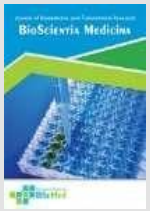
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

A Mechanistic Approach to Post-Operative Analgesia: Safe Use of Etoricoxib in a Patient with Confirmed NSAID-Induced Urticaria/Angioedema (NIUA)

Anindita Rahma Putri[1*], Melati Narulita Inriana[2], Pratiwi Prasetya Prasetya Primisawitri[2], Suswardana[3]

[1]General Practitioner, Department of Dermatology and Venereology, Dr. Mintohardjo Navy Hospital, Jakarta, Indonesia

[2]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Regional General Hospital, Surakarta, Indonesia

[3]Department of Dermatology and Venereology, Dr. Mintohardjo Navy Hospital, Jakarta, Indonesia

ARTICLE INFO

Keywords:
Angioedema
COX-2 inhibitors
Etoricoxib
NSAID hypersensitivity
NSAID-induced urticaria/angioedema

***Corresponding author:**
Anindita Rahma Putri

E-mail address:
aninditarahmaputri@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i10.1402

A B S T R A C T

Background: The management of acute pain in patients with NSAID-induced urticaria/angioedema (NIUA) is a clinical challenge. These cross-reactive hypersensitivity reactions are driven by cyclooxygenase-1 (COX-1) inhibition, precluding the use of most conventional analgesics. This report presents the successful management of severe post-operative pain in a patient with a confirmed, long-standing NIUA phenotype. **Case presentation:** A 56-year-old male with a 40-year history of angioedema induced by multiple COX-1-inhibiting NSAIDs, confirmed by a previous oral provocation test, required urgent herniotomy. Baseline serum tryptase was normal. Post-operatively, initial analgesia with tramadol proved ineffective and induced emesis. Consequently, the patient was administered etoricoxib 90 mg once daily, a highly selective COX-2 inhibitor. This resulted in excellent and sustained pain control, with the Numeric Rating Scale (NRS) score decreasing from 8/10 to ≤2/10 over a seven-day course, and importantly, without eliciting any hypersensitivity reaction. **Conclusion:** This case supports the hypothesis that a highly selective COX-2 inhibitor can provide safe and effective analgesia in patients with severe, cross-reactive NIUA. The analgesic choice was directly informed by the underlying pathophysiology, which involves shunting of the arachidonic acid pathway towards pro-inflammatory leukotriene production following COX-1 blockade. This report reinforces that selective COX-2 inhibition is a rational, first-line strategy for managing pain in this high-risk patient population.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a cornerstone of modern pharmacotherapy, ubiquitously prescribed for their potent analgesic, anti-inflammatory, and antipyretic effects.[1] Their widespread use, however, is significantly constrained by a notable prevalence of hypersensitivity reactions. These reactions are estimated to affect between 0.3% and 2.5% of the general population, with this figure rising substantially in specific patient cohorts, particularly those with underlying chronic inflammatory conditions such as asthma or chronic urticaria.[2]

A clinically significant and challenging subset of these adverse drug reactions is defined by cross-reactivity.[3] In these cases, patients react to multiple, structurally diverse NSAIDs that share a common pharmacological mechanism of action: the inhibition of the cyclooxygenase-1 (COX-1) enzyme. As these reactions are not mediated by drug-specific IgE or T-

cell responses, they are classified as non-immunologic, representing a form of pharmacological idiosyncrasy.[4] Recognizing the need for a standardized nosology, the European Academy of Allergy and Clinical Immunology (EAACI), in conjunction with the European Network on Drug Allergy (ENDA), has developed a comprehensive classification system. This system categorizes NSAID hypersensitivity syndromes based on clinical phenotype, timing of the reaction, and the presence of underlying chronic disease.[5]

The primary phenotypes of cross-reactive, non-immunologic NSAID hypersensitivity include NSAID-exacerbated respiratory disease (NERD), which manifests as acute asthma and rhinosinusitis in patients with underlying chronic respiratory inflammation, and NSAID-exacerbated cutaneous disease (NECD), defined as the acute worsening of symptoms in patients with pre-existing chronic spontaneous urticaria (CSU).[6] A third, crucial phenotype, and the focus of this report, is NSAID-induced urticaria/angioedema (NIUA). NIUA is characterized by the de novo development of urticaria and/or angioedema, typically within minutes to a few hours of NSAID ingestion, in individuals who do not have CSU.[7] This distinction is fundamental for accurate diagnosis and management. NIUA represents a significant portion of NSAID hypersensitivity cases, accounting for up to 56% of such reactions in studies from the Asia-Pacific region.

The pathophysiology uniting these cross-reactive syndromes is a profound disruption of eicosanoid homeostasis, initiated by the blockade of the COX-1 enzyme.[8] This inhibition leads to two critical downstream consequences: first, a marked reduction in the synthesis of protective prostaglandins, most notably Prostaglandin E_2 (PGE_2), and second, a resultant metabolic shunting of the parent substrate, arachidonic acid, down the 5-lipoxygenase (5-LOX) pathway. This leads to the substantial overproduction of pro-inflammatory cysteinyl-leukotrienes (CysLTs). These leukotrienes are potent vasoactive and pro-inflammatory mediators that drive mast cell activation and increase vascular permeability, culminating in the clinical manifestations of urticaria and angioedema.[9]

This well-defined biochemical mechanism creates a profound clinical dilemma, particularly in the peri-operative setting, where effective pain management is not just a matter of comfort but a crucial component of patient recovery, mobilization, and prevention of complications. Clinicians are frequently confronted with the challenge of managing moderate to severe pain in patients for whom the entire class of conventional NSAIDs, and often paracetamol as well, is strictly contraindicated.[10] The development of NSAIDs that selectively inhibit the inducible cyclooxygenase-2 (COX-2) enzyme—which is upregulated at sites of inflammation and trauma—while sparing the constitutive, homeostatic COX-1 enzyme, presents a targeted, mechanistically coherent solution to this therapeutic impasse.

