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REPORTS OF ORIGINAL INVESTIGATIONS

Nonsteroidal anti-inflammatory drugs for analgesia in intensive care units: a survey of Canadian critical care physicians

Anti-inflammatoires non stéroïdiens pour l'analgésie dans les unités de soins intensifs : un sondage auprès des médecins intensivistes au Canada

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Abstract

Purpose *Opioids remain the mainstay of analgesia for critically ill patients, but its exposure is associated with negative effects including persistent use after discharge. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be an effective alternative to opioids with fewer adverse effects. We aimed to describe beliefs and attitudes towards the use of NSAIDs in adult intensive care units (ICUs).*

Methods *Our survey of Canadian ICU physicians was conducted using a web-based platform and distributed through the Canadian Critical Care Society (CCCS) email distribution list. We used previously described survey development methodology including question generation and reduction, pretesting, and clinical sensibility and pilot testing.*

Results *We received 115 completed surveys from 321 CCCS members (36%). Nonsteroidal anti-inflammatory drugs use was most described as "rarely" (59 respondents, 51%) with the primary concern being adverse events (acute kidney injury [108 respondents, 94%] and gastrointestinal bleeding [92 respondents, 80%]). The primary preferred analgesic was acetaminophen (75 respondents, 65%) followed by opioids (40 respondents, 35%). Most respondents (91 respondents, 80%) would be willing to participate in a randomized controlled trial examining NSAID use in critical care.*

Conclusions *In our survey, Canadian critical care physicians did not mention commonly using NSAIDs primarily because of concerns about adverse events. Nevertheless, respondents were interested in further studying ketorolac, a commonly used NSAID outside of the ICU, in critically ill patients.*

Résumé

Objectif *Les opioïdes restent le pilier de l'analgésie pour les patient·es gravement malades, mais l'exposition à ces agents est associée à des effets négatifs, notamment à leur utilisation persistante après le congé de l'hôpital. Les anti-inflammatoires non stéroïdiens (AINS) pourraient constituer une alternative efficace aux opioïdes avec moins d'effets indésirables. Nous avons cherché à décrire les croyances et les attitudes à l'égard de l'utilisation des AINS dans les unités de soins intensifs (USI) pour adultes.*

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Méthode *Notre sondage auprès des médecins intensivistes au Canada a été mené à l'aide d'une plateforme Web et distribué aux personnes sur la liste de distribution électronique de la Société canadienne de soins intensifs (SCSI). Nous avons utilisé une méthodologie d'élaboration d'enquêtes décrite précédemment, y compris la génération et la réduction de questions, les tests préalables, la sensibilité clinique et les tests pilotes.*

Résultats *Nous avons reçu 115 sondages remplis par 321 membres de la SCSI (36 %). L'utilisation d'anti-inflammatoires non stéroïdiens a été décrite comme « rare » (59 répondant·es, 51 %), la principale préoccupation étant les événements indésirables (insuffisance rénale aiguë [108 répondant·es, 94 %] et saignements gastro-intestinaux [92 répondant·es, 80 %]). Le principal analgésique préféré était l'acétaminophène (75 répondant·es, 65 %), suivi des opioïdes (40 répondant·es, 35 %). La plupart des répondant·es (91 répondant·es, 80 %) seraient prêt·es à participer à une étude randomisée contrôlée examinant l'utilisation des AINS en soins intensifs.*

Conclusion *Dans notre sondage, les médecins intensivistes au Canada n'ont pas mentionné l'utilisation courante d'AINS, principalement en raison de préoccupations concernant leurs effets indésirables. Néanmoins, les répondant·es étaient intéressé·es à étudier plus avant le kétorolac, un AINS couramment utilisé en dehors des soins intensifs, chez les patient·es gravement malades.*

Keywords critical care · ketorolac · morbidity · mortality · NSAIDs · pain control

