Development of an NSAID decision tool for perioperative pain management in adult orthopaedic patients: a modified Delphi study

Groote Schuur Hospital Adult Reconstructive Orthopaedic Surgery Research Group:

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Abstract

Background

Orthopaedic surgery is rated among the most painful of surgeries, leaving patients at risk of experiencing moderate to severe postoperative pain. A multimodal analgesic approach helps reduce opioid requirements, with nonsteroidal anti-inflammatory drugs (NSAIDs) playing a key role in this strategy, provided they are not contraindicated. However, only limited guidance exists for safe perioperative NSAID use in orthopaedic patients with comorbidities. The objective of the study was to achieve consensus on safe, short course (≤ 1 week) administration of NSAIDs in adult orthopaedic patients with comorbidities, and to convert the results into a decision tool to aid clinicians in safe perioperative NSAID administration.

Methods

A Delphi panel of 18 experienced orthopaedic surgeons, physicians and anaesthetists participated in a three-round Delphi process. The panel assessed 42 patient characteristics using a nine-point Likert scale in the first two rounds. After the second round, consensus was defined as ≥ 75% either 'disagreeing' (Likert scale 1–3) or 'agreeing' (Likert scale 7–9) that NSAIDs ± proton pump inhibitors (PPIs) could or could not be administered safely. Characteristics without consensus by round 2 moved to round 3, where subspecialty experts conducted a rapid review of the literature. Consensus in this round required ≥ 75% support for expert recommendations.

Results

All panel members participated in the first and third rounds, with 16 in the second. After the second round, consensus was achieved for 24 of 42 patient characteristics. However, in preparation for the third round, three characteristics which had achieved consensus after round 2 were added to the pool of characteristics to be considered by subspeciality experts, resulting in 21 proceeding to the third round. In round 3, consensus for all remaining subspeciality expert recommendations was achieved and an NSAID decision tool with guidance in safe perioperative NSAIDs use ± PPIs was subsequently developed for the 42 patient characteristics.

Conclusion

This study establishes a consensus on short-term NSAID administration in adult orthopaedic patients with comorbidities, offering a decision tool to guide clinicians in safely incorporating NSAIDs into perioperative pain management strategies.

Level of evidence: 5

Keywords: NSAIDs, decision tool, perioperative pain management, orthopaedic surgery, multimodal analgesia, Delphi consensus

Introduction

Orthopaedic surgery is rated among the most painful of surgeries, leaving patients at risk of experiencing moderate to severe postoperative pain.[1] Inadequate postoperative pain control is associated with delayed recovery, increased length of hospital stay and risk of persistent postoperative pain.[2-4] A multimodal analgesic strategy, which combines two or more analgesic methods with different mechanisms of action, is widely regarded as a cornerstone of opioid-sparing postoperative pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs), when not contraindicated, are a vital component of this approach, enhancing its effectiveness.[5-9] Two categories of NSAIDs exist: non-selective NSAIDs, which inhibit both cyclooxygenase (COX) 1 and 2, and selective COX-2 inhibitors, which predominantly inhibit COX-2.[10] Both provide analgesic and anti-inflammatory effects by inhibiting the COX-2 isoform.[11]

Nevertheless, NSAIDs are often underutilised in the perioperative period.[12-14] Reasons might include drug misconceptions, e.g. the effect of NSAIDs on bone healing,[15] a culture favouring the use of opioids for perioperative pain management,[14] and erring on the side of caution in patients with comorbidities.[16] This final reason reflects a cautionary conservative approach, as the evidence of serious adverse events following perioperative use of NSAIDs in the orthopaedic and surgical population is limited.[17-20] In fact, the literature documenting adverse events originates mainly from non-surgical patient cohorts dominated by patients with chronic pain conditions receiving NSAIDs for an extended period of time.[21] Extrapolating this evidence to short-course treatment with NSAIDs in a surgical population can result in inadvertent under-prescription and inferior pain management.[16,22]

The aim of our study was to identify which orthopaedic patients can safely receive NSAIDs as part of a multimodal approach to relieve postoperative pain. The objectives of our study were two-fold. The first was to conduct a modified Delphi survey to gather expert consensus on safe, short course (≤ 1 week) administration of NSAIDs in adult orthopaedic patients with a variety of comorbidities. A Delphi method is used in medical research to achieve consensus and produce guidelines among experts on specific clinical issues, especially when high-quality evidence is lacking.[23,24] It is characterised by anonymity, iteration, controlled feedback of the panellists' judgements, and statistical aggregation of group members' responses, allowing experts to refine their opinions and move towards agreement.[25] The modified Delphi is based on the principles of the Delphi process but allows for adaptation of the traditional framework. Our second objective was to translate the results of the Delphi study into a decision tool to aid clinicians in safe perioperative NSAID administration.