The aim of this report is to detail the safe and effective use of the highly selective COX-2 inhibitor, etoricoxib, for the management of acute post-surgical pain in a patient with a rigorously documented, severe NIUA phenotype. We use this illustrative case as a foundation to discuss the outcome within the broader context of the underlying pathophysiology and the evidence-based hierarchy for analgesic selection in this high-risk population. The novelty of this report lies not in the novelty of the intervention itself, but in its presentation of a methodologically robust case with a 40-year history and formal diagnostic confirmation, serving as a clear educational paradigm for applying first-principle pharmacology to solve a complex clinical problem.

2. Case Presentation

A 56-year-old male physician presented to the emergency department with a two-day history of escalating groin pain and the presence of a non-reducible, tender mass at the umbilicus. A diagnosis of an incarcerated umbilical hernia was made, necessitating an urgent surgical intervention (cito-herniotomy). The patient's past medical history was highly significant. He had a well-established atopic diathesis, including a diagnosis of intermittent

asthma since childhood, which was well-controlled and required only occasional use of an inhaled short-acting beta-agonist, and multiple known IgE-mediated food allergies (to shellfish and peanuts), confirmed by previous skin-prick testing. His history also included essential hypertension, which was stable and well-controlled on a daily regimen of a single-pill combination of an angiotensin II receptor blocker and a diuretic (Table 1).

Table 1. Summary of clinical findings.

Patient Clinical Summary

Comprehensive Baseline and Historical Data

Patient Demographics

Age:	56 Years
Sex:	Male
Occupation:	Physician

Presenting Complaint

Acute, severe abdominal pain diagnosed as an **incarcerated umbilical hernia** requiring urgent cito-herniotomy.

Key Medical History

Atopic History (Well-Controlled)

- **Intermittent Asthma:** Diagnosed since childhood.
- **IgE-Mediated Food Allergies:** Confirmed allergy to shellfish and peanuts.

Comorbidities (Well-Controlled)

- **Essential Hypertension:** Stable on daily medication.

NSAID Hypersensitivity Profile (40-Year History)

DRUG NAME	INDICATION	REACTION DETAILS	LATENCY	CONFIRMATION METHOD
Aspirin	Diagnostic Test	Generalized urticaria progressing to marked periorbital angioedema	~1-2 hours	Formal Oral Provocation Test (OPT)
Paracetamol	Fever / Headache	Mild to moderate periorbital & facial angioedema	~1-2 hours	Formal OPT
Metamizole	Post-procedural Pain	Moderate periorbital & facial angioedema	~1-2 hours	Patient History
Mefenamic Acid	Dental Pain	Severe periorbital & facial angioedema	~1-2 hours	Patient History
Ibuprofen	Muscular Pain	Severe periorbital & facial angioedema	~1-2 hours	Patient History
Sodium Diclofenac	Muscular Pain	Severe periorbital & facial angioedema	~1-2 hours	Patient History

The most critical component of his medical history was a severe, long-standing hypersensitivity to NSAIDs. For four decades, since his teenage years, the ingestion of any standard COX-1-inhibiting analgesic or antipyretic agent consistently precipitated a stereotypical reaction. This reaction was characterized by the onset of pruritus followed by the development of marked periorbital and facial angioedema, occurring within one to two hours of drug administration. The patient provided a detailed list of triggering medications from his personal experience over the years, which included aspirin, paracetamol

(acetaminophen), metamizole, mefenamic acid, ibuprofen, and sodium diclofenac. A crucial diagnostic point was his explicit denial of any history of daily or weekly hives or swelling in the absence of an NSAID trigger. This firmly established that he did not have chronic spontaneous urticaria, thereby distinguishing his condition from NSAID-exacerbated cutaneous disease (NECD) and pointing definitively towards a diagnosis of NIUA (Table 1).

The patient's diagnosis was not based on history alone. Seventeen years prior to the current admission, seeking to formally clarify his condition, he had undergone a comprehensive allergological workup at a specialized center. This included a formal, single-blind, placebo-controlled oral provocation test (OPT) with aspirin, which remains the gold standard for diagnosis. Following a negative challenge with a placebo on the first day, he was administered escalating doses of aspirin on the second day under close medical supervision. After receiving a final cumulative dose of 490 mg, he developed generalized urticaria that rapidly progressed to significant, symmetrical periorbital angioedema, requiring treatment with antihistamines and corticosteroids. This unequivocally confirmed a diagnosis of NSAID-Induced Angioedema. A subsequent OPT with paracetamol was also performed, which elicited a similar, albeit milder, episode of orbital angioedema after a cumulative dose of 1000 mg.

As a physician with insight into pharmacology, the patient had, over the years, cautiously managed rare episodes requiring mild analgesia with a unique, self-devised strategy. He reported anecdotally that he had successfully prevented the onset of angioedema by pre-medicating with the leukotriene receptor antagonist (LTRA) zafirlukast (20 mg) approximately two hours prior to consuming a low dose of an NSAID for minor ailments like a headache. While not a recommended or standard clinical practice, this personal experiment provided a compelling in vivo demonstration of the central role of the leukotriene pathway in the pathophysiology of his specific condition. A summary of his extensive hypersensitivity history is provided in Table 1.

In preparation for the urgent surgery, a panel of pre-operative laboratory investigations was conducted (Table 2). The complete blood count was largely unremarkable, with the exception of a mild peripheral eosinophilia (absolute eosinophil count of 650 cells/μL; laboratory normal range <500 cells/μL), a finding consistent with his underlying atopic phenotype. Liver function tests, renal function tests (including serum creatinine and blood urea nitrogen), and coagulation profiles were all within normal limits.

To exclude a confounding diagnosis of an underlying systemic mast cell disorder (such as systemic mastocytosis or monoclonal mast cell activation syndrome), which can sometimes mimic or overlap with drug hypersensitivity phenotypes, a baseline serum tryptase level was measured. The result was 5.2 μg/L, which is well within the normal range (laboratory normal range <11.4 μg/L), making an underlying mast cell neoplasm highly unlikely and further strengthening the diagnosis of NIUA.

The patient underwent a successful urgent cito-herniotomy with mesh repair under spinal anesthesia, which proceeded without any immediate complications. Upon arrival in the post-anesthesia care unit (PACU), as the effects of the spinal anesthesia began to wane, he reported the onset of severe incisional pain, which he rated as an 8 out of 10 on the numeric rating scale (NRS) (Figure 1). The initial analgesic plan, formulated to avoid the COX-1 pathway, involved the intravenous administration of the weak opioid tramadol (100 mg). However, this intervention proved suboptimal. The patient experienced only minimal pain relief (NRS remained at 7/10), and the administration was poorly tolerated, causing significant nausea and two episodes of vomiting. Due to the lack of efficacy and the distressing side effects, the tramadol was promptly discontinued.

Table 2. Pre-operative laboratory assessment of the patient.

Pre-Operative Laboratory Assessment

Detailed Hematology, Biochemistry, and Immunology Panel

Hematology Panel

PARAMETER	RESULT	REFERENCE RANGE	STATUS
Hemoglobin	14.5 g/dL	13.5 - 17.5 g/dL	Normal
Absolute Eosinophil Count	650 cells/µL	<500 cells/µL	Mildly Elevated
White Blood Cell Count	7.2 × 10^9/L	4.0 - 11.0 x 10^9/L	Normal
Platelet Count	250 × 10^9/L	150 - 450 × 10^9/L	Normal

Specialized Immunology

PARAMETER	RESULT	REFERENCE RANGE	STATUS
Baseline Serum Tryptase	5.2 µg/L	< 11.4 µg/L	Normal

Clinical Interpretation:

A normal baseline serum tryptase level makes an underlying systemic mast cell disorder, such as mastocytosis, highly unlikely. This finding is critical to confidently attribute the patient's symptoms to NSAID-Induced Urticaria/Angioedema (NIUA).

Biochemistry & Coagulation

Liver Function Tests (LFTs):

ALT (Alanine Aminotransferase):	25 U/L
AST (Aspartate Aminotransferase):	22 U/L
Bilirubin (Total):	0.8 mg/dL

All Within Normal Limits

Renal Function Tests (RFTs):

Serum Creatinine:	0.9 mg/dL
Blood Urea Nitrogen (BUN):	15 mg/dL

All Within Normal Limits

Coagulation Profile:

Prothrombin Time (PT):	12.1 sec
INR:	1.0

All Within Normal Limits

Assessment Summary

Laboratory findings were largely unremarkable, confirming the patient was metabolically stable for surgery. The two key findings were:

- **Mild Eosinophilia:** Consistent with the patient's known atopic diathesis (asthma, food allergies).
- **Normal Tryptase:** Effectively ruled out a systemic mast cell disorder as a cause for his hypersensitivity.

These results solidified the diagnosis of NIUA and guided safe peri-operative management.

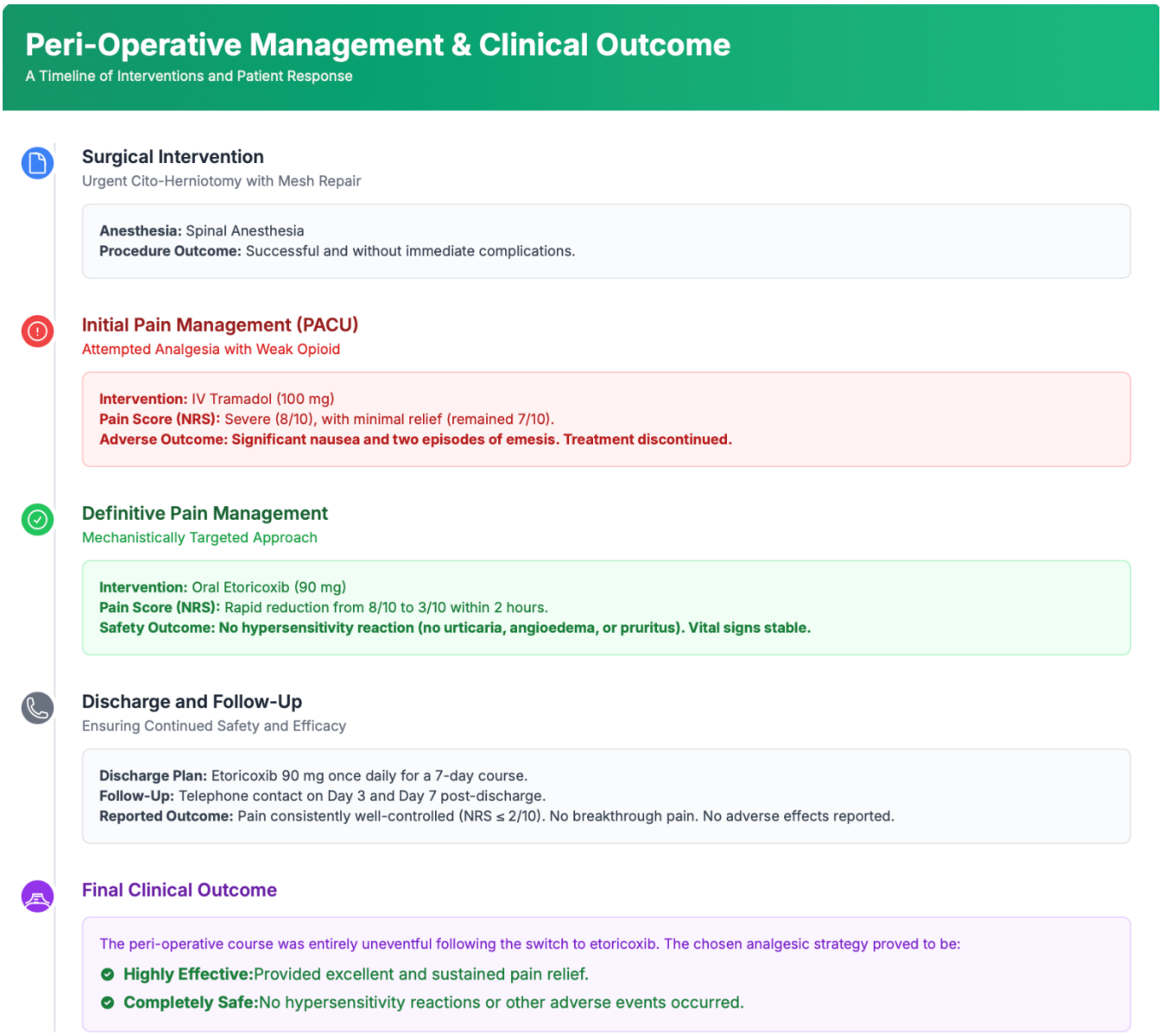


Figure 1. Peri-operative management and clinical outcome.

Given the failure of the initial strategy and the patient's comprehensive and well-documented history of NIUA contraindicating all conventional NSAIDs and paracetamol, a mechanistically targeted approach was implemented. After discussion between the surgical and anesthesiology teams, the decision was made to use a highly selective COX-2 inhibitor. He was administered a 90 mg oral tablet of etoricoxib. The patient was monitored closely for any signs of a hypersensitivity reaction. Within two hours of administration, the patient reported a dramatic and significant reduction in pain, with his NRS score decreasing from 8/10 to 3/10. Critically, he experienced no signs or symptoms of a hypersensitivity reaction: there was no urticaria, no angioedema, no pruritus, no bronchospasm, and no rhinorrhea. His vital signs, including blood pressure, heart rate, respiratory rate, and oxygen saturation, remained stable throughout the monitoring period.

Based on this excellent response, the patient was discharged from the hospital the following day with a prescription for a once-daily regimen of etoricoxib 90 mg to be taken for a total of seven days to manage post-operative pain. Telephone follow-up was conducted on day 3 and day 7 post-discharge. The patient reported that his pain remained consistently well-controlled for the entire duration of the treatment, with NRS scores remaining at or below 2/10. He reported no breakthrough pain and required no rescue analgesia. Furthermore, he reported no adverse effects whatsoever, specifically noting the complete absence of any cutaneous reactions (angioedema or hives), gastrointestinal discomfort, or other side effects. The post-operative course was entirely uneventful, allowing him to ambulate comfortably and participate in his recovery. This outcome demonstrated that etoricoxib was both a safe and a highly effective agent for managing acute, moderate-to-severe surgical pain in this high-risk patient. The clinical course is summarized graphically in Figure 2.

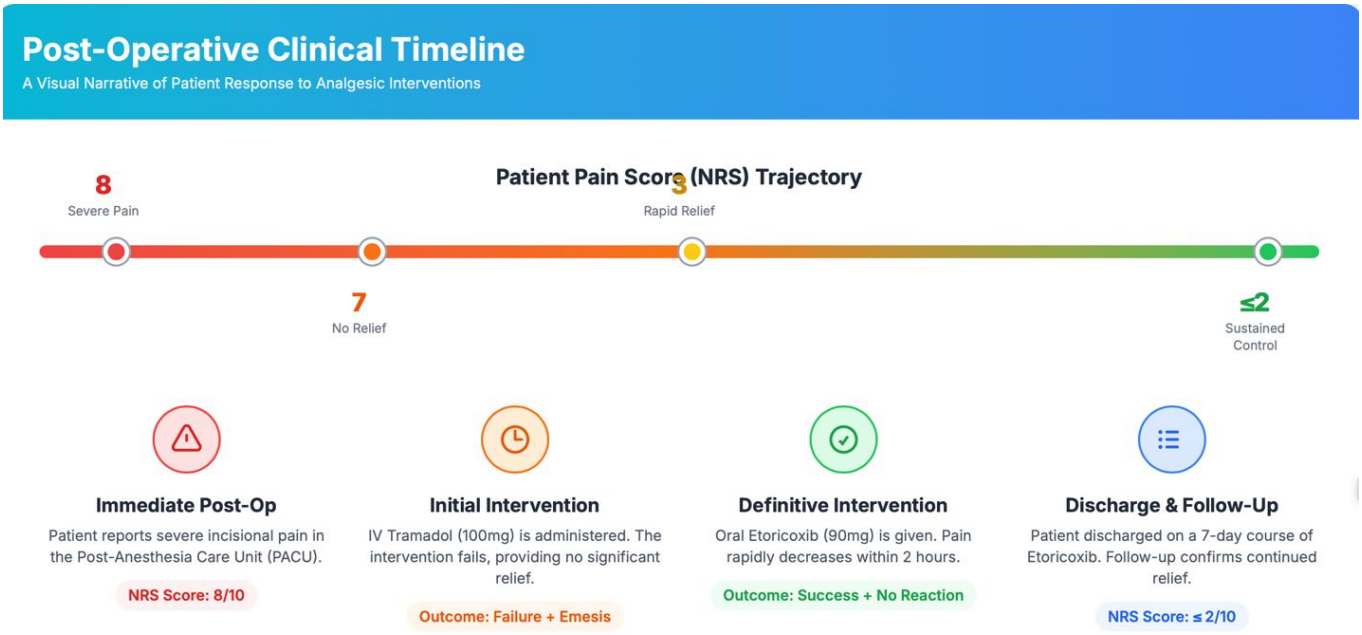


Figure 2. Timeline of post-operative pain management and clinical response.

3. Discussion

This case report details the successful management of severe post-operative pain in a patient with a classic, severe, and formally diagnosed NIUA phenotype.[11] While the safe use of selective COX-2 inhibitors in this population is supported by clinical guidelines and is not, in itself, a novel finding, the strength and educational value of this particular case reside in its methodologically sound diagnostic foundation and its function as a clear, real-world example of applying fundamental pathophysiological principles directly to clinical practice. This case serves as an ideal framework to critically explore the intricate pathophysiology of NIUA and to delineate the evidence-based hierarchy for analgesic management in this challenging clinical scenario.[12]

The core mechanism of NIUA and other cross-reactive NSAID hypersensitivity syndromes is not an immunological reaction in the classic adaptive sense (it is not mediated by drug-specific IgE or T-lymphocytes), but rather a pharmacological one, deeply rooted in the complex biochemistry of the arachidonic acid (AA) cascade (Figure 3). AA is a 20-carbon polyunsaturated fatty acid that is typically

esterified in the phospholipids of cell membranes. In response to various stimuli, such as surgical trauma or inflammation, AA is liberated by the enzyme phospholipase A_2.[13] Once in the cytoplasm, free AA serves as the substrate for two primary, competing enzymatic pathways: the cyclooxygenase (COX) pathway and the 5-lipoxygenase (5-LOX) pathway.

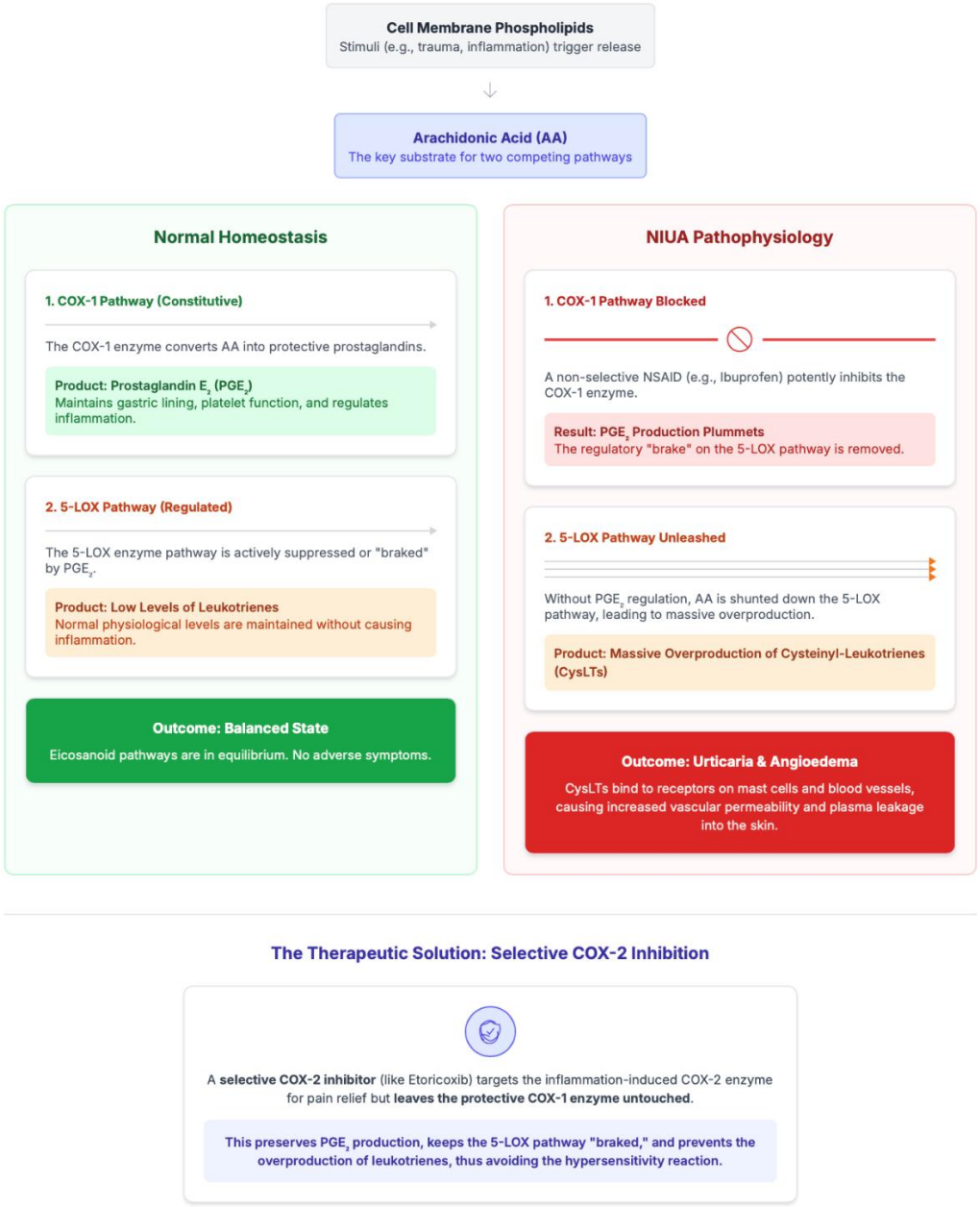


Figure 3. The pathophysiology of NIUA.

Under normal physiological conditions, these two pathways exist in a state of dynamic equilibrium. The COX pathway contains two principal isoforms with distinct roles. COX-1 is a constitutive enzyme, expressed in nearly all tissues, where it is responsible for synthesizing "housekeeping" prostanoids.[14] These include thromboxane A_2, which is essential for platelet aggregation, and cytoprotective prostaglandins that

maintain gastric mucosal blood flow and bicarbonate secretion. In contrast, the COX-2 isoform is typically expressed at very low levels in most tissues but is dramatically upregulated by pro-inflammatory cytokines (such as TNF-α and IL-1β) at sites of inflammation and injury, where it is the primary source of prostaglandins that mediate pain, fever, and the cardinal signs of inflammation.[15]

The key to understanding NIUA lies in the nuanced, dual role of Prostaglandin E_2 (PGE_2), a major product of both COX-1 and COX-2. While PGE_2 is itself a pro-inflammatory mediator at high concentrations, it simultaneously functions as a crucial negative feedback regulator of the allergic inflammatory response.[16] By binding to the EP_2 receptor, which is expressed on mast cells, basophils, and eosinophils, PGE_2 triggers an increase in intracellular cyclic AMP (cAMP). Elevated cAMP levels stabilize these cells, inhibiting their degranulation and, most importantly, directly inhibiting the activity of the 5-LOX enzyme, thereby acting as a powerful brake on the production of leukotrienes. When a susceptible individual with the NIUA phenotype ingests a non-selective NSAID (such as ibuprofen) or even a weak but significant COX-1 inhibitor (such as paracetamol), the potent blockade of the COX-1 enzyme causes a precipitous and systemic drop in the production of this regulatory PGE_2. The loss of this essential braking signal unleashes the 5-LOX pathway, shunting the available AA substrate towards a massive and uncontrolled overproduction of cysteinyl-leukotrienes (CysLTs): LTC_4, LTD_4, and LTE_4.

These CysLTs are exceptionally potent biological mediators, hundreds to thousands of times more potent than histamine on a molar basis in inducing bronchoconstriction and increasing vascular permeability.[17] They exert their effects primarily by binding to the $CysLT_1$ receptor, which is highly expressed on vascular endothelial cells, airway smooth muscle, eosinophils, and mast cells. Activation of the $CysLT_1$ receptor on the vascular endothelium of the skin's post-capillary venules leads to endothelial cell contraction and the opening of inter-endothelial gaps.[17] This results in a dramatic increase in vascular permeability, allowing plasma to leak into the superficial dermis, which manifests clinically as urticarial wheals, and into the deep dermis and subcutaneous tissues, manifesting as angioedema. The patient's reported success in preventing his angioedema by pre-treating with zafirlukast—a direct and selective antagonist of the $CysLT_1$ receptor—serves as a compelling real-world validation of this precise pathophysiological mechanism.

The underlying susceptibility that defines the NIUA phenotype is believed to be genetic, though it is likely polygenic and complex. Research has identified polymorphisms in the genes encoding key enzymes and receptors within this biochemical pathway, such as ALOX5 (the gene for the 5-LOX enzyme), LTC4S (leukotriene C_4 synthase, the terminal enzyme for CysLT production), and CYSLTR1 (the $CysLT_1$ receptor), which may predispose certain individuals to this profound eicosanoid dysregulation upon exposure to COX-1 inhibitors.[18]

Given this well-elucidated pathophysiology, the selection of an appropriate analgesic for a patient with NIUA must be a deliberate, mechanism-based decision. The primary objective is to provide effective pain relief without inhibiting the COX-1 enzyme, thus avoiding the triggering cascade. This imperative establishes a clear therapeutic hierarchy (Figure 4). Often trialed as a first-line alternative, paracetamol is a weak inhibitor of both COX-1 and COX-2 in peripheral tissues, with its primary analgesic and antipyretic effects thought to be mediated through central mechanisms, possibly involving inhibition of a CNS-specific COX-3 variant or modulation of the serotonergic or endocannabinoid systems. While it is tolerated by approximately 70-80% of patients with NIUA at standard therapeutic doses (≤1000 mg per dose), a significant minority of 20-30% will experience a hypersensitivity reaction. This risk is higher in patients with a more severe phenotype or those with co-existing respiratory disease. The patient in this report fell into this higher-risk subgroup, with a

history of reacting to paracetamol confirmed by an OPT, thus eliminating it as a viable option.

Agents such as tramadol and codeine, which exert their analgesic effects through central opioid receptor agonism and do not interact with the COX pathway, are valid mechanistic alternatives. Tramadol's dual mechanism, which includes weak μ-opioid receptor agonism and inhibition of serotonin and norepinephrine reuptake, can be effective for moderate pain.[19] While this class of drugs is a sound choice from a hypersensitivity perspective, its clinical utility is frequently limited by a high incidence of adverse effects, most notably nausea, vomiting, dizziness, somnolence, and constipation. As was clearly demonstrated in this case, these side effects can be severe enough to negate the analgesic benefit and necessitate discontinuation of the drug.

This class of drugs represents a mechanistically targeted and highly effective solution for the NIUA dilemma. By selectively inhibiting the COX-2 enzyme, which is highly expressed at the site of surgical trauma and inflammation, they provide potent, targeted analgesia and anti-inflammatory action. Critically, they spare the COX-1 enzyme at therapeutic doses. This preserves the constitutive production of regulatory PGE_2 from non-inflammatory tissues, maintaining the physiological brake on the 5-LOX pathway and preventing the pathological shunting of AA metabolism towards leukotriene overproduction.[20]

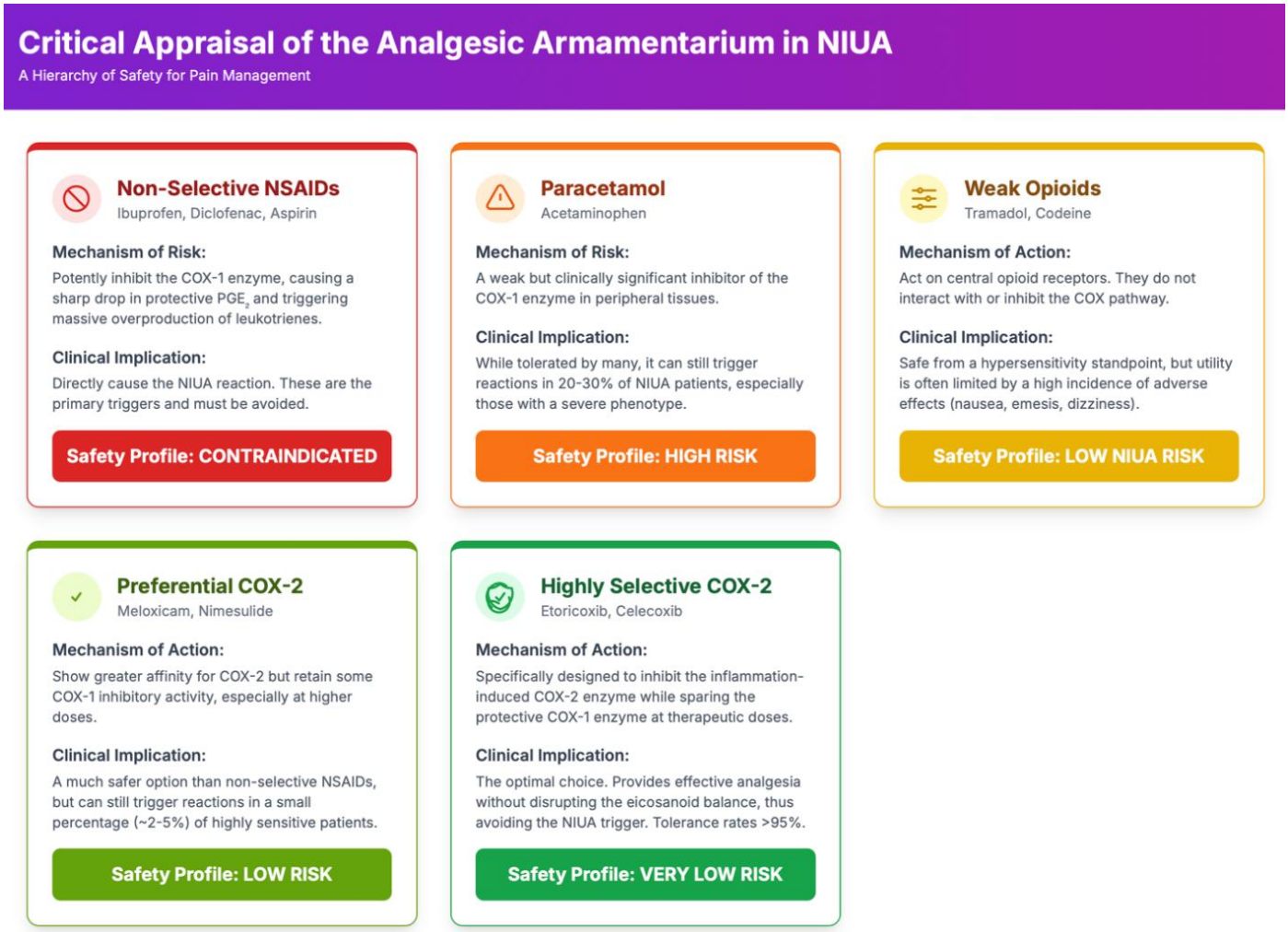


Figure 4. A hierarchy of safety for pain management in NIUA.

Within this class, however, there is an important spectrum of COX-2 selectivity. The preferential COX-2 inhibitors group, which includes drugs like meloxicam and nimesulide, demonstrates a greater affinity for COX-2 over COX-1. However, they still retain a degree of COX-1 inhibitory activity, especially at higher therapeutic doses. While they are significantly better tolerated than non-selective NSAIDs, they can still trigger hypersensitivity reactions in a small percentage (typically 2-5%) of highly sensitive patients. The highly selective COX-2 inhibitors (Coxibs) group, which includes celecoxib and etoricoxib, was specifically designed to possess a very high COX-2/COX-1 selectivity ratio, making them potent anti-inflammatory agents with minimal impact on COX-1. Etoricoxib is among the most selective agents currently available.[19] The evidence supporting their safety in patients with cross-reactive NSAID hypersensitivity is robust. Large-scale studies and case series have consistently demonstrated tolerance rates to both celecoxib and etoricoxib exceeding 95% in this population. The successful and safe outcome in this meticulously documented case adds further support to this strong body of evidence. It is, however, scientifically prudent to avoid the term "completely safe." Rare, idiosyncratic reactions to coxibs have been documented. The mechanisms for these are often unclear and may be distinct from the classic CysLT-mediated pathway. For instance, some reactions to celecoxib, which contains a sulfonamide moiety, have been attributed to sulfonamide allergy, a mechanism not relevant to the non-sulfonamide structure of etoricoxib.[20] Other rare reactions may represent true, drug-specific IgE-mediated responses. Therefore, while the risk is very low, vigilance is always warranted.

4. Conclusion

This case report provides a detailed account of the safe and effective use of the highly selective COX-2 inhibitor, etoricoxib, for the management of severe post-operative pain in a patient with a comprehensively documented, severe NIUA phenotype. The clinical decision-making was predicated on a detailed understanding of the underlying pathophysiology; specifically, selecting a pharmacological agent that targets inflammation-induced COX-2 without disrupting the crucial homeostatic, regulatory functions of constitutive COX-1, thereby circumventing the pathological overproduction of cysteinyl-leukotrienes.

These findings, derived from a single but methodologically well-defined and longitudinally followed case, reinforce the position of highly selective COX-2 inhibitors as a rational, safe, and effective therapeutic choice for pain management in patients with NIUA. The selection of an analgesic in this high-risk population must always be an individualized process, based on a meticulous clinical history, an understanding of the patient's specific phenotype and its severity, and a firm grasp of the pharmacological mechanisms of the available drugs. This report underscores the clinical imperative for surgeons, anesthesiologists, and general practitioners to be thoroughly familiar with these mechanisms to safely and effectively navigate this common and challenging clinical scenario. Finally, there remains a need for further research, including the development of national patient registries and large-scale, prospective, multicenter studies—particularly within genetically diverse populations such as those in Indonesia—to further solidify these management algorithms, confirm safety across different ethnic groups, and continue to enhance patient safety.

5. References

1. Stryjewska-Makuch G, Janik M, Kolebacz B, Ścierski W, Lisowska G. Allergies, asthma or hypersensitivity to NSAIDs - are they an equally important risk factor for the development of a specific CRS phenotype? Otolaryngol Pol. 2019; 74(2): 8–16.
2. Branicka O, Rogala B, Glück J. Eosinophil/neutrophil/platelet-to-lymphocyte ratios in various types of immediate hypersensitivity to NSAIDs: a

preliminary study. Int Arch Allergy Immunol. 2020; 181(10): 774–82.
3. Li L, Laidlaw T. Cross-reactivity and tolerability of celecoxib in adult patients with NSAID hypersensitivity. J Allergy Clin Immunol Pract. 2019; 7(8): 2891-2893.e4.
4. Ben Mahmoud L, Bahloul N, Ghozzi H, Sahnoun R, Khmekhem H, Hakim A, et al. Cross-reactive hypersensitivity to NSAIDs: Experience of a Tunisian allergology center. Rev Fr Allergol (2009). 2021; 61(3): 165–9.
5. Özdemir E, Damadoğlu E, Karakaya G, Kalyoncu AF. A new classification option for NSAID hypersensitivity: Kalyoncu classification. Allergol Immunopathol (Madr). 2022; 50(6): 122–7.
6. Thalappil S, Al-Nesf M. Selective COX-2 inhibitor continues to be a safe alternative in patients with nonselective NSAIDs hypersensitivity. Qatar Med J. 2022; 2022(2): 4.
7. Levenberg G, Bleier J, Leibowitz A, Salomon O, Misgav M, Agmon-Levin N, et al. Nsaids linked to IgA-mediated hypersensitivity vasculitis and Purpura fulminans-like eruption. Eur J Case Rep Intern Med. 2023; 10(11): 004072.
8. Shannon C, Lee J, Sun D. Indomethacin as an alternative to aspirin in determining nsaid hypersensitivity reaction type. Ann Allergy Asthma Immunol. 2023; 131(5): S114–5.
9. Minaldi E, Cahill K. Recent updates in understanding NSAID hypersensitivity. Curr Allergy Asthma Rep. 2023; 23(3): 181–8.
10. Romano A, Gaeta F, Caruso C, Fiocchi A, Valluzzi RL. Evaluation and updated classification of acute hypersensitivity reactions to nonsteroidal anti-inflammatory drugs (NSAIDs): NSAID-exacerbated or -induced food allergy. J Allergy Clin Immunol Pract. 2023; 11(6): 1843-1853.e1.
11. Bellanti JA, Settipane RA. Unraveling allergic, pseudoallergic, and idiosyncratic complexities of hypersensitivity reactions to NSAIDs. Allergy Asthma Proc. 2024; 45(1): 1–4.
12. Nguyen D, Thi Ha TT, Hoang MT, Le NN, Ngoc NN, Minh TP, et al. Polygenic risk score of common genetic variants for NSAIDS hypersensitivity prediction in Vietnamese. J Allergy Clin Immunol. 2024; 153(2): AB157.
13. Trickett J, Chow T. Assessing drug hypersensitivity quality of life in a United States cohort with NSAID allergy label. J Allergy Clin Immunol. 2024; 153(2): AB162.
14. Ben Fadhel N, Chahed F, Ben Romdhane H, Chaabane A, Ben Fredj N, Aouam K. Paracetamol tolerance in patients with previous NSAID hypersensitivity: Identifying risk factors and threshold dosages. J Eur Acad Dermatol Venereol. 2024; 38(6): e490–2.
15. Leong CS, Man CC, Kan AKC, Li PH. Review of NSAID hypersensitivity reactions based on clinical phenotyping. J Clin Rheumatol Immunol. 2024; 24(01): 1–10.
16. Nurmesa A, Zakiyah N, Insani WN. Clinical presentations and characteristics of NSAIDs hypersensitivity in a tertiary care hospital in Indonesia: a case series. Int Med Case Rep J. 2025; 18: 163–71.
17. Simon RA, Woessner K, White AA. Can NSAID-induced urticaria be treated? J Allergy Clin Immunol Pract. 2016; 4(6): 1213–4.
18. DoÑa I, Salas M, Barrionuevo E, Daga OM, Sánchez-Rivas MI, Guerrero MA, et al. Natural evolution of NSAID-induced urticaria/angioedema over a 10-year follow-up. J Allergy Clin Immunol. 2017; 139(2): AB35.
19. Tay SH, Santosa A, Goh ECH, Xu CX, Wu LH, Bigliardi-Qi M, et al. Distinct transcriptomic and metabolomic profiles characterize NSAID-induced urticaria/angioedema patients undergoing aspirin desensitization. J Allergy Clin Immunol. 2022; 150(6): 1486–97.

20. Majid S, Hamzavi-Abedi Y. Dose dependent: a case report of NSAID-induced urticaria and angioedema in an otherwise asymptomatic individual. Ann Allergy Asthma Immunol. 2023; 131(5): S114.