Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Use in the Critically Ill: A Scoping Review

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INTRODUCTION

- Opioids in the acute care setting have well known adverse effects including constipation, central nervous system and respiratory depression, and opioid use disorder with prolonged inappropriate use. [1]
- Despite the recommendation from current clinical practice guidelines to use opioid-sparing therapies such as NSAIDs, adverse effects including gastrointestinal bleeding and acute kidney injury may be amplified in the critically ill. [2]
- The purpose of this scoping review is to conduct a thorough search of the current literature concerning NSAID adverse effects in critically ill patients.

OBJECTIVES

- Our aim is to collect data on the rate and types of NSAID adverse effects in this patient population in order to help guide therapy recommendations and monitoring parameters. We also intend to provide information on gaps in the literature to guide further research and clinical decision making concerning NSAID use in critically ill patients.

METHODS

- **Protocol and Registration:** The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) was used with the help of the University librarian.
- **Eligibility Criteria:** Literature included were randomized control trials, case series, and retrospective studies. Case reports, letters, review articles, and commentaries and studies restricted to patients in emergency medicine settings were excluded. The focus was on critically ill patient populations.
- **Information Resources**: From January 2016 to January 2020 the databases used include: PubMed, Cochrane Library, EMBASE, Stat!Ref, Access Pharmacy. The search strategies were drafted by the librarian refined through team discussion. Duplications were removed on Mendeley. Other consulting sources guidelines supplemented the search: Society of Critical Care Medicine (SCCM), American Pain Society Guidelines (APS), American Thoracic Society (ATS), and American College of Chest Physicians (ACCP), 2020 ACS TQP best practice guidelines.
- **Data Analysis and Synthesis of Results:** After an initial screening, full text-articles were assessed for eligibility. See attached PRISMA diagram for a depiction of the process used in the synthesis of information for this scoping review (Figure 1). NSAIDs that were included could be any NSAID commercially available in the United States or internationally with mention of an adverse reaction that could be associated with NSAID use.

RESULTS

Figure 1

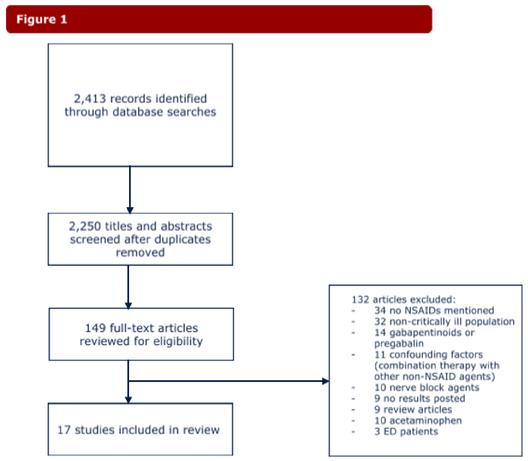

Table 1: Study Characteristics

References	Opioid	Adjuvant Used	Duration	Patient Subgroup	Mean Age (years) Intervention group	% Female patients intervention group
Arslans et al. (10)	Tramadol IV	Diclofenac IM	24hr	Surgical-cardiac	56	16%
Bakr et al. (11)	Morphine IV	Ketorolac IV	24hr	Surgical-oncology	46	100%
Bergese et al. (12)	None	Meloxicam IV	28hr	Surgical-orthopedic	53	58%
Camu et al. (13)	Morphine IV	Parecoxib IV	48hr	Surgical-orthopedic	65	42%
Claus et al. (14)	None	Ketorolac IV	48hr	Surgical-orthopedic	61	53%
Dehghanpisheh et al. (15)	None	Ketorolac IV	12hr	Surgical-general	26	100%
Eftekharian HR et al. (16)	None	Ketorolac IV	4hr	Surgical-mandibular	30	40%
Eljezi et al. (17)	Morphine IV	Ketoprofen IV	48hr	Surgical-cardiac	61	16%
Erdogan et al. (18)	Morphine IV	Ibuprofen IV	24hr	Surgical-bariatric	37	34%
Liu et al. (19)	Morphine IV	Parecoxib IV	5days	Surgical-general	63	38%
Liu et al. (20)	Morphine*	Diclofenac*	28days	Critical illness-oncology	55	45%
	Morphine*	Celecoxib PO	28days	Critical illness-oncology	54	44%
Mu et al. (21)	Morphine IV	Parecoxib IV	5days	Surgical-orthopedic	69	74%
Sivasundaram et al. (22)	Oxycodone-APAP	Ketorolac IV	5days	Surgical-orthopedic	56	25%
	Oxycodone-APAP	Ketorolac PO	5days	Surgical-orthopedic	56	25%
Wang et al. (23)	Fentanyl IV	Parecoxib IV	48hr	Surgical-hepatic	55	17%
Winkler et al. (24)	None	Etoricoxib PO	9days	Surgical-orthopedic	62	46%
	None	Diclofenac PO	9days	Surgical-orthopedic	60	47%

