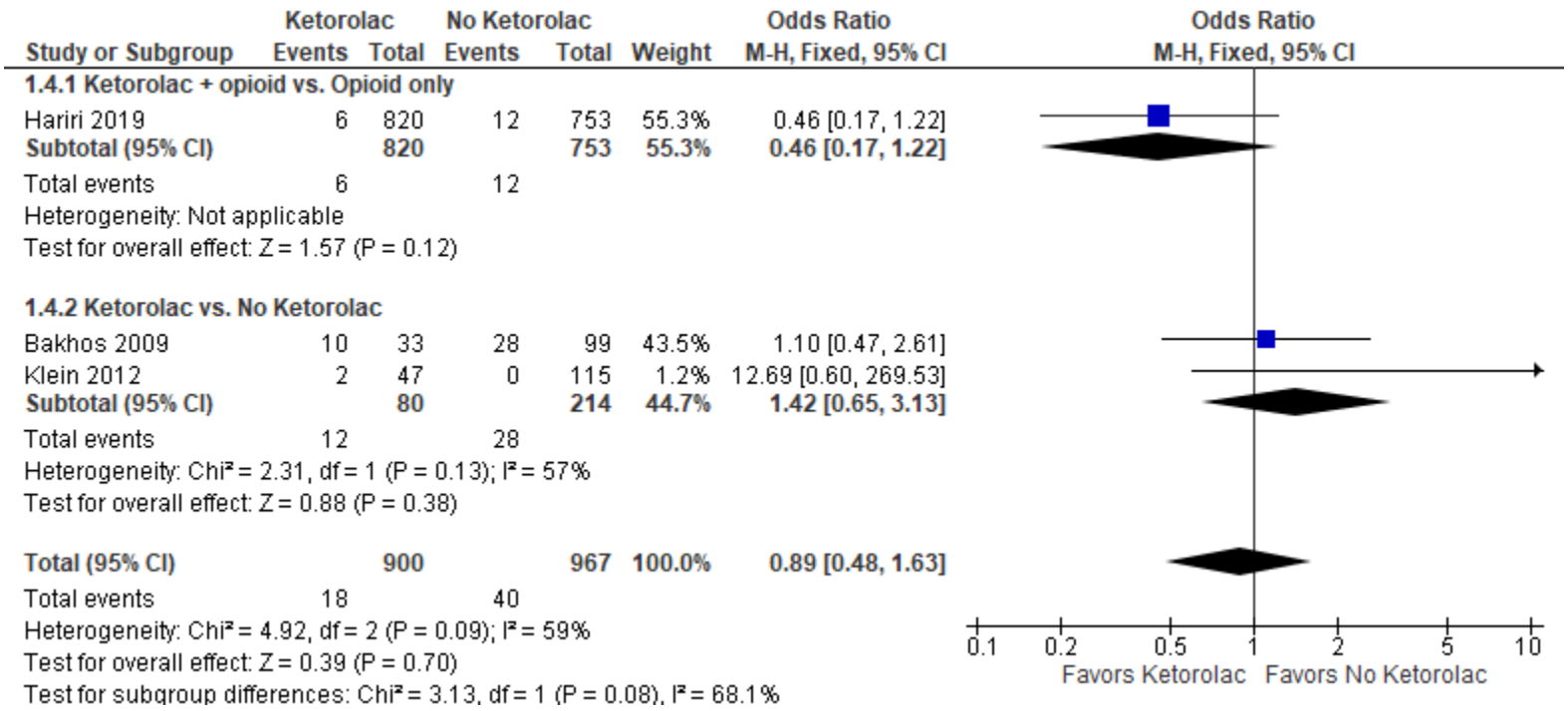
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketorolac	No Ketorolac	Relative (95% CI)	Absolute (95% CI)		
Bleeding												
3	observational studies	not serious	serious [a]	not serious	serious [b]	none	18/900 (2.0%)	40/967 (4.1%)	**OR 0.89** (0.48 to 1.63)	**4 fewer per 1,000** (from 21 fewer to 24 more)	⨁◯◯◯ VERY LOW	

Explanations
a. Heterogeneity is moderate at 57%
b. limited number of events

Meta-analysis

Figure 2

Comparison: Ketorolac versus No Ketorolac, Outcome: Bleeding



Characteristics of Observational Studies

Bakhos et al., 2009

Methods	Retrospective Cohort
Participants	**Participants:** Adults undergoing laparoscopic or open Roux-en-Y gastric bypass (RYGBP), 2003-2005 **Setting:** USA, CT, 511 bed teaching hospital **Number of patients who underwent procedure during timeframe:** *N* = 1025 • **Group 1:** Patients who experienced significant post op bleeding: *n* = 33 • **Group 2:** Patients who did not experience significant post-op bleeding: *n* = 99 (this is reported as a random sample of the total 1025 patients) **Gender, males** (as defined by researchers): • **Group 1:** 21% • **Group 2:** 18% **Race / ethnicity or nationality (as defined by researchers):** • Not specified for this study **Age, mean/median in years:** • **Group 1:** 47.5 +/-8.7 • **Group 2:** 42.8+/-10.8 **Inclusion Criteria:** • Patients who underwent an open or laparoscopic RYGBP for elevated BMI **Exclusion Criteria:** • None mentioned **Covariates Identified:** • Use of pre/post op deep vein thrombosis (DVT) prophylaxis (lovenox or heparin) • Use of post op ketorolac
Interventions	• The medical records of patients who required postoperative blood transfusions were reviewed for clinical presentation, diagnostic evaluation, and management • Patients were matched for surgical approach (open vs. laparoscopic) in a 1:3 ratio and compared to a random group of patients who underwent RYGBP during the same time frame
Outcomes	**Primary Outcome:** • Review the incidence and management of bleeding post-operative