Opiates are a mainstay of analgesia in critical care to facilitate pain control and augment sedation given the burden of distressing symptoms commonly experienced by critically ill patients.[1,2] Opioid exposure in hospital is associated with an increased risk of adverse events such as respiratory depression, opioid toxicity, and iatrogenic withdrawal[3–6] along with increased duration of mechanical ventilation and hospital length of stay.[7] Based on large, population-based studies, 20% of previously opioid-naive patients are discharged home with new opioid prescriptions[8] and approximately 5% of opioid-naive intensive care unit (ICU) patients develop persistent opioid use within one year of their index ICU stay.[8–10] The use of adjunctive analgesic medications such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) is effective in reducing opioid usage and associated adverse effects.[11–13] In fact, guidelines from the American Society of Anesthesiologists strongly recommend that patients receive multimodal analgesia.[14]

Nonsteroidal anti-inflammatory drugs block cyclooxygenase (COX) enzymes, which decreases prostaglandin production to ultimately reduce pain.[15] They are used frequently in the emergency department, operating room, and recovery unit.[16–18] Ketorolac, a commonly used NSAID, has been shown to have similar analgesic effects and decreased adverse effects at lower doses compared with higher doses,[19] and has a Health Canada indication for short-term management of acute pain.[20] Nevertheless, recent guidelines from the Society of Critical Care Medicine (SCCM) provided a weak recommendation against the use of NSAIDs, citing only mild reduction in opioid use and a theoretically increased risk of adverse outcomes including acute kidney injury (AKI) and gastrointestinal bleeding.[2] Since these guidelines were published, new evidence suggests that the opioid-sparing effect of NSAIDs may have been understated, while the risk of adverse outcomes may have been overstated.[11,21]

Management of acute pain is a highly variable practice,[22,23] although there is limited evidence on current analgesic prescribing practices of Canadian ICU physicians nor their level of comfort in using them in critically ill patients. To help clarify this gap in the knowledge, we conducted a survey to describe the beliefs and opinions regarding multimodal analgesia, specifically NSAID use, of Canadian intensive care physicians practicing in adult critical care settings. We intended to establish whether equipoise exists for NSAID use in ICUs and to determine the comfort of clinicians to enrol patients in an eventual clinical trial to explore the safety and utility of NSAIDs as part of multimodal analgesia in critically ill patients.

Methods

Research question

Our research question was the following: for critical care physicians looking after adult critically ill patients who have pain, what are the opinions and believed practices regarding the use of NSAIDs as adjuncts to pain management?

Our aims were to: 1) gather information and the perspectives of critical care physicians regarding NSAID use in the adult, critically ill patient population for analgesia; 2) determine if equipoise exists for NSAID use in ICUs; and 3) determine ICU providers' comfort to randomize critically ill patients to various ketorolac treatment regimens.

Working definitions

We used Statistics Canada[24] definitions for centre population size (small, 1,000–29,999 residents; medium, 30,000–199,999 residents; large, > 200,000 residents). We used Canadia Institute of Health Information definitions for academic (confirmed teaching status by Canadian government) *vs* community hospitals;[25] "community hospital" was defined as a hospital that provides a range of services to a local community, is led by community-based health professionals, and provides inpatient beds.[26]

We defined equipoise as a disagreement at the level of a community of physicians.[27] Randomized controlled trials (RCTs) involving human participants ethically require a level of equipoise of < 80% (80:20 distribution of uncertainty) to ensure patients have equal chance of benefits or potential harm by participating.[28] Using this standard, an agreement of < 80% of responses would indicate equipoise, and > 80% agreement would mean that no equipoise exists.

Design, setting, and population

Our study is a survey of Canadian ICU physicians. We recruited survey participants through e-mail advertisement using the Canadian Critical Care Society (CCCS) e-mail list, which includes mainly Canadian intensivists although is open to residents, nonintensivists, and non-Canadian members. Prior to completing the survey, respondents were provided with the study purpose and consent information specifying the target population as critical care physicians/intensivists. This survey was distributed with support from the Alberta Critical Care Strategic Clinical Network™ and the Canadian Critical Care Trials Group (CCCTG).

