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

Appendix 2.1: Renal

In the second Delphi round, neither selective NSAIDs nor nsNSAIDs + PPI were found to be superior (did not achieve majority vote) when compared to use of non-selective NSAIDs in the six renal patient categories.

This is supported by the literature, as selective COX-2 inhibitors cause adverse kidney effects at a rate and severity comparable to non-selective NSAIDs (Gambaro, 2003) and PPIs do not affect renal physiology.

Therefore, only non-selective NSAIDs (ibuprofen) will be considered with respect to risk of renal adverse events in this third Delphi round. However, if a patient is unable to take oral medication (e.g. during surgery), parecoxib (IVI) or indomethacin (suppository) can be used.

Please consider that there are currently no international guidelines to inform risk of short-term NSAID treatment in patients with or without increased risk of renal toxicity.

A short course (≤ 1 week) of nsNSAIDs (ibuprofen) can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/ references if you disagree with the recommendation
Risk of renal adverse events		**Round 2 Delphi results**	**Literature/expert opinion/recommendation**			
Q1	Normal renal function; eGFR ≥ 90 ml/min	15/15 (100%) agree	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q2	Mildly decreased renal function; eGFR 60–89 ml/min	5/16 (31%) undecided - 11/16 (69%) agree. Median (IQR): 7 (6–8)	Expert recommendation from Delphi panel member on perioperative NSAID use: The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guidelines (Table 32) recommend GFR < 60 ml/min as the cut-off value for safe administration of prolonged NSAID therapy. Accordingly, short term NSAID treatment in patients with GFR ≥ 60 ml/min is acceptable. **Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q3	Mildly moderately decreased renal function; eGFR ≤ 59 ml/min	7/13 (54%) disagree - 5/13 (38%) undecided - 1/13 (8%) agree. Median (IQR): 3 (3–5)	Expert comment and recommendation from Delphi panel member on perioperative NSAID use: The severity of renal impairment for which short term treatment with NSAIDs should be avoided is not well defined and thus perioperative guidelines are lacking. In the KDIGO guidelines, NSAIDs are not recommended if eGFR < 60 ml/min in patients who have serious intercurrent illness that increases the risk of AKI (section 4.4.3) – surgery is a risk factor for developing AKI. In patients with eGFR < 30 ml/min, NSAIDs should be avoided (KDIGO, Table 32). **Recommendation: A short course of nsNSAIDs is not recommended.**			
Q4	Perioperative concern of renal hypoperfusion	9/12 (75%) disagree	**Recommendation: A short course of nsNSAIDs is not recommended.**			
Q5	Diabetes ± insulin dependent, well controlled (HbA1c ≤ 6.5%)	16/16 (100%) agree	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q6	Diabetes ± insulin dependent, poorly controlled (HbA1c > 6.5%)	4/15 (27%) undecided - 11/15 (73%) agree. Median (IQR): 7 (7–8)	A case control observational registry study, not directly addressing causality, showed an increased risk of CCF after 2 weeks of NSAID treatment in people with DM and HbA1c> 6.5% (Holt, 2023). Literature on the risk associated with ≤ 1 week NSAID treatment in patients with poorly controlled DM is lacking. Expert comment and recommendation from Delphi panel member on perioperative NSAID use: The HbA1c-level is not associated with risk of NSAID-induced nephrotoxicity in diabetic patients treated with NSAIDs ≤ 1 week. Rather, pre-existing renal and cardiovascular status determines the safety of perioperative NSAID use among diabetics. **Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			

NSAIDs: non-steroidal anti-inflammatory drugs; nsNSAIDs: non-selective NSAIDs; IQR: interquartile range; PPI: proton pump inhibitor; eGFR: estimated glomerular filtration rate; HbA1c: haemoglobin A1c test

Literature

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Appendix 2.2: Cardiovascular