*Unspecified administration route

Table 2: Adverse Events

Study Name	Adverse Event	Adjuvant Group	Control Group
Ketorolac			
Bakr 2016	N/V	0/20	N/A
	Respiratory depression	0/20	N/A
Claus 2022	AKI	2/119	2/127
	Wound hematoma	1/119	0/127
Dehghanpisheh 2021	Hypotension	16/49	16/48
	Bradycardia	3/49	4/49
Sivasundaram 2021	N/V	2/20	2/19
	Abdominal pain	1/20	0/19
	Drowsiness	1/20	4/19
	Insomnia	2/20	1/19
	Headache	2/10	1/19
Diclofenac			
Arslans 2018	N/V	3/50	5/50
Liu 2017	Nausea	15/111	N/A
	Dizziness	31/111	N/A
	Constipation	35/111	N/A
	Drowsiness	46/111	N/A
	Respiratory inhibition	6/111	N/A
	Peripheral edema	3/111	N/A
Winkler 2015	Nausea	6/50	N/A
	Vomiting	4/50	N/A
	Dizziness	4/50	N/A
	Diarrhea	3/50	N/A
	Hypertension	2/50	N/A
Meloxicam			
Bergese 2018	Nausea	123/539	51/183
	Constipation	51/539	17/183
	Vomiting	27/539	14/183
	Bleeding	26/539	7/183
	Hepatic	35/539	15/183
	Wound Healing Complications	31/539	7/183
Celecoxib			
Liu 2017	Nausea	17/115	N/A
	Dizziness	30/115	N/A
	Constipation	36/115	N/A
	Drowsiness	43/115	N/A
	Respiratory inhibition	6/115	N/A
	Peripheral edema	1/115	N/A
Etoricoxib			
Winkler 2015	Nausea	7/50	N/A
	Vomiting	5/50	N/A
	Dizziness	1/50	N/A
	Diarrhea	2/50	N/A
	Hypertension	2/50	N/A
Parecoxib			
Camu 2017	Hypotension	2/72	0/38
	Fever	5/72	7/38
	Nausea	34/72	22/38
	Vomiting	19/70	11/38
Mu 2017	Delirium	19/310	34/310
Wang 2020	N/V	6/40	10/40
	Pruritus	2/40	3/40
	Hypotension	1/40	1/40
	Respiratory depression	0/40	0/40
	Wound infection	3/40	4/40
	Lung infection	1/40	2/40
Ketoprofen			
Eljezi 2017	Nausea	4/25	5/23
	Vomiting	1/25	5/23
	Delayed acute renal insufficiency	3/25	3/25
	Fever	5/25	5/25
Ibuprofen			
Erdogan 2018	N/V	24/35	28/39
	Headache	7/35	7/39
	Dizziness	15/35	6/39
	Dyspepsia	7/35	7/39

DISCUSSION

- The results of this scoping review demonstrate a paucity of evidence supporting the safety of NSAIDs in critically ill patients and lend support to the recommendation in the most recent SCCM PADIS clinical practice guideline to avoid routine use of COX-1 selective NSAIDs as adjuncts to opioid therapy in critically ill patients. [2]
- None of the available studies evaluated an NSAID in a heterogeneous critically ill population, but instead most of the investigations were limited to postoperative cardiac surgery patients. Of the limited studies involving NSAIDs available in an injectable form, some involved products such as ketoprofen that do not have an injectable formulation approved for human use in the US.
- Other issues common to all of the published studies include the difficulty in attribution of adverse drug events given the frequent occurrence of complications such as bleeding and acute kidney injury in critically ill patients and limited duration of NSAID administration. For these reasons, our findings suggest that the SCCM PADIS recommendation is applicable to all NSAIDs, not just COX-1 selective agents.
- The SCCM PADIS clinical practice guideline has a conditional recommendation based on low quality evidence, which states that NSAIDs (by a variety of routes) are alternatives to opioids for discrete or infrequent procedures. The basis for this suggestion is one study in which patients were randomized to a single 4 mg dose of IV morphine or a single 30 mg dose of IV ketorolac for alleviating pain in association with chest tube removal in patients on a cardiac surgery service. [3] We recommend caution in extrapolating the results of this single study to heterogeneous critically ill patients.
- The primary limitations of this scoping review are similar to those of other systematic and scoping reviews, which include the potential for missing studies or publication bias due to unpublished investigations.

CONCLUSION

- In most, if not all, critically ill patients, it is best to avoid NSAIDs regardless of COX-1 selectivity given that that there is insufficient evidence to conclude that NSAIDs have an acceptable safety profile in heterogeneous critically ill patient populations predisposed to complications such as bleeding and acute kidney injury.

REFERENCES

1. Erstad BL, Puntillo K, Gilbert HC, et al. Pain management principles in the critically ill. Chest. 2009;135(4):1075-1086. doi:10.1378/chest.08-2264
2. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825-e873. doi:10.1097/CCM.0000000000003299.
3. Puntillo K, Ley SJ. Appropriately timed analgesics control pain due to chest tube removal. Am J Crit Care. 2004 Jul;13(4):292-301.