Ethical considerations

We received a delegated research ethics board review from the University of Alberta Research Ethics Office (Edmonton, AB, Canada; Pro00121949). All respondents provided implied consent by electronically participating in the survey. We ensured that all survey data were anonymous and deidentified. All data were housed in encrypted files on password-protected computers.

Survey methodology

We conducted a cross-sectional survey of Canadian ICU providers. We used standard survey development methodology[26] to design our survey, in accordance with the following steps.

Item generation and reduction

Items were generated through a combination of literature review and discussion with coauthors. Key themes identified included current analgesia practices, limiting factors of NSAID use in the ICU, and considerations for a potential RCT. Using these themes, we drafted an extensive list of questions for the proposed survey and invited several coauthors, including members of the CCCTG and intensivists, to review and provide feedback on the accuracy and relevance of the survey content and questions. We removed similar or duplicate questions.

Pretesting and clinical sensibility testing

We distributed the surveys to all study coauthors, which then included 15 questions. We asked pretesters to review the survey to ensure that each question's content was comprehensible, accurate, comprehensive, and likely to yield pertinent information regarding the attitudes and opinions of participants. We then modified the survey after a single round/stage according to the feedback provided (see eAppendix for survey questions).

Pilot testing

We conducted pilot testing of the survey among five intensivists across Canada. We then reviewed the comments to identify if certain questions were not clear to participants, with final modifications to the survey completed prior to survey distribution through the SurveyMonkey® platform (SurveyMonkey Inc., San Mateo, CA, USA).

Survey administration

We distributed the survey through the CCCS mailing listservs. The survey remained open from 1 September 2022 to 31 December 2022, with three e-mail reminders sent out to survey participants.

At the time of the study distribution, there were 321 members of the CCCS. We aimed to obtain a response rate of > 30%, like other nonincentivized, web-based surveys of health care providers.[30,31]

Data analysis

We used Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA) to produce descriptive statistics that summarize the characteristics of respondents (frequency for nominal and ordinal variables) and cross-tabulate results. We summarized aggregate responses to questions related to NSAID use across the entire sample.

Results

Study baseline characteristics

We had 115 respondents out of 321 members (36%) from the CCCS with all respondents completing 100% of the survey. Baseline demographic characteristics of respondents are summarized in Table 1.

Most respondents' primary specialty in their clinical practice was medical (78 respondents, 68%) (Table 1). The experience in critical care practice varied, with 32% (37 respondents) having 0–4 years' experience, 23% (26 respondents) having 5–10 years' experience, 23% (25 respondents) having 11–15 years' experience, and 24% (27 respondents) having > 16 years' experience. Participants primarily worked in academic centres (92 respondents, 80%), academic community centres (13 respondents, 11%), and community centres (10 respondents, 9%). The total number of critical care beds in the participant's primary practice setting was 31–50 beds (47 respondents, 41%), 16–30 beds (38 respondents, 33%), > 50 beds (17 respondents, 15%), 10–15 beds (11 respondents, 10%), and 0–9 beds (2 respondents, 2%). The majority responded that their primary practice setting had the research infrastructure to participate in clinical trials, with 102 respondents (89%) reporting yes and 12 respondents (11%) reporting no.

Beliefs towards the use of NSAIDs

The frequency of NSAID use was most reported as rarely, defined as 1–19% of the time, (59 respondents, 51%), followed by sometimes, defined as 20–39% of the time (35 respondents, 30%), and never (11 respondents, 10%). The most common factors that would make respondents more likely to use NSAIDs as a first-line analgesic or adjunct include the patient having another indication for NSAID use (e.g., pericarditis) (46 respondents, 40%), musculoskeletal pain (30 respondents, 26%), and trauma (16 respondents, 14%). The most important reported factor limiting the use of NSAIDs in critically ill patients was side effects, with the primary adverse events of concern being AKI (108 respondents, 94%), gastrointestinal bleeding (92 respondents, 80%), other bleeding/coagulopathy (53 respondents, 46%), and interactions with other medications (33 respondents, 29%).

Beliefs on first-line analgesics

The most common first-line analgesic used by respondents was acetaminophen (75 respondents, 65%) followed by opioids (40 respondents, 35%). Other analgesics (NSAIDs, tramadol, meperidine, ketamine, lidocaine, antidepressants/anticonvulsants) were not selected as first-line analgesics by any respondents. Reported second-line analgesics were opioids (69 respondents, 60%), acetaminophen (24 respondents, 21%), and NSAIDs (11 respondents, 10%).

A further summary of opinions of respondents on first-line analgesia, on the use of NSAIDs, and on the considerations of use of NSAIDs in critically ill adult patients can be found in the Electronic Supplementary Material (ESM) eTable 1 and eFigs 1 and 2.

Willingness for an eventual clinical trial

The majority of respondents ($N = 114$) indicated that they would be willing to enrol patients in an RCT (91 respondents, 80%) examining the use of ketorolac as an adjunctive analgesic, as seen in the Figure. Eighteen respondents (16%) answered "maybe," with comments specifying cautious exclusion criteria (i.e., older patients, patients with diabetes), need for further information before making a decision, and hesitation due to adverse events. The majority indicated that it is more important to study NSAIDs as adjunctive analgesics (80 respondents, 70%) rather than a primary analgesic (16 respondents, 14%). The most frequent groups of patients that respondents would not feel comfortable enrolling in such an RCT included those with a known allergy to NSAIDs (97 respondents, 84%), those with active bleeding (90 respondents, 78%), known peptic ulcer disease (84 respondents, 73%), or renal impairment (i.e., estimated glomerular filtration rate of < 40 mL·min·1.73 m^{-2}) (83 respondents, 72%).

Table 2 displays respondents' preference for ketorolac dosing and duration in a proposed RCT. The majority of respondents suggested 15 mg *iv* every six hours (59 respondents, 51%), followed by 30 mg *iv* every six hours (44 respondents, 38%), and 7.5 mg *iv* every six hours (eight respondents, 7%). The suggested duration of ketorolac use was three days (54 respondents, 45%), followed by five days (41 respondents, 36%), then seven days (17 respondents, 15%), with 3 respondents (3%) not being comfortable with any duration. In cross-tabulation, the most frequent ketorolac dose and duration mentioned was 15 mg *iv* every six hours over five days (25%), followed by 15 mg *iv* every six hours over three days (21%), and then 30 mg *iv* every six hours over three days (20%).

Further considerations of respondents regarding their potential involvement in an RCT to examine NSAID use in critically ill patients can be found in ESM eTable 2.

Discussion

Our survey describes reported beliefs of Canadian ICU physicians on the use of NSAIDs in critically ill patients,

Table 1 Clinical practice specialty, level of experience, intensive care unit setting, number of beds, and research infrastructure for randomized controlled trials of primary practice setting of research respondents

Specialty, *n*/total *N* (%)	Number of responses, *n*/total *N* (%)
Medicine	78/115 (68%)
Surgery	4/115 (4%)
Trauma	7/115 (6%)
Neurosciences	4/115 (4%)
Cardiac surgery	4/115 (4%)
Burns	0/115 (0%)
Pediatrics	1/115 (0.9%)
Other (comments)	17/115 (15%)
Comments	
Anesthesiology (6/17)	
Mixed medical/surgical ICU (5/17)	
Emergency medicine (3/17)	
Unclear (2/17)	
Fellow (1/17)	
Level of experience, *n*/total *N* (%)	
0–4 years	37/115 (32%)
5–10 years	26/115 (23%)
11–15 years	25/115 (25%)
> 16 years	27/115 (24%)
ICU setting, *n*/total *N* (%)	
Academic centre	92/115 (80%)
Community centre	10/115 (9%)
Academic community centre	13/115 (11%)
Critical care beds, *n*/total *N* (%)	
0–9 beds	2/115 (2%)
10–15 beds	11/115 (10%)
16–30 beds	38/115 (33%)
31–50 beds	47/115 (41%)
> 50 beds	17/115 (15%)
Research infrastructure for RCTs, *n*/total *N* (%)	
Yes	102/114 (89%)
No	12/114 (11%)