	• Identify contributing clinical and technical risk factors **Secondary Outcome:** • *Bleeding with Ketorolac *Outcome of interest

Notes	• Postop Ketorolac (number of patients given Ketorolac) *p*-value = .82
	  ○ Bleeding Group: *n* = 10 (30%)
	  ○ Nonbleeding group: *n* = 28 (28%)
	• Total number of patients who underwent RYGBP during study period = 1025
	• Total number of patients included in statistical calculations = 132
	• It appears that the non-bleeding group was a random sampling of the entire nonbleeding RYGBP population that was "control matched" for statistical purposes
	• This study reflects several surgical techniques, including laparoscope, open, different GJ anastomoses technique, different staplers, etc.
	• There were five different surgeons, each of whom had their preferred technique
	• Each surgeon had different preferences for administered dose of DVT prophylaxis

Hariri et al., 2019

Methods	**Retrospective Cohort**
Participants	**Participants:** 1555 obese individuals undergoing sleeve gastrectomy (SG) or Roux-en-Y gastric bypass surgery (RYGB) between 2011 and 2015 **Setting:** USA, Tertiary Academic Medical Center **Number enrolled into study:** *N* = 1,555 • **Group 1, Ketorolac-Opioid:** *n* = 820 • **Group 2, Opioid Only:** *n* = 735 **Gender, males:** • **Group 1:** *n* = 184 (22.3%) • **Group 2:** *n* = 187 (25.4%) **Race / ethnicity or nationality:** • **White** ○ **Group 1:** *n* = 437 (53.5%) ○ **Group 2:** *n* = 469 (63.8%) • **Black/African American** ○ **Group 1:** *n* = 178 (21.7%) ○ **Group 2:** *n* = 127 (17.3%) • **Unknown/not reported/other** ○ **Group 1:** *n* = 205 (25%) ○ **Group 2:** *n* = 139 (18.9%) **Age, mean years + SD,** • **Group 1:** 41.1 + 12 • **Group 2:** 41.6 + 12.3 **Inclusion Criteria:** • Adults 18 years and greater • Undergoing SG or RYGB **Exclusion Criteria:** • Hospital length of stay greater than 6 days **Covariates Identified:** • Not reported
Interventions	• **Group 1:** Prescribed ketorolac in addition to opioids (morphine or hydromorphone) • **Group 2:** Prescribed opioids only (morphine or hydromorphone)

Outcomes	**Primary outcome(s):** • Opioid consumption • LOS • *Bleeding risk ***Outcomes of interest**
Notes	**Limitations:** • Retrospective study Second • Findings may be unique to this patient population. • Authors did not perform detailed analysis in patients with and without clinically significant post-operative bleeding for the entire cohort. • This study relates only to the effects of ketorolac on bleeding: other side effects, such as gastric or marginal ulcer, or leaks, were not studied.

Klein et al., 2012

Methods	**Retrospective Cohort**
Participants	**Participants:** Adult patients undergoing Laparoscopic Roux-En-Y Gastric By-Pass Surgery, between January 1, 2020, and March 1, 2010 **Setting:** Denmark **Number enrolled into study:** *N* = 162 • **Group 1, Intraoperative ketorolac:** *n* = 47 • **Group 2, Standard of care without ketorolac:** *n* = 115 **Gender, males (as defined by researchers):** • **Group 1:** *n* = 26% • **Group 2:** *n* = 17% **Race / ethnicity or nationality (as defined by researchers):** • Not reported **Age, mean in years** • **Group 1:** *n* = 38 ± 11 • **Group 2:** *n* = 40 ± 11 **Inclusion Criteria:** • Consecutive patients undergoing laparoscopic Roux-En-Y gastric by-pass surgery **Exclusion Criteria:** • None reported **Covariates Identified:** • Low-molecular weight heparin
Interventions	**Both:** Prior to surgery any non-steroidal anti-inflammatory drug (NSAID) treatment was discontinued at least one week preoperatively. Anticoagulation therapy, if present, was substituted with the low-molecular weight heparin (LMWH) 4000 IE daily three days prior to the procedure. For the remaining patients, dalteparin 4000 IE was administered only once pre-operatively and on the first postoperative day. Post-op transfusions were prescribed if hemoglobin level were below 4.5 mmol/l in otherwise healthy patients, and below 6.0 mmol/l in patients with cardiac co-morbidities or if the patients had symptoms of anemia. • **Group 1:** The first 47 patients operated in the given period received intravenous ketorolac 30 mg 5-10 minutes before the end of surgery • **Group 2:** Standard of care without ketorolac

Outcomes	**Primary outcome(s):** • *Hemoglobin change • Duration of surgery • Crystalloid fluid treatment • Bleeding requiring surgical intervention • *Bleeding requiring transfusion • *Length of postoperative stay *Outcomes of interest

Notes	**Results:**
	
	Length of Postoperative Stay: *p*-value = .24
	• **Group 1:**
	  ○ 1 day: *n* = 40
	  ○ 2 days: *n* = 3
	  ○ 3+ days: *n* = 4
	• **Group 2:**
	  ○ 1 day: *n* = 103
	  ○ 2 days: *n* = 9
	  ○ 3+ days: *n* = 3

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