While the study was at first intended as a tool to support safe administration of NSAIDs as part of a multimodal pain management plan at Groote Schuur Hospital (GSH), the end result could be valuable to orthopaedic departments and settings throughout South Africa.

Methods

The study was prospectively registered with the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (ref no. 715/2022), and is reported using the ACcurate COnsensus Reporting Document (ACCORD).[26]

Panel selection

UP and BMB, both experienced in directing multidisciplinary Delphi consensus studies,[27,28] established a Delphi panel including specialists in perioperative patient management (anaesthetists and orthopaedic surgeons) and experts in medical adverse events (physicians). Clinical heads from the Departments of Orthopaedic Surgery (ten) and Medicine (nine) at GSH were invited to participate. Six orthopaedic surgeons representing spine, upper limb, lower limb and pelvic surgery (involving oncology, trauma and elective surgery) and six physicians from the divisions of Nephrology, Rheumatology, Medical Gastroenterology, Clinical Haematology, General Internal Medicine and Cardiology were recruited. We aimed for an equal inter-speciality representation; thus, six anaesthetists with a special interest in orthopaedic anaesthesia were invited (four from GSH and two full-time private practitioners). All 18 panel members consented to participate. Due to the highly technical and scientifically nuanced nature of the topic, members of the public and patients were not considered eligible for study inclusion.

Preparatory work

Scientific literature addressing the risk of adverse events following a short course of NSAIDs (≤ 7 days) in surgical patients with pre-existing comorbidities was limited at the time of study initiation.[22,29,30] Thus, the Delphi members' clinical experience and individual appraisals of the existing NSAID literature were sought over a pre-emptive group-based literature review. A list of 39 general patient comorbidities considered relevant for a perioperative NSAID tool was drafted for evaluation and modification by the Delphi participants. The result was 42 patient characteristics, categorised by adverse event risk: a. renal (six), b. cardiovascular (11), c. gastrointestinal (ten) and d. miscellaneous (15) (*Table I*).

The Delphi processes

Two electronically conducted Delphi rounds using Excel spreadsheets and a third and final virtual round to discuss patient characteristics that had not reached consensus, were planned 'a priori'.

First and second Delphi rounds

In the first two rounds, the Delphi panel members documented their level of agreement with three statements concerning perioperative pain management in adult orthopaedic patients, taking each of the 42 patient characteristics into account. Statement 1: A short course of non-selective NSAIDs can be administered with acceptable risk. Statement 2: A short course of selective COX-2 inhibitors is superior to a short course of non-selective NSAIDs AND can be administered with acceptable risk. Statement 3: Adding proton pump inhibitors (PPIs) to a short course of non-selective NSAIDs improves safety of non-selective NSAID administration AND can be administered with acceptable risk. A nine-point Likert scale was used to assess the level of agreement with each statement, where a Likert score of 1 represented the least level of agreement and a score of 9 represented the highest level of agreement (*Appendix 1** – available online only). Scores 1–3 were categorised as 'disagree', 4–6 as 'undecided' and 7–9 as 'agree' with the statement.

After each round, participants anonymously received their individual, total group and inter-specialist group scores for each patient characteristic presented as median and interquartile range (IQR). They re-evaluated the previous round's scoring, taking into consideration the group scores. If their score differed greatly from that of the group, they were asked to provide comments or references supporting their decision, which were also shared anonymously.

After the second round, the Delphi panel's responses were assessed for agreement. Consensus was achieved if at least 75% of participants 'disagreed' (1–3) or 'agreed' (7–9) with a statement.[31] For a given patient characteristic, consensus reached in support (Likert scores 7–9) of either COX-2 selective inhibitors (statement 2) or non-selective NSAIDs combined with

Table I: Results from the first and second Delphi rounds, establishing if a short course of NSAIDs ± PPI can be administered with acceptable risk in the perioperative period in adult orthopaedic patients with a variety of comorbidities

	Risk of renal adverse events	Round 1	Round 2
Q1	Normal renal function, eGFR ≥ 90 ml/min		
Q2	Mildly decreased renal function; eGFR 60–89 ml/min		
Q3	Mildly moderately decreased renal function, eGFR ≤ 59 ml/min		
Q4	Intraoperative concern of renal hypoperfusion (e.g. due to > 500 ml blood loss + requring vasopressor support in an elderly patient)		
Q5	Diabetes ± insulin dependent, well-controlled (HbA1c ≤ 6.5%)		
Q6	Diabetes ± insulin dependent, poorly controlled (HbA1c > 6.5%)		
	Risk of cardiovascular adverse events	**Round 1**	**Round 2**
Q1	Acute coronary syndrome < 3 months ago		
Q2	Acute coronary syndrome ≥ 3 months ago		
Q3	Percutaneous/surgical coronary revascularisation < 3 months ago		
Q4	Percutaneous/surgical coronary revascularisation ≥ 3 months ago		
Q5	Chronic stable angina		
Q6	Well-controlled hypertention		
Q7	Poorly controlled hypertention		
Q8	Stroke/TCI < 3 months ago		
Q9	Stroke/TCI ≥ 3 months ago		
Q10	Heart failure (NYHA I–II)		
Q11	Heart failure (NYHA III–IV)		
	Risk of gastrointestinal adverse events	**Round 1**	**Round 2**
Q1	Heartburn caused by gastro-osophageal reflux disease		
Q2	Peptic ulcer disease		
Q3	Gastrointestinal bleeding/perforation		*
Q4	*Helicobacter pylori*-positive		
Q5	Concomitant use of low-dose aspirin (≤ 100 mg daily)		
Q6	Concomitant use of antiplatelet or anticoagulant treatment (other than low-dose aspirin)		
Q7	Concomitant use of low-dose corticosteroids (≤ 10 mg prednisone daily)		
Q8	Concomitant use of high-dose corticosteroids (> 10 mg prednisone daily)		
Q9	Concomitant use of selective serotonin reuptake inhibitors		*
Q10	Severe rheumatoid arthritis disability		
	Risk of miscellaneous adverse events	**Round 1**	**Round 2**
Q1	Aspirin/NSAID-induced asthma or allergic reactions		*
Q2	Inflammatory bowel disease		
Q3	Impaired liver function		
Q4	Patients with non-union healing of bone		
Q5	Patients with an upper limb fracture		
Q6	Patients with a lower limb fracture		
Q7	Patients with an acute fracture known with high risk of problem healing (e.g. scaphoid)		
Q8	Multiple myeloma		
Q9	Bleeding disorders (e.g. haemophilia, von Willebrand disease, qualitative or quantitative platelet defects, etc.)		
Q10	Neutropenic patients		
Q11	Porphyria		
Q12	ASA 1 patients (healthy, no systemic comorbidities)		
Q13	< 65 years old		
Q14	65–75 years old		
Q15	> 75 years old		

Light blue: Delphi consensus in support of a short course of NSAIDs ± PPI; gold: Delphi consensus against the use of a short course of NSAIDs ± PPI; grey: Delphi consensus not achieved. * Patient characteristics which were reconsidered in the third round, despite achieving consensus in round two.
NSAIDs: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitor; eGFR: estimated glomerular filtration rate; TCI: transient ischaemic attack: NYHA: New York Heart Association; ASA: American Society of Anaesthesiologists Physical Status

PPIs (statement 3) would trump a treatment regimen with non-selective NSAIDs only (statement 1). Conversely, if the votes did not reach consensus in statements 2 or 3, consensus reached for statement 1 would prevail. Patient characteristics that achieved consensus were excluded from round 3 unless comments indicated that the overall group score was not supported by expert opinion or relevant literature. In such cases, the disputed characteristics were included in round 3 for further consideration.

Third Delphi round

We had originally planned to run the final third round as a virtual, non-anonymous meeting to discuss patient characteristics that did not reach consensus after the second Delphi round. However, due to a high number of 'undecided' Likert scores and panel members' appeal for subspecialty information and guidance to improve the quality of their voting, we decided to provide additional evidence and expert recommendation. Thus, UP consulted seven internal and ten external experts in fields such as haematology, psychiatry, clinical pharmacology, nephrology, neurology, allergology & immunology, gastroenterology, hepatology and anaesthesia to obtain specialised knowledge on NSAID safety for each remaining patient characteristic. This resulted in a rapid literature review, adjustments in wording (e.g. changing 'aspirin/NSAID-induced asthma or allergic reactions' to 'aspirin/NSAID-exacerbated respiratory disease'), and simplification of the format to involve only one statement per remaining characteristic. Thus, in round 3, the Delphi panel received subspeciality expert recommendations linked with relevant articles for the remaining patient characteristics (*Appendix 2.1–2.4**) along with round 2 scores (median and IQR) and panel members' comments, which were distributed electronically in an anonymous questionnaire. Consensus was achieved if at least 75% of participants agreed with the recommendation.

Recognising that NSAID adverse events are linked to the type and dose, we specified tablet ibuprofen ≤ 1 200 mg/day as the preferred non-selective NSAID, as it offers an effective analgesic dose range within the lower end of cardiovascular (CVS) thrombotic risk estimates.[32,33] When combined with a PPI, this regimen provides a level of gastrointestinal protection in patients with moderate risk of gastrointestinal toxicity (one to two risk factors) comparable to that of selective COX-2 inhibitors.[34,35] Moreover, ibuprofen is included in South Africa's Essential Medicines List and is available in state hospitals. For patients unable to take oral medications, for example during surgery, suppository indomethacin or intravenous parecoxib were considered.

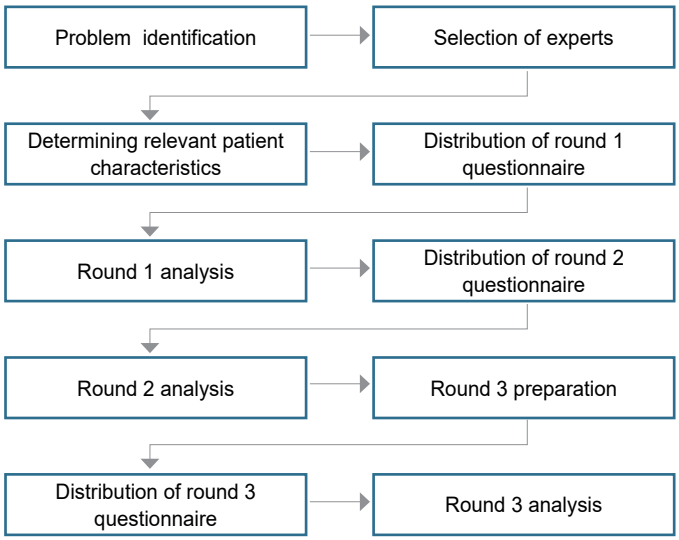

Figure 1. Diagram of the Delphi study

Panel members who failed to return their answers on time were offered one email as a reminder. UP and BMB were neutral in the scoring process throughout the study.

A fourth virtual round was not needed as consensus was achieved for all 42 patient characteristics by the end of the third round.

Our work classifies as a modified rather than a classic Delphi study, as we started with a predetermined set of patient characteristics and statements rather than an open-ended first round. This preparatory work provided a comprehensive and clinically relevant starting point for the Delphi group. Furthermore, the direct interaction with subject experts within and external to the Delphi group in preparation for round 3, and development of expert recommendations, nullifies the principle of complete anonymity and thus categorises the study as a modified Delphi. *Figure 1* illustrates the Delphi process.

Results

The Delphi study

Participants and response rate

All 18 panel members participated in the first and third Delphi rounds, while one anaesthetist and one physician did not partake in the second round.

Delphi rounds 1 and 2

The first Delphi round questionnaire was sent to the panel on 11 November 2022, and responses were returned nine days later. The second Delphi round was distributed on 24 November and completed by 4 December. In the first round, consensus was reached for 12 patient characteristics, with nine in favour and three against the use of NSAIDs ± PPIs. As per protocol, all moved on to the second Delphi round, which saw 24 patient comorbidities reaching consensus (20 in favour and four against the use of NSAIDs ± PPIs) (*Table I* and *Appendices 3–6**).

In the **renal category**, the Delphi panel did not support using selective COX-2 inhibitors or non-selective NSAIDs combined with PPIs over non-selective NSAIDs in either of the first two Delphi rounds. Three patient characteristics reached consensus with respect to safe administration of non-selective NSAIDs after round 2. This result was unchanged from round 1.

In the **cardiovascular category**, the panel did not support using selective COX-2 inhibitors or non-selective NSAIDs plus PPIs to lower the risk for CVS adverse events during perioperative treatment with NSAIDs. Rather, consensus regarding a short course of non-selective NSAIDs was achieved for four patient characteristics in round 2, which was a change from round 1, where only one achieved consensus.

Nine out of ten patient characteristics reached consensus in the second round in the **gastrointestinal category**, which was a marked increase from three in round 1. The Delphi group favoured a gastro-protective profile with selective COX-2 inhibitors or non-selective NSAIDs with PPIs in eight characteristics, while one patient group, patients on concomitant treatment with selective serotonin reuptake inhibitors (SSRIs), reached consensus in support of non-selective NSAIDs only.