ICU = intensive care unit; RCTs = randomized controlled trials

on considerations and hesitations towards the use of NSAIDs, and on their willingness to participate in an RCT examining the use of ketorolac as an analgesic in critically ill patients. Around half of respondents reported that they rarely use NSAIDs in the ICU setting and none reported using it as a first-line analgesic agent. The most frequent primary analgesic mentioned was acetaminophen, followed by opioids. Opinions on second-line analgesic agents were much less unanimous, with respondents still most commonly reporting their choice as being opioids or acetaminophen, but others stating to choose other agents including NSAIDs, tramadol, ketamine, or antidepressants/anticonvulsants. This divergence of uniform practice further suggests that equipoise exists in the selection of analgesics in a multimodal analgesia model for critically ill patients. Nevertheless, this may also be influenced by highly variable patient presentations in the ICU and may reflect subspecialized critical care provider preferences rather than true clinical equipoise.

There is little current evidence describing analgesic prescribing practices of ICU physicians in Canada and little to no evidence specifically identifying physician beliefs or opinions regarding the use of NSAIDs in critically ill patients. Nevertheless, previous observational studies have identified that approximately 80% of mechanically ventilated ICU patients receive opioids,[31] which is in keeping with our results where opioids remain a preferred analgesic second only to acetaminophen. Given the current SCCM guidelines,[2] it is unsurprising that physicians in our study reportedly rarely used NSAIDs as part of multimodal analgesia because of concerns for potential adverse events, including gastrointestinal bleeding and AKI. New emerging evidence supporting the use of NSAIDs in reducing opioid use, in addition to potentially overstated adverse effects of these medications in the critically ill,[32,33] likely has contributed to respondents indicating interest in exploring the use of NSAIDs in future studies. Our results show that physicians are aiming to prioritize opioid reduction in the ICU and identify clear physician interest in further clinical studies to explore the safety and utility of NSAIDs as part of multimodal analgesia in critically ill patients.

Future research must be designed to minimize patient harm while maximizing provider buy-in for participation in an RCT. The results of this survey suggest that key factors to be considered in the development of such an RCT may include patient age (e.g., excluding geriatric patients) and clinical presentation (e.g., excluding patients with active bleeding and/or kidney injury). The most favoured regimen for a proposed future RCT was 15 mg *iv* every six hours over five days. Nevertheless, the ideal duration from a feasibility perspective may need to be shorter, such as three days, to maximize provider buy-in and to potentially minimize risk. Cyclooxygenase-2 selective NSAIDs, such as celexobib, may be another avenue of interest for future research given the reduced risk of gastrointestinal bleeding, although the risk of other side effects such as AKI are comparable to those of other nonspecific NSAIDs.[34,35] Celexobib is, however, the only COX-2 selective inhibitor available in Canada and is only available as an oral formulation. This would present another challenge given that oral routes of administration are often not feasible for various reasons in critically ill patients. Therefore, given its