In the second Delphi round, selective NSAIDs were not found to be superior (did not achieve consensus) when compared to administration of nsNSAIDs in the 11 cardiovascular patient categories
This is supported by the literature, where – if an NSAID is chosen – a SHORT course of ibuprofen (≤ 1 200 mg/daily) or naproxen (≤ 500 mg/daily) is recommended in patients with pre-existing cardiovascular comorbidity as both have an effective analgesic dose range within the lower end of cardiovascular thrombotic risk estimates (Schmidt, 2016 & Schjerning, 2020)
As ibuprofen has a better GI-risk profile than naproxen (and is the non-selective NSAID available to us), ibuprofen (≤ 1 200 mg/daily) will be considered with respect to risk of cardiovascular adverse events in this third Delphi round. However, if a patient is unable to take oral medication (e.g. during surgery), parecoxib (IVI) or indomethacin (suppository) can be used
In patients with increased risk of NSAID-induced GI toxicity (e.g. in patients on antithrombotic treatment as secondary cardiac prevention), adding a PPI provides gastroprotection (Lanza, 2009 & Schjerning, 2020)
Please consider that the 2022 European Society of Cardiology (ESC, Halvorsen) Guideline on management of patients undergoing non-cardiac surgery, does NOT recommended NSAIDs as first line analgesics in patients with established or high risk of cardiovascular disease – section 7.5 (class III, evidence level B). However, the paper by Moore (2020) critically appraises the studies used to inform coronary risks associated with NSAIDs, highlighting lack of data on short-term NSAID treatment in patients with pre-existing cardiovascular risk factors
Please also consider that poorly controlled postoperative pain is associated with myocardial injury in patients undergoing non-cardiac surgery (Turan, 2020)