The **miscellaneous category** included patient characteristics with various comorbidities. For patients with aspirin/NSAID-induced asthma or allergic reactions, the Delphi group reached consensus against the use of non-selective NSAIDs in both rounds, with undecided views on selective COX-2 inhibitors. For the other 14 characteristics, the panel generally voted against both selective COX-2 inhibitors and non-selective NSAIDs + PPIs,

Table II: Patient characteristics that reached consensus after the second Delphi round

A short course of non-selective NSAIDs can be administered with acceptable risk in patients with:	
Normal renal function; eGFR ≥ 90 ml/min	Neutropenia
Diabetes ± insulin-dependent, well controlled (HbA1c ≤ 6.5%)	Upper limb fracture Lower limb fracture
Percutaneous/surgical coronary revascularisation ≥ 3 months ago	No systemic comorbidities = ASA 1 patients
Chronic stable angina	< 65 years old
Well-controlled hypertension	65–75 years old
A short course of non-selective NSAIDs + PPI can be administered with acceptable risk in patients with:	
Heartburn caused by gastro-oesophageal reflux disease	Concomitant use of low-dose corticosteroids (≤ 10 mg prednisone daily)
Peptic ulcer disease (if minimum 3 months since peptic ulcer event)	Concomitant use of high-dose corticosteroids (> 10 mg prednisone daily)
Helicobacter pylori-positive (fully eradicated)	Severe rheumatoid arthritis disability
Concomitant use of low-dose aspirin (≤ 100 mg daily)	
A short course of NSAIDs (±PPI) is *not* recommended in patients with:	
Intraoperative concern of renal hypoperfusion (e.g. due to > 500 ml blood loss + requiring vasopressor support in an elderly patient)	Bleeding disorders (e.g. haemophilia, von Willebrand disease, qualitative or quantitative platelet defects, etc.)
Heart failure (NYHA III–IV)	

Light blue: Delphi consensus *in support* of a short course of NSAIDs ± PPI; grey: Delphi consensus *against* the use of a short course of NSAIDs ± PPI; short course: ≤ 1 week; NSAIDs: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitor; eGFR: estimated glomerular filtration rate; ASA: American Society of Anaesthesiologists Physical Status; NYHA: New York Heart Association

Table III: Results of the third Delphi round

Renal	**A short course of ibuprofen can be administered with acceptable risk in adult orthopaedic patients with the following comorbidities to treat perioperative pain:**	**Round 3**
	Mildly decreased renal function; eGFR 60–89 ml/min	
	Mildly moderately decreased renal function; eGFR ≤ 59 ml/min	
	Diabetes ± insulin dependent, poorly controlled (HbA1c > 6.5%)	
CVS & CNS	**A short course of ibuprofen (+ PPI if on secondary cardiovascular prevention with LDA) can be administered with acceptable risk in adult orthopaedic patients with the following comorbidities to treat perioperative pain:**	**Round 3**
	Acute coronary syndrome < 3 months ago	
	Acute coronary syndrome ≥ 3 months ago	
	Percutaneous/surgical coronary revascularisation < 3 months ago	
	Poorly controlled hypertension	
	Ischaemic stroke	
	Haemorrhagic stroke > 1 month ago (if not on LDA) & > 3 months ago, if on concomitant LDA	
	Heart failure (NYHA I–II)	
GI	**A short course of ibuprofen + PPI improves the safety of ibuprofen AND can be administered with acceptable risk in adult orthopaedic patients with the following comorbidities to treat perioperative pain:**	**Round 3**
	Gastrotestinal bleeding/perforation (in the absence of alternative analgesia, a short course of selective NSAIDs (e.g. celecoxib/parecoxib) + PPI can be administered if > 3 months since GI-bleed/perforation)	
	Concomitant use of antiplatelet (other than LDA) or anticoagulant treatment	
	Concomitant use of selective serotonin reuptake inhibitors	
	> 75 years old	
Miscellaneous	**A short course of selective COX-2 inhibitors can be administered with acceptable risk in adult orthopaedic patients with the following comorbidity to treat perioperative pain:**	**Round 3**
	Aspirin/NSAID-exacerbated respiratory disease; if isolated respiratory reactions to non-selective NSAIDs. This includes patients with mild to moderate asthma, who experience worsening of their asthma on exposure to COX-1 inhibitors	
	A short course of ibuprofen can be administered with acceptable risk in adult orthopaedic patients with the following comorbidities to treat perioperative pain:	**Round 3**
	Inflammatory bowel disease (not active)	
	Impaired synthetic liver function (In the absence of alternative analgesia, a short course of non-selective NSAIDs can be administered to patients with mild liver impairment (Child-Pugh A) with fully compensated liver disease, i.e. no jaundice, ascites or abnormal synthetic liver function (INR > 1.4; albumin < 35 g/L; platelets < 150)	
	Patients with non-union healing of bone	
	Patients with an acute fracture known with high risk of problem healing (e.g. scaphoid)	
	Multiple myeloma	
	Porphyria	

Light blue: Delphi consensus in support of a short course of NSAIDs ± PPI: grey: Delphi consensus against the use of a short course of NSAIDs ± PPI; short course: ≤ 1 week: NSAIDs: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitor; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c test; LDA: low-dose aspirin; NYHA: New York Heart Association; COX: cyclooxygenase

favouring non-selective NSAIDs. In total, consensus was achieved in five characteristics in round 1 and eight in round 2.

Thus, 24/42 patient comorbidities reached consensus after the second round. In preparation for the third round, UP, in discussion with appointed Delphi panel members, suggested three patient characteristics with consensus after round 2 be further evaluated by subspeciality experts due to concerns raised by participants. Thus, patients with a history of a. gastrointestinal bleeding/perforation, b. concomitant use of SSRIs, and c. aspirin/NSAID-induced asthma or allergic reactions were reconsidered, leaving 21 patient characteristics to proceed to the third Delphi round. *Table II* depicts round 2 results. Finally, patients older than 75 years were reclassified to the gastrointestinal adverse events' category, as epidemiological studies suggest that ageing is an independent risk factor for NSAID-related gastrointestinal toxicity.[36]

Third Delphi round

The third round, conducted in May/June 2023, achieved consensus on all remaining characteristics (see *Table III*). Expert recommendations received unanimous support (100%) for 15 characteristics and 94% support for six.

Development of the NSAID decision tool

The study outcomes were synthesised into a practical NSAID decision tool (*Figure 2*) and approved as Standard Operating Procedure at GSH and orthopaedic departments in the Western Cape, October 2023 (*Appendix 7**). The tool organises recommendations into five sections: renal, cardiovascular and central nervous system (CVS and CNS, respectively), gastrointestinal, miscellaneous, and respiratory, highlighting areas where NSAID use poses risk.

To improve compliance with NSAID administration, a specific ibuprofen dosing schedule was recommended, aligning with dosing of other around-the-clock analgesics. Adjustments made to the decision tool included clarifying kidney hypoperfusion risks across all perioperative stages, moving diabetes to the CVS/CNS category, and advising staggered ibuprofen dosing in patients on low-dose aspirin for CVS prevention, as ibuprofen may reduce the irreversible antiplatelet effect of aspirin by interfering with aspirin acetylation of the COX-1 binding site on platelets.[37] For patients experiencing prolonged fasting periods, NSAIDs were recommended alongside a daily PPI dose to help minimise gastrointestinal risks. As a result, this group of patients was categorised under gastrointestinal adverse events.

Discussion

This study reports a consensus on short-term NSAID administration in adult orthopaedic patients with various comorbidities, and aims to guide clinicians in the safe use of NSAIDs as part of a perioperative pain management regimen through the development of our NSAID decision-tool.

NSAIDs are key to multimodal, opioid-sparing perioperative pain management; however, their association with severe adverse events (SAEs) remains uncertain.[19] As highlighted in a recent systematic review of patients undergoing gastrointestinal procedures, 'high-quality randomised clinical trials with low risk of bias, adequate power to assess safety, and long-term follow-up' are essential to fully understand the impact of short-term NSAIDs on SAEs in this population.[18] A similar study is underway in orthopaedic surgery.[17] This evidence gap explains the lack of unified guidelines for perioperative NSAID administration across specialties such as nephrology, cardiology, neurology, gastroenterology, and their surgical counterparts – a gap that our study seeks to address.

Assessing the safe administration of NSAIDs is particularly challenging in patients with multiple comorbidities. Our NSAID decision tool did not account for clusters of comorbidities; instead, consensus was reached based on individual patient characteristics. This highlights the need for careful clinical judgement when managing such patients. Additionally, ibuprofen was the preferred NSAID in our decision tool due to its balance of analgesic efficacy, safety profile, and affordability within our resource-limited setting. It is important to note, however, that the risk profiles of non-selective NSAIDs may differ, and healthcare providers should remain cognisant of these variations when making treatment decisions.

Encouragingly, a recently published guidance on safe use of NSAIDs in the postoperative period in patients with various comorbidities, broadly aligns with the findings of the Delphi group.[38] Exceptions include their recommendations against the use of NSAIDs ± PPI in patients with a history of heart failure, inflammatory bowel disease, gastrointestinal ulceration and uncontrolled hypertension (see *Appendix 2.2–2.4** for our detailed commentary). Notably, the guidance uses 65 years, rather than 75 years as in our study, as the threshold for initiating PPI co-prescription with non-selective NSAIDs. It also emphasises the importance of individualised risk–benefit analyses when prescribing NSAIDs, advocating for the lowest effective dose (e.g. ibuprofen 1.2 g/day ± PPI) for the shortest duration necessary to mitigate NSAID-related adverse events, particularly in patients over 75 years of age.

Methodological strengths include establishing a multidisciplinary Delphi panel. While a Delphi panel is expected to consist of members with expert knowledge of the subject at hand,[31] identifying experts with deep clinical and/or pharmacological knowledge concerning perioperative administration of NSAIDs in patients with various comorbidities was not deemed feasible. Instead, a heterogeneous panel allowed critical appraisal from experienced orthopaedic surgeons, anaesthetists and physicians. To minimise bias from knowledge gaps, the panel could vote 'undecided' (4–6 on a nine-point Likert scale), and if any vote appeared unsafe, panellists could request reconsideration. Thus, safety-directed expert opinion would supersede consensus. Furthermore, the panel was encouraged to modify the preliminary list of patient characteristics to ensure that clinically relevant cases were considered, including high-risk fracture scenarios suggested by orthopaedic surgeons. Lastly, participation remained high in all three rounds, keeping attrition bias low.

Limitations include potential investigator selection bias as the researcher directly contacted the six participating anaesthetists to ensure equal inter-speciality representation; however, they all possess expertise in orthopaedic anaesthesia and thus represent the population of interest. Second, to encourage independent appraisals, a pre-emptive literature review was deferred. By round 2, the need for expert input prompted a targeted rapid review with internal and external specialists. While consensus achieved remained consistent with the evidence base, a literature review before starting the Delphi process would have allowed the panel to identify the questions that have clear data supporting certain clinical situations, thus limiting the number of scenarios being presented. For example, selective COX-2 inhibitors and non-selective NSAIDs + PPI confer a similar level of gastrointestinal protection in patients with moderate risk of gastrointestinal toxicity,[34] and reduce neither the risk of CVS adverse events[32,33] nor renal toxicity,[39] compared to non-selective NSAIDs only. Furthermore, this approach would have allowed the questions to be presented to all participants in the same form as they were in the final round. Third, the Delphi panel and all but one of the external subspecialty experts were affiliated with our institution. Despite professionalism and clinical work experience gained elsewhere, we encourage our fellow colleagues to undertake a larger scale study in South or Southern Africa to test the external validity of the NSAID tool. Fourth, with the paucity of

Perioperative NSAID decision-tool for adult patients undergoing orthopaedic surgery

1	**Ibuprofen (≤ 7 days)** should be considered in all patients undergoing orthopaedic procedures
2	All ASA 1 patients may receive **ibuprofen (400 mg TDS for ≤ 7 days)**
3	Prescribe **ibuprofen** for **10h00, 16h00 & 22h00**
4	Consider using **parecoxib 40 mg 12 hourly intravenously** or **indomethacin 100 mg 12 hourly per rectum** when oral intake not possible

Kidney

Concern of preoperative, intraoperative or postoperative hypovolaemia causing kidney hypoperfusion	YES → NSAIDs not recommended
eGFR < 60 ml/min	
Ibuprofen (≤ 7 days) can be administered with acceptable risk in patients with:	
eGFR ≥ 60 ml/min	

CVS & CNS

Acute coronary syndrome ± revascularisation < 3 months ago	YES → NSAIDs not recommended
Angina class CCS III & IV	
Heart failure NYHA III & IV	
Haemorrhagic stroke < 1 month ago	
Haemorrhagic stroke < 3 months ago & concomitant low-dose aspirin	
Ibuprofen (≤ 7 days) can be administered with acceptable risk in patients with*:	
Acute coronary syndrome ± revascularisation ≥ 3 months ago	
Chronic stable angina class CCS I & II	
Hypertension (well controlled and poorly controlled)	
Diabetes (well controlled and poorly controlled)	
Heart failure NYHA I & II	
Haemorrhagic stroke > 1 month ago, if not on low-dose aspirin and > 3 months ago, if on concomitant low-dose aspirin	
Ischaemic stroke on concomitant low-dose aspirin	

*In patients on low-dose aspirin for secondary cardiovascular prevention, ibuprofen should be administered minimum 30 minutes after aspirin administration

Gastrointestinal

GI bleeding/perforation**	YES → NSAIDs not recommended
Peptic ulcer disease < 3 months ago	
Co-administration of single agent antiplatelet (P2Y12 antagonists - e.g. clopidogrel), dual antiplatelet treatment or anticoagulants (DOACs/vit K antagonists)	
Add **daily proton pump inhibitor*** to ibuprofen treatment (≤ 7 days)** in patients with:	
Gastro-oesophageal reflux disease (GORD)	
Peptic ulcer disease ≥ 3 months ago	
Eradicated *Helicobacter pylori*	
Concomitant use of low dose aspirin, corticosteroids or SSRIs	
Severe rheumatoid arthritis	
Age ≥ 75 years	
Prolonged periods (> 12 hours) NPO awaiting urgent or emergency surgery	

**In the absence of alternative analgesia, a short course of selective NSAIDs (e.g. celecoxib/parecoxib) + PPI can be administered if > 3 months since GI bleed/perforation

***Administer daily omeprazole 20 mg or lansoprazole 30 mg during NSAID treatment

Miscellaneous

Impaired synthetic liver function****	YES → NSAIDs not recommended
Multiple myeloma	
Bleeding disorders (eg. haemophilia, von Willebrand disease, qualitative or quantitative platelet defects)	
Ibuprofen (≤ 7 days) can be administered with acceptable risk in patients with:	
Inflammatory bowel disease (non-active)	
Neutropenia	
Porphyria (indomethacin, parecoxib & celecoxib are also safe to use)	
Age < 75 years	

****In the absence of alternative analgesia, a short course of ibuprofen can be administered to patients with mild liver impairment (Child-Pugh A) with fully compensated liver disease, i.e. no jaundice, ascites or abnormal synthetic liver function (INR > 1.4, albumin < 35 g/L, platelets < 150)

Respiratory

Aspirin/NSAID-exacerbated respiratory disease	
Poorly controlled asthma with hyper-reactivity to COX-1 inhibitors	YES → NSAIDs not recommended
A history of a severe reaction involving angioedema, urticaria or cardiovascular collapse to COX-1 inhibitors	
Isolated respiratory reactions***** to non-selective NSAIDs (COX-1 inhibitors, e.g. aspirin/ibuprofen)	YES → **Selective COX-2 inhibitors, e.g. celecoxib/parecoxib can safely be administered**
Patients with mild to moderate asthma, who experience worsening of their asthma on exposure to COX-1 inhibitors	

*****i.e. wheezing, rhinitis, nasal congestion, cough, shortness of breath or asthma exacerbation

Canadian Cardiovascular Society (CCS) grading of angina pectoris		New York Heart Association (NYHA) functional classification	
Class I	Angina only during strenuous or prolonged physical activity	Class I	No limitation of physical activity
Class II	Slight limitation; angina only during vigorous physical activity	Class II	Slight limitation of physical activity
Class III	Moderate limitation; symptoms with everyday living activities	Class III	Marked limitation of physical activity
Class IV	Severe limitation; angina at rest/inability to perform any activity without angina	Class IV	Any physical activity causes discomfort – symptoms of heart failure at rest

Figure 2. Perioperative NSAID decision tool for adult patients undergoing orthopaedic surgery

data regarding the risk of short-term NSAID use, recommendations are based on clinical experience and extrapolation of data by experts mainly from published literature on adverse effects with long-term use. We await high-quality, well-designed studies that can inform us of SAEs associated with perioperative NSAID treatment in patients with single and multiple comorbidities.

Conclusion

In conclusion, our multidisciplinary Delphi group achieved consensus on safe short-term NSAID treatment in 42 patient characteristics in adult orthopaedic patients. The results were translated into an NSAID decision tool intended to aid clinicians in safe prescribing of NSAIDs as part of a multimodal analgesic strategy to improve postoperative pain control and hence quality of recovery.

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Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

Prior to the commencement of the study ethical approval was obtained from the following ethical review board: University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee, HREC ref: 715/2022.

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

The Delphi panel members all consented to participate in the study.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

UP: contributed to study conceptualisation and design; data analysis and interpretation; drafting of the manuscript; critical revision for important intellectual content; final approval of the version to be published; and agrees to be accountable for all aspects of the work

ML: contributed to study conceptualisation and data acquisition; drafting the work for the third Delpi round and revised the manuscript for important intellectual content; approved the final version for publication; and agrees to be accountable for all aspects of the work

MBN: involved in data collection; critically revised the manuscript for intellectual content; approved the final version; and accepts full responsibility for the integrity of the work

SM: contributed to data acquisition; reviewed the manuscript for important intellectual contributions; approved the final draft for submission; and agrees to be accountable for all aspects of the work

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**** Please note that the appendices are available online.***