Table 2 Crosstabulation of preferred dose and duration of ketorolac

Crosstab: dose and duration $N = 115$		What would be the maximum duration of ketorolac use you would be willing to randomize to? Number of responses, *n*/total *N* (%)				
		3 days	5 days	7 days	None	Total
What dose of ketorolac would you feel comfortable randomizing to?	7.5 mg *iv*	5/115 (4%)	2/115 (2%)	1/115 (2%)	0/115 (0%)	8/115 (7%)
	15 mg *iv*	24/115 (21%)	29/115 (25%)	6/115 (5%)	0/115 (0%)	59/115 (51%)
	30 mg *iv*	23/115 (20%)	10/115 (9%)	10/115 (9%)	1/115 (0.9%)	44/115 (38%)
	None	2/115 (2%)	0/115 (0%)	0/115 (0%)	2/115 (2%)	4/115 (4%)
	Total	54/115 (47%)	41 (36%)	17/115 (15%)	3/115 (3%)	

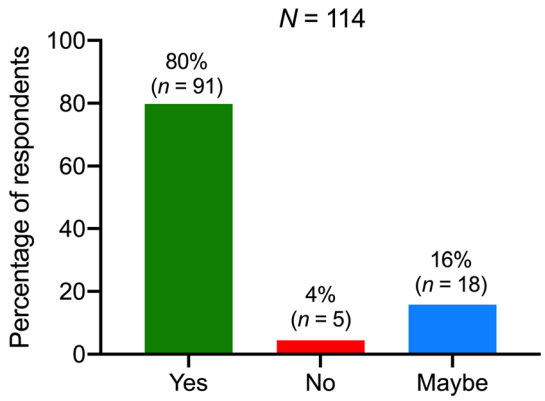

Figure Willingness of respondents to enrol patients in a randomized controlled trial examining the use of ketorolac as an adjunctive analgesic in the intensive care unit

efficacy with low dosing and availability in intravenous formulation, ketorolac may be the ideal NSAID for further investigation in critically ill patients in Canada.

Strengths

Our study has several strengths. The demographic diversity of the respondents allows for a robust and reliable representation of the opinion on the use of NSAIDs in Canada. In addition, our survey was developed with rigorous pretesting and comprehensive methodology.[26] Our findings will be essential in informing the development of an RCT examining the use of NSAIDs as analgesia in critically ill patients.

Limitations

While we were able to ascertain provider perspective and reported practices, this may not fully represent actual practice. Further investigations including observational studies are required to ascertain true prescribing practices. Furthermore, as with all surveys, there is participant volunteer bias as certain subgroups may feel more motivated to respond than others (e.g., certain age groups being open to online surveys). In our survey, 80% of respondents identified their primary practice being in an academic centre with more than two third in medical ICUs. With the majority being in academic centres, this may also bias the response on their willingness to participate in an RCT and the results may not be generalizable to community ICUs. In addition, despite using a national mailing list of ICU providers, our survey did not assess practices by region and may not be generalizable to all regions and provinces. Although CCCS members represent a large portion of ICU physicians in Canada, we recognize that not all ICU physicians are members of the CCCS and these nonmembers were not surveyed. Although we surpassed our goal of > 30% response rate (similar to other surveys during the pandemic), we recognize that we were unable to reach a significant portion of physicians. This is similar to other nonincentivized, web-based surveys[29,30,36] and may be further influenced by survey fatigue,[37] specifically with our target population of critical care providers.

Conclusion

Our survey described the opinions and beliefs of Canadian critical care physicians with respect to NSAID use and analgesic regimens in ICU patients. We observed that equipoise exists among ICU physicians in their prescribing practices for first- and second-line analgesia. Hesitation for NSAID use remains and is related to the potential risk of adverse events; however, respondents were willing to participate in an RCT examining the use of NSAIDs as an analgesic adjunct in critically ill adult patients.

Author contributions *Kimberly Tworek*, *Chen-Hsiang Ma*, *Oleksa Rewa*, *Sean Bagshaw*, and *Vincent Lau* were involved in conceptualization. *Kimberly Tworek* and *Vincent Lau* were involved in survey development and dissemination and in writing the original draft. All authors were involved in formal analysis and interpretation of results. All authors were involved in reviewing and editing the writing.

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