A short course (≤ 1 week) of nsNSAIDs (ibuprofen) can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/references if you disagree with the recommendation
Risk of cardiovascular adverse events		Round 2 Delphi results	Literature/expert opinion/recommendation			
Q1	Acute coronary syndrome < 3 months ago	9/16 (56%) disagree - 5/16 (31%) undecided - 2/16 (13%) agree. Median (IQR): 3 (3–5)	Patients with ACS have been diagnosed with unstable angina, NSTEMI or STEMI – coronary revascularisation will be performed in most of these patients (2020 ESC Guideline for the management of ACS in patients without persistent ST-segment elevation, Section 6.2, Collet). It follows that this patient group largely represents the same as in Q3. A Danish nationwide registry study found that short-term treatment with NSAIDs (≤ 1 week) in patients with newly diagnosed myocardial infarct was associated with increased risk of bleeding and cardiovascular events (Schjerning, 2015). Expert comment and recommendation from Delphi panel member on perioperative NSAID use: The evidence is strongest within one month of ACS for risk of NSAID use. The evidence from 1–3 months is less strong. **Recommendation: A short course of non-selective NSAIDs (+ PPI) is not recommended**			
Q2	Acute coronary syndrome ≥ 3 months ago	2/16 (13%) disagree - 4/16 (25%) undecided - 10/16 (63%) agree. Median (IQR): 7 (5–7)	As above; the majority of patients diagnosed with ACS will have coronary revascularisation performed and therefore this patient group largely represents the same as in Q4. Expert comment and recommendation from Delphi panel member on perioperative NSAID use: The evidence is poor for the bleeding and thrombosis risk associated with ≤ 1 week NSAID treatment in patients with ACS ≥ 3 months ago. Specifically, bleeding risk associated with different antithrombotic regimens and risk reduction when adding PPIs is poorly investigated. However, a short course of NSAIDs with gastroprotection is unlikely to increase the risk significantly (please see Q6 in the GI section for recommendation of co-prescribing NSAIDs with antiplatelet or/and anticoagulant treatment). **Recommendation: A short course of nsNSAIDs (+ PPI) can be administered with acceptable risk.**			
Q3	Percutaneous/ surgical coronary revascularisation < 3 months ago	8/16 (50%) disagree - 6/16 (38%) undecided - 2/16 (13%) agree. Median (IQR): 4 (3–4)	See Q1. **Recommendation: A short course of nsNSAIDs (+ PPI) is not recommended.**			
Q4	Percutaneous/ surgical coronary revascularisation ≥ 3 months ago	13/16 (81%) agree	See Q2. **Recommendation: A short course of nsNSAIDs (+ PPI) can be administered with acceptable risk.**			
Q5	Chronic stable angina (Class CCS I & II)	12/16 (75%) agree	**Recommendation: A short course of nsNSAIDs (+ PPI) can be administered with acceptable risk in patients with angina CCS Class I/II. NSAIDs are not recommended in patients with angina CCS Class III & IV.**			
Q6	Well-controlled hypertension	15/16 (94%) agree	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q7	Poorly controlled hypertension	5/16 (31%) disagree - 1/16 (6%) undecided - 10/16 (63%) agree. Median (IQR): 7 (4–7)	NSAIDs increase blood pressure at least in part by reducing sodium excretion by the kidney. Most studies show an increase in systolic BP of around 2–4 mmHg after > 4–8 weeks of NSAID treatment in patients with preexising hypertension. Data on patients with treatment resistant hypertension treated with short term NSAIDs is lacking (Szeto, 2020). Expert comment and recommendation from Professor Erica Jones (Department of Nephrology, GSH) on perioperative NSAID use: 1. Optimise BP control going into surgery and perioperatively. 2. Yes, it is OK to use NSAIDs short term but the BP may get worse. 3. However, pain may be driving bad BP control and pain should be addressed prior to uptitrating antihypertensives postoperatively. 4. Careful if renal function is off (see renal category). **Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q8	Stroke/TCI < 3 months ago	7/16 (44%) disagree - 6/16 (38%) undecided - 3/16 (19%) agree. Median (IQR): 4 (3–5)	Stroke events are characterised as ischaemic or haemorrhagic, with the majority being ischaemic (88%). In patients with a history of spontaneous intracerebral haemorrhage (ICH), regular long-term use of NSAIDs is not recommended due to increased risk of recurrent ICH (class III, level of evidence B; section 9.1.4, 2022 AHA/ASA Guideline for the management of patient with spontaneous intracerebral haemorrhage). Guidelines on NSAID treatment in patients with a history of ischaemic stroke (IS) are lacking. In a multi-country European case controlled database study, patients with a prior history of IS treated with ibuprofen were associated with a (marginally) increased risk of recurrent IS/TCI; however, concomitant use of anti-thrombotic treatment mitigated this risk (Fig. 5 A, Schink, 2018). Expert comment and recommendation from Kathleen Bateman (Department of Neurology, GSH) on perioperative NSAID use - amended: 1. Literature on risk associated with ≤ 1 week NSAID treatment in patients with a history of ICH or IS is lacking. 2. Stroke patients on dual antiplatelet treatment (DAPT), DOAC or warfarin have increased risk of ICH when NSAIDs are co-prescribed and in these patients even a short course of NSAIDs should be avoided (Penner-Warfarin/ NSAIDs, Table 2, 2022). 3. Patients with ICH NOT on antithrombotic treatment can receive NSAIDs from 4 weeks after their stroke. 4. Patients with ICH ON antithrombotic treatment is not recommended NSAIDs in the first 3 months after the stroke. 5. Patients with IS on single agent antiplatelet treatment (LDA) can receive NSAIDs without a time delay from their stroke event. **Recommendation: A short course of nsNSAIDs (+ PPI) can be administered in patients with IS on single agent antiplatelet treatment (LDA). In patients with ICH NOT on antithrombotic treatment, a short course of nsNSAIDs can be administered from 4 weeks after the event. In patients with ICH ON antithrombotic treatment (for secondary CV prevention), NSAIDs are not recommended in the first 3 months after the stroke. In stroke patients on anticoagulants (DOAC/VKA) or antithrombotic treatment (P2Y12 receptor antagonist/DAPT), NSAIDs should be avoided.**			

A short course (≤ 1 week) of nsNSAIDs (ibuprofen) can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/references if you disagree with the recommendation
Risk of cardiovascular adverse events		Round 2 Delphi results	Literature/expert opinion/recommendation			
Q9	Stroke/TCI ≥ 3 months ago	2/16 (13%) disagree - 7/16 (44%) undecided - 7/16 (44%) agree. Median (IQR): 6 (6–7)	Expert comment and recommendation from Kathleen Bateman (Department of Neurology, GSH) on perioperative NSAID use: See comment above (Q8). **Recommendation: A short course of nsNSAIDs (+ PPI) can be administered in stroke patients on single agent antiplatelet treatment. In stroke patients on anticoagulants (NOAC/VKA) or DAPT, NSAIDs should be avoided.**			
Q10	Heart failure (NYHA I–II)	4/16 (25%) disagree - 5/16 (31%) undecided - 7/16 (44 %) agree. Median (IQR): 6 (5–7)	For patients with heart failure, chronic use of NSAIDs is discouraged in clinical guidelines owing to NSAIDs' inhibition of renal prostaglandin synthesis resulting in reduced glomerular filtration and sodium excretion in susceptible individuals (class III, level of evidence B; 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, McDonagh). A SR/MA of observational studies reporting on incident HF (i.e. not pre-existing HF) in NSAID users vs non-NSAID users found increased risk among nsNSAID users (RR 1.35; 95% CI: 1.15–1.57) - patients received NSAIDs for 7–30 days (Ungprasert, 2016). However, literature on the risk associated with ≤ 1 week NSAID treatment in patients with CCF NYHA I–II is lacking. Expert comment and recommendation from Professor Erica Jones (Department of Nephrology, GSH) and Delphi panelmember on perioperative NSAID use: 1. Fluid overload may be a major concern so that would need to be watched and any worsening symptoms would need to beaddressed timeously. 2. NSAIDs should be avoided in patients with decompensated heart failure (NYHA III & IV), this includes CCF patients with low BP (see Q11 below). 3. If renal function is off, avoid NSAIDs (see renal category). **Recommendation: A short course of nsNSAIDs (+ PPI) can be administered with acceptable risk.**			
Q11	Heart failure (NYHA III–IV)	13/16 (81%) disagree	**Recommendation: A short course of nsNSAIDs (+ PPI) is not recommended.**			

PPI: proton pump inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs; nsNSAIDs: non-selective NSAIDs; ICH: intracranial haemorrhage; IS: ischaemic stroke; DAPT: dual antiplatelet treatment; DOAC: direct oral acting anticoagulants; VKA: vitamin K antagonist; CCF: congestive cardiac failure; NYHA: New York Heart Association

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Appendix 2.3: Gastrointestinal

In the second Delphi round, both sNSAIDs and nsNSAIDs + PPI were found to be superior (achieved consensus) when compared to administration of nsNSAIDs in most of the ten gastrointestinal (GI) patient categories.
This is supported by the literature, as nsNSAIDs + PPI confers similar level of gastroprotection in patients with moderate risk of GI toxicity (1–2 risk factors) as sNSAIDs and both are superior to non-selective NSAIDs (Lanza, 2009 & Szeto, 2020).
We will consider ibuprofen + PPI with respect to risk of GI adverse events in this third Delphi round. However, if a patient is unable to take oral medication (ex. during surgery), IV-parecoxib can be used. The exception to this aproach is stated in Q3, as patients with a history of GI bleeding/perforation – in the absence of alternative analgesia – will need maximal GI protection with selective NSAIDs + PPI.
One patient category is added from the miscellaneous section, as the main concern with short term NSAID treatment in the elderly is GI toxicity.
Please be aware that the data on NSAIDs in patients with GI risk factors exists mainly on long-term NSAID use and there are currently no international guidelines to inform risk of short-term NSAID treatment in patients with risk factors for GI-toxicity. Below are the best 'expert' recommendations given the limited data available; these recommendations take practical clinical medicine and cost-effectiveness into account.

A short course (≤ 1 week) of nsNSAIDs (ibuprofen) + PPI improves the safety of nsNSAIDs AND can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/ references if you disagree with the recommendation
Risk of gastrointestinal adverse events		**Round 2 Delphi results**	**Literature/expert opinion/recommendation**			
Q1	Heartburn caused by gastro-oesophageal reflux disease (GORD)	15/16 (94%) agree	**Recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs AND can be administered with acceptable risk.**			
Q2	Peptic ulcer disease	15/16 (94%) agree	**Delphi panel expert recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs AND can be administered with acceptable risk if minimum 3 months since peptic ulcer event. NSAIDs are best avoided in patients with PUD < 3 months ago.**			
Q3	GI-bleeding/perforation	12/16 (75%) agree	Majority vote was reached in support of nsNSAIDs + PPI. However, Delphi panel expert comment and recommendation on perioperative NSAID use: These patients are at the highest risk of GI complications and should be treated with extreme caution. Among such patients, it is best to avoid NSAIDs entirely, but if anti-inflammatory treatment is unavoidable, an sNSAID + PPI should be employed (Guideline statement in Lanza (2009), Szeto-4.2.2 (2020) & Barkun (2019)). **Recommendation: In the absence of alternative analgesia, a short course of sNSAIDs + PPI can be administered if > 3 months since GI-bleeding/ perforation. NSAIDs are not recommended in patients with GI-bleeding/perforation < 3 months ago.**			
Q4	*Helicobacter pylori* positive	13/16 (81%) agree	**Delphi panel expert recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs and can be administered with acceptable risk in patients eradicated for *H. pylori*.**			
Q5	Concomitant use of low-dose aspirin (≤ 100 mg daily)	14/16 (88%) agree	**Recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs AND can be administered with acceptable risk.** (NB: Ibuprofen may reduce the irreversible antiplatelet effect of aspirin by interfering with aspirin acetylation of the COX-1 binding site on platelets or by providng insufficient COX-1 inhibition during the dosing cycle. It is recommended to delay NSAID treatment 1–2 hours after aspirin use).			
Q6	Concomitant use of antiplatelet or anticoagulant treatment (other than low-dose aspirin)	7/16 (44%) undecided – 9/16 (65%) agree. Median (IQR): 7 (6–7)	Combining NSAIDs with anticoagulation treatment (Davidsen, 2014 & Olsen, 2020 & Penner, 2022) or antiplatelet treatment (ACCF/ACG/AHA 2010 Expert Consensus Document: Antiplatelets, NSAIDs and GI Risk, Abraham) is associated with increased risk of bleeding, which is further enhanced when combining two or more antithrombotic agents with NSAIDs (Lamberts, 2014 & Schjerning 2015). The absolute risk when PPI is added to short-term NSAID treatment in this patient category is poorly documented. However, from a clinical perspective, P2Y12 ADP receptor antagonist (clopidogrel), dual antiplatelet treatment (DAPT), direct oral anticoagulants (DOACs), VKAs or combined antiplatelet and anticoagulant treatment will usually be paused before an orthopaedic surgical intervention. Expert comment and recommendation from Prof. Marius Coetzee (Department of Haematology and Cell Biology, Bloemfontein) on perioperative use: 1. NSAIDs should be avoided in patients on P2Y12 ADP receptor antagonist, DAPT, DOAC or VKA. 2. A short course of NSAIDs can be administered with LMWH without adding PPI. **Recommendation: A short course of nsNSAIDs (+ PPI) is not recommended in patients on P2Y12 ADP receptor antagonists, DAPT, DOAC or VKA. (NSAIDs can be administered with LMWH without adding PPI.)**			
Q7	Concomitant use of low-dose corticosteroids (≤ 10 mg prednisone daily)	14/16 (88%) agree	**Recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs AND can be administered with acceptable risk.**			
Q8	Concomitant use of high-dose corticosteroids (> 10 mg prednisone daily)	13/16 (81%) agree	**Recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs AND can be administered with acceptable risk.**			
Q9	Concomitant use of selective serotonin reuptake inhibitors (SSRIs)	1/16 (6%) disagree – 11/16 (69%) undecided – 4/16 (25%) agree. Median (IQR): 5 (5–6)	In the second Delphi round, the majority of votes were in support of prescribing nsNSAIDs without GI protection in patients on SSRIs. However, increased risk of GI bleeding and peptic ulcer is well established when NSAIDs are co-prescribed with SSRIs (latest SR/MA - OR 1.75; 95% CI 1.32–2.33, Alam, 2022) and observational studies suggests reduced bleeding risk when PPIs are added (Table 2, Bixby, 2019). Proposed mechanisms of SSRIs: 1. Platelets release serotonin in response to vascular injury which triggers vasoconstriction and platelet aggregation. This resulting haemostasis is inhibited by SSRI. 2. SSRIs increase vagal tone which increases gastric acidity (Edinoff, 2022). Expert comment and recommendation from Prof. Jackie Hoare (division of Psychiatry, GSH) and Prof. Marc Blockman (Clinical Pharmacology, GSH) on perioperative NSAID use: SSRI treatment should be included in bleeding risk assessment. Literature on the risk associated with ≤ 1 week NSAID treatment in patients on SSRIs is lacking. However, gastroprotection is recommended when NSAIDs are co-prescribed with SSRI. **Recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs and can be administered with acceptable risk.**			

A short course (≤ 1 week) of nsNSAIDs (ibuprofen) + PPI improves the safety of nsNSAIDs AND can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/ references if you disagree with the recommendation
Risk of gastrointestinal adverse events		Round 2 Delphi results	Literature/expert opinion/recommendation			
Q10	Severe rheumatoid arthritis disability	9/16 (56%) undecided – 7/16 (44%) agree. Median (IQR): 6 (6–7)	In the second Delphi round, the majority of votes were in support of prescribing nsNSAIDs without GI protection to patients with severe RA. However, patients with severe RA disability are likely on treatment with anti-inflammatory agents (steroids/DMARDs/methotrexate) increasing risk of GI toxicity. A recently published SR/MA reported that in RA patients treated with NSAIDs, intestinal adverse events were the most common (Paglia, 2021). This is supported in a South African update on NSAIDs and GI risk, which stated that patients with severe RA disability had an increased risk of GI-complications, suggesting adding PPIs when nsNSAIDs are administered (van Schoor, 2014). Expert comment and recommendation from Delphi panel member on perioperative NSAID use: Literature on the risk associated with ≤ 1 week NSAID treatment in severe RA patients (with/without PPI) is lacking. However, patients with severe RA disability are at increased risk of GI toxicity. **Recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs and can be administered with acceptable risk.**			
Q15 (M)	> 75 years old	5/16 (31%) undecided – 11/16 (69%) agree. Median (IQR): 7 (6–7)	Epidemiological studies have demonstrated that ageing is an independent risk factor for NSAID-related GI toxicity (Hernandez-Diaz, 2000) and adding gastroprotection is recommended (Lanza, 2009). Expert comment and recommendation from Delphi panel member on perioperative NSAID use: Literature on the risk associated with ≤ 1 week NSAID treatment in patients > 75 years (with/without PPI) is lacking. However, the elderly are at increased risk of GI vulnerability. **Recommendation: A short course of nsNSAIDs + PPI improves safety of nsNSAIDs and can be administered with acceptable risk.**			

GI: gastrointestinal; PPI: proton pump inhibitor; NSAIDs:non-steroidal anti-inflammatory drugs; nsNSAIDs: non-selective NSAIDs; sNSAIDs: selective COX-2 inhibitors; P2Y12 ADP receptor antagonist: e.g. clopidogrel; DAPT: dual antiplatelet treatment; DOAC: direct oral anticoagulants; VKAs: vitamin K antagonists; SSRI: selective serotonin reuptake inhibitor

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

Appendix 2.4: Miscellaneous

Question 1: In the second Delphi round, non-selective NSAIDs ± proton pump inhibitors (PPIs) were contraindicated (majority of votes disagreed) in patients with a history of aspirin/NSAID induced asthma. Prof. Jonny Peter has advised on the safety of administering selective COX-2 inhibitors in this patient group.

The selective COX-2 inhibitors available to use is parecoxib (IV) and on special request celecoxib (oral).

Questions 2–14: In the second Delphi round, neither selective COX-2 inhibitors nor non-selective NSAIDs + PPI were found to be superior (did not achieve majority vote) when compared to use of non-selective NSAIDs.

Therefore, only non-selective NSAIDs (ibuprofen) will be considered with respect to risk of miscellaneous adverse events (Q2–14) in this third Delphi round. However, if a patient is unable to take oral medication (e.g. during surgery), parecoxib (IVI) or indomethacin (suppository) can be used.

A short course (≤ 1 week) of selective NSAIDs can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/ references if you disagree with the recommendation
	Risk of miscellaneous adverse events	Round 2 Delphi results	Literature/expert opinion/recommendation			
Q1	Aspirin/ NSAID-exacerbated respiratory disease (i.e. wheezing, rhinitis, nasal congestion, cough, shortness of breath or asthma exacerbation)	4/16 (25%) disagree - 11/16 (69%) undecided - 1/16 (6%) agree. Median(IQR): 5(4–-5)	Expert comment and recommendation from Prof. Jonny Peter (Department of Allergology and Clinical Immunology, GSH) on periopertive NSAID use: Aspirin/NSAID-exacerbated respiratry disease (AERD/NERD) is a hypersensitivity reaction (rather than an immunologic reaction) mediated by pharmacologic inhibition of the constitutively expressed COX-1 enzyme. In patients with AERD/NERD phenotype, administration of nsNSAIDs will result in bronchospasm/compromised lung function. However, selective COX-2 inhibitors target the COX-2 enzyme and will not activate the detrimental effects of COX-1 inhibition (Minaldi, 2022). A cross-reactivity study of COX-2 inhibitors in a population with AERD/NERD found that of 753 total drug provocation challenges, only one patient was reported to have a reaction (0.13%, transient urticaria) (Li, 2019). **Recommendation: Patients with a history of isolated respiratory reactions to nsNSAIDs (COX-1 inhibitors) are safe to receive selective COX-2 inhibitors. This includes patients with mild to moderate asthma, who experience worsening of their asthma on exposure to COX-1 inhibitors.**			
NB!	**It is contraindicated to give selective COX-2 inhibitors to patients with poorly controlled asthma with hyperreactivity to COX-1 inhibitors (i.e. only patients with mild to moderate asthma and COX-1 hyperactivity are safe to receive a COX-2 inhibitor). It is contraindicated to give selective COX-2 inhibitors to any patient with a history of a severe reaction involving angioedema, urticaria or cardiovascular collapse to COX-1 inhibitors unless they have been previously challenged and shown to be tolerant to this group of selective cyclooxygenase inhibitors.**					

A short course (≤ 1 week) of nsNSAIDs (ibuprofen) can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/ references if you disagree with the recommendation
	Risk of miscellaneous adverse events	Round 2 Delphi results	Literature/expert opinion/recommendation			
Q2	Inflammatory bowel disease	8/16 (50%) undecided - 8/16 (50%) agree. Median (IQR): 6 (5–7)	The evidence linking NSAID use with inflammatory bowel disease (IBD) flare is inconsistent; it is unlikely that short-term use is detrimental (ECCO Curent Practice position 10; European Crohn's and Colitis Organisation Topical Review on Environmental Factors in IBD, Maaser, 2017). Thus, short-term regimens at lov doses of NSAIDs are safe and should not be avoided in patients with IBD if they are considered necessary (Hijos-Mallada, 2022). Expert comment and recommendation from Professor Gillian Watermeyer (department of Gastroenterology) on perioperative NSAID use: Evidence is conflicting. NSAIDs are generally avoided, however, a short course of NSAIDs less than a week is acceptable in a perioperative setting. **Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q3	Impaired (synthetic) liver function	1/16 (6%) disagree - 8/16 (50%) undecided - 7/16 (44%) agree. Median (IQR): 6 (5–7)	NSAIDs are contraindicated in patients with cirrhosis/advanced chronic liver disease (± portal hypertension) as they can precipitate acute kidney injury (AKI) and gastrointestinal bleeding due to prostaglandin inhibition and increased bioavailability (Recommendation BPA 11; AGA Clinical Practice Update on Surgical Risk Assessment and Perioperative Management in Cirrhosis, 2019 & Canillas, 2023). Expert comment and recommendation from Prof. Mark Sonderup (Department of Hepatology) & Dee Batty ('liver' anaesthetist) on perioperative NSAID use: NSAIDs should preferably not be used in patients with a history of impaired liver function. **Recommendation: In the absence of an alternative analgesia, a short course of NSAIDs (ibuprofen) may be given to patients known with chronic liver disease and classified as Child-Pugh A (mild liver impairment) with fully compensated liver disease, i.e. no jaundice, ascites or abnormal synthetic function (INR > 1.4, albumin < 35 g/L, platelets < 150). NSAIDs are not recommended in patients with advanced chronic liver disease.**			
Q4	Patients with non-union healing of bone	4/16 (25%) disagree - 7/16 (44%) undecided - 5/16 (31%) agree. Median (IQR): 5 (4–7)	Expert comment and recommendation from Delphi panel member on perioperative NSAID use: 1. There is currently no high level evidence that a short perioperative course of NSAIDs would be detrimental to the union in patients undergoing surgery for non-union of fractures (Fragomen, 2020). 2. There are studies showing reduced opioid usage in limb reconstructon patients when NSAIDs are prescribed postoperative. **Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q5	Patients with an upper limb fracture	15/16 (94%) agree	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q6	Patients with a lower limb fracture	16/16 (100%) agree	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q7	Patients with an acute fracture known with high risk of problem healing (e.g. scaphoid)	2/16 (13%) disagree - 7/16 (44%) undecided - 7/16 (44%) agree	Expert comment and recommendation from Delphi panel member on perioperative NSAID use: 1. Current evidence demonstrate no impact of short term NSAID use on fracture healing in patients undergoing fracture surgery. 2. Continued use of > 3 weeks of NSAIDs may be associated with higher rates of non-union or delayed union (Kim, 2021). **Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q8	Multiple myeloma	3/16 (19%) disagree - 7/16 (44%) undecided - 6/16 (38%) agree. Median (IQR): 5 (5–7)	Multiple myeloma (MM) is a disease of the elderly and renal toxicity is a major concern. In MM patients, the kidney function is usually affected by the disease itself and by treatment with bisphosphonates. In the European Myeloma Network Guidelines for the management of Multiple Myeloma-related Complications from 2015, neither short- or long-term NSAID treatment is recommended, which is repeated in the most recent update on pain management for MM patients (Coluzzi, 2019). Expert comment and recommendation from Delphi panel member on perioperative NSAID use: Generally speaking, NSAIDs in myeloma patients should be avoided, even if the creatinine is normal as there is often subclinical renal dysfunction, nephotic syndrome, etc., which places these patients at risk. **Recommendation: A short course of nsNSAIDs is not recommended.**			

A short course (≤ 1 week) of nsNSAIDs (ibuprofen) can be administered with acceptable risk in adult orthopaedic patients with the following characteristics/comorbidities to treat perioperative pain:				I agree with the recommendation	I disagree with the recommendation	Please add comments/ references if you disagree with the recommendation
Risk of miscellaneous adverse events		Round 2 Delphi results	Literature/expert opinion/recommendation			
Q9	Bleeding disorders (e.g. haemophilia, von Willebrand disease, qualitative or quantitative platelet defects, etc.)	12/16 (75%) disagree	**Recommendation: A short course of nsNSAIDs is not recommended.**			
Q10	Neutropenic patients	12/16 (75%) agree	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q11	Porphyria	1/16 (6%) disagree - 12/16 (75%) undecided - 3/16 (19%) agree. Median (IQR): 5	In the American porphyria foundation drug database, ibuprofen is categorised as OK! = Very likely to be safe for prolonged use by individuals with an acute porphyria, based on consistent evidence (https://porphyriafoundation.org/drugdatabase/drug-safety-database-search/). In a recent update on pain managment in acute hepatic porphyrias, treatment with ibuprofen and celecoxib was rated as safe/probably safe (Kazamel, 2022). Expert recommendation from Peter Meissner (UCT porphyria lab) on perioperative NSAID use: Ibuprofen is safe to administer in patients with porphyria. **Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q12	ASA 1 patient	15/15 (100%)	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q13	< 65 years old	16/16 (100%)	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			
Q14	65–75 years old	14/16 (88%)	**Recommendation: A short course of nsNSAIDs can be administered with acceptable risk.**			

NSAIDs: non-steroidal anti-inflammatory drugs; nsNSAIDs: non-selective NSAIDs; COX: cyclooxygenase; PPI: proton pump inhibitor; IQR: interquartlie range; AERD/NERD: aspirin/NSAID-exacerbated respiratory disease; IBD: inflammatory bowel disease; AKI: acute kidney injury; MM: multiple myeloma

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