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THE ROLE OF A FIXED COMBINATION OF IBUPROFEN/PARACETAMOL IN THE MANAGEMENT OF ACUTE PAIN: AN ITALIAN EXPERT NARRATIVE REVIEW

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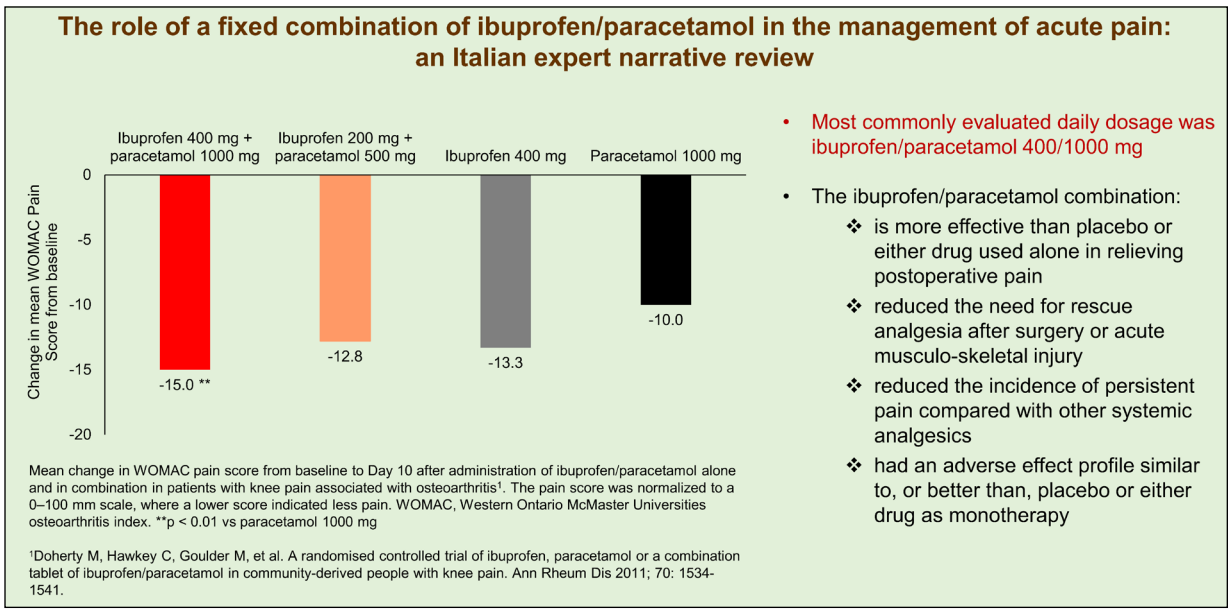
ABSTRACT – An Italian multidisciplinary team of pain management experts reviewed ibuprofen and paracetamol in combination for acute pain. Effective treatment of acute pain should target both inflammation and pain signaling to reduce suffering and prevent the development of persistent pain. The combination of a non-steroidal anti-inflammatory drug (NSAID) and paracetamol appears to be a logical choice: paracetamol primarily acts centrally, while NSAIDs inhibit the inflammation that perpetuates the pain response. Both drugs are rapidly absorbed, reaching maximal concentrations within 1-2 hours. Coadministration may enhance paracetamol absorption, leading to earlier onset of pain relief. The rate of drug interactions between ibuprofen and paracetamol is low, and the two do not directly interact with each other. Multiple studies and meta-analyses have shown that the combination is more effective than placebo or either drug used alone in relieving postoperative pain and reducing the need for rescue analgesia after surgery or acute musculoskeletal injury. The most commonly evaluated daily dosage was ibuprofen/paracetamol 400/1,000 mg. A single-pill combination of ibuprofen and paracetamol also reduces the incidence of persistent pain compared with other systemic analgesics, with an adverse-effect profile similar to, or better than, placebo or monotherapy. When prescribing ibuprofen/paracetamol, physicians should consider age, blood pressure, and concomitant medications, particularly aspirin and warfarin.

KEYWORDS: Analgesia, Post-operative pain, Combination therapy, Inflammation, Non-steroidal anti-inflammatory drugs, Pain relief, Synergic drugs.

INTRODUCTION

The Declaration of Montreal, developed by the International Association for the Study of Pain (IASP) in 2010, states that effective pain relief is a fundamental human right[1]. Unrelieved pain not only causes significant suffering for the individual but also negatively impacts sleep quality, daily functioning, interpersonal relationships, and imposes substantial economic burdens through increased healthcare utilization and lost productivity[2,3]. Acute pain is defined as "the physiologic response to and experience of noxious stimuli that can become pathologic, is normally sudden



Graphical Abstract. Efficacy of ibuprofen and paracetamol alone or in combination at different dosages.

in onset, time-limited, and motivates behaviors to avoid potential or actual tissue loss"[4]. It usually lasts up to 7 days, although it may persist longer in some patients[5]. Acute pain resolves with complete tissue recovery and the cessation of nociceptive stimuli[6].

If nociceptive stimulation persists during the acute phase of pain, patients may develop chronic pain due to pathophysiological changes in peripheral and central signaling pathways[6]. Therefore, effective treatment of acute pain not only alleviates suffering in the acute setting but also reduces the risk of chronic pain and the associated individual and societal burdens.

Acute pain is a significant issue in Italy. Approximately 42% of Italian patients who consulted a primary care physician experienced pain symptoms[7]. Additionally, a study among patients seen in Italian emergency services[8] revealed that two-thirds were experiencing acute pain at the time, with 42% describing it as moderate to unbearable. A survey of hospitalized patients in Italy[9] found that more than one-third (37.3%) had pain at any one time during their admission and more than half (53.3%) had reported pain in the prior 24 hours. Acute pain is more common in Italy than chronic pain; research indicates that 60-75% of Italian patients with any form of pain experience acute pain or acute exacerbation of chronic pain[10,11] and approximately 70% of patients with chronic pain report acute episodes during hospitalization[9].

When pain is present, it is often considerable; a separate report found that 63% of Italian patients who experienced pain during hospitalization in an internal medicine ward rated their pain as more than three on a numerical rating scale of 0-10 (with 0 representing no pain and 10 the worst imaginable pain), which is considered an indication of significant pain[12]. Among patients consulting Continuing Care Services for pain, 88.5% ranked their pain as severe, and 53.9% had been suffering from pain for a number of days (an average of 3 days), despite a high rate of self-medication[13]. Postoperative pain surveys conducted in 2006 and 2012 showed that, while the number of Italian hospitals with an active Acute Pain Service (APS) increased between the surveys, only 50% had an active APS[14]. These findings highlight the unmet need for improved management of acute pain in Italy.

Although the World Health Organization analgesic ladder was originally developed for cancer pain, it is also used for managing chronic non-cancer and acute pain[15]. The ladder recommends starting with simple analgesics and anti-inflammatory agents, escalating treatment as needed to achieve effective analgesia[15]. Although the World Health Organization analgesic ladder has limitations in its application to manage all types of pain, its principles of using oral medications whenever possible, providing around-the-clock pain relief based on pharmacokinetics, and individualizing treatment remain crucial for the management of acute pain[15]. In accordance with these recommendations, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used pain treatments in Italy[7,10,11,16].

The aim of the present article is to describe the rationale for combining paracetamol with the

NSAID ibuprofen for acute pain management in Italy, its therapeutic role, and the evidence supporting its use. The content is based on discussions among a multidisciplinary group of Italian pain management experts (the authors of this manuscript), including specialists in anesthesiology, pharmacology, orthopedics, and physiotherapy.

MATERIALS AND METHODS

A multidisciplinary panel of pain management experts convened in October 2023 to discuss the therapeutic role of the ibuprofen/paracetamol combination for acute pain. The panel included an anesthesiologist (Flaminia Coluzzi), two orthopedic surgeons and traumatologists (Dario Perugia and Paolo Tranquilli Leali), a pharmacologist (Patrizia Romualdi), and a physiatrist (Raffaello Pellegrino). The outcomes of a brainstorming session were gathered using the Metaplan® technique[17]. All inputs were recorded as "Post-it notes" on a virtual whiteboard and then organized into themes to create a conceptual map without redundancies.

These discussions served as the basis for this narrative review. To evaluate the evidence for the combination of ibuprofen and paracetamol, a search of PubMed was conducted in December 2023 using the MeSH terms ("paracetamol" AND "ibuprofen") AND ("acute pain"). The results were screened for relevance and supplemented with additional articles identified from the bibliographies of selected papers or through *ad hoc* searches related to specific topics. Articles in English or Italian were included. The search was updated in May 2024, but no additional relevant papers were identified.

THE RATIONALE FOR IBUPROFEN/PARACETAMOL IN THE TREATMENT OF ACUTE PAIN

Complementary mechanisms of action

Acute pain occurs when tissue injury (mechanical, chemical, or thermal) stimulates nociceptors, triggering a localized inflammatory response and, subsequently, a systemic response[6]. Inflammatory mediators amplify and perpetuate pain by stimulating peripheral nociceptors and afferent C fibres[6]. Therefore, treatment of acute pain should target both inflammation and pain signaling.

NSAIDs exert their anti-inflammatory effects by inhibiting the cyclo-oxygenase (COX) isoenzymes, which convert arachidonic acid to prostaglandins, thromboxane, and prostacyclin[18,19]. In more simplified terms, COX-1 is constitutively expressed and responsible for maintaining renal function, the integrity of the gastric mucosa, and platelet aggregation, while COX-2 is induced during inflammation[18]. However, the reality of COX expression is more complex: COX-2 is also present in healthy tissues, and both isoforms are upregulated in pathological conditions[20]. Furthermore, there are multiple isoforms of COX-1 and COX-2, including one termed COX-3, which is constitutively expressed and has actions overlapping those of both COX-1 and COX-2[21,22]. Nevertheless, the adverse effect profile of NSAIDs depends on their relative selectivity for COX-1 and COX-2 when they are administered at therapeutic doses[23].

The mechanism of action of paracetamol is complex[24,25]; up to seven possible mechanisms have been proposed. Paracetamol can inhibit COX-1 and COX-2, but (unlike NSAIDs) its actions on these enzymes depend on the levels of arachidonic acid and peroxide[24]. This peroxide-dependent inhibition explains the differential activity of paracetamol in the brain, where peroxide concentrations are very low, and accounts for its analgesic and antipyretic effects[25]. Conversely, it does not inhibit COX outside the central nervous system; therefore, its anti-inflammatory activity is negligible, with no clinically significant effects. One hypothesis to explain the antipyretic effect of paracetamol is that it is mediated by COX-3 inhibition in the central nervous system[21]. Paracetamol exerts its analgesic effects centrally *via* several pathways, such as the endocannabinoid and the opioid systems[26,27], serotonergic circuits, and transient receptor potential vanilloid subtype (TPRV) channels, as well as T-type Cav3.2 calcium channels. Peripherally, it acts *via* transient receptor potential ankyrin 1 (TRPA1) channel on sensory nerve endings and Kv7 potassium channels in the dorsal root ganglion[25].

The combination of an NSAID and paracetamol is a logical choice for acute pain because paracetamol is primarily an analgesic. At the same time, the NSAID reduces the inflammation that exacerbates and perpetuates the pain response. The combination has additive effects on pain[24] and allows for the use of lower doses compared with the analgesic doses needed if each drug were used as monotherapy[28].

Ibuprofen is a rational choice for the NSAID in this combination because it is relatively non-selective (i.e., it inhibits both COX-1 and COX-2 to a similar extent) (Figure 1). NSAIDs that are selective for COX-1 tend to carry a higher risk of adverse effects (e.g., renal dysfunction and gastric damage), while those selective for COX-2 are associated with an increased cardiovascular risk[29]. As a result, ibuprofen is the most commonly used NSAID in fixed combination with paracetamol.

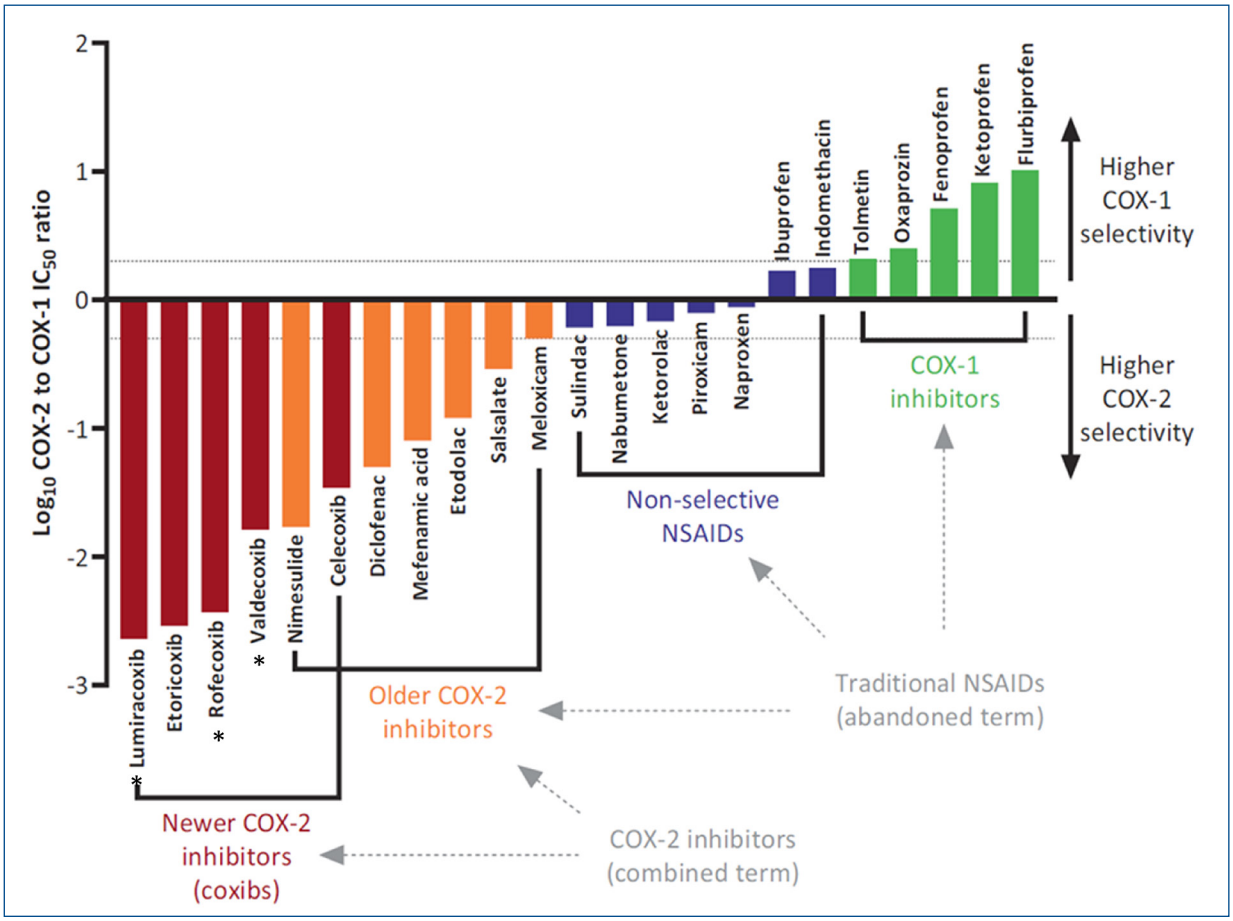


Figure 1. Selectivity of NSAIDs for COX-1 and COX-2 based on the IC_{50} ratio. *Lumiracoxib, rofecoxib and valdecoxib have been withdrawn from the market in most countries worldwide. Reproduced from Bonnesen and Schmidt *Can J Cardiol* 2021; 37(11): 1705-1707[29] (doi: 10.1016/j.cjca.2021.06.014) under a CC-BY 4.0 license (http://creativecommons.org/licenses/by/4.0). COX, cyclo-oxygenase; IC_{50}, half maximal inhibitory concentration; NSAID, non-steroidal anti-inflammatory drug.

Pharmacological compatibility

To successfully combine two drugs in a single pill form, one must not interfere with the pharmacokinetics of the other. Ibuprofen is acidic and highly protein-bound, so it tends to accumulate at sites of inflammation. However, it has a short plasma half-life, which improves its tolerability profile while retaining localized anti-inflammatory activity even during plasma clearance[23].

Numerous studies[30-33] have demonstrated that the pharmacokinetics of both ibuprofen and paracetamol are largely unaffected when they are coadministered. A population pharmacokinetic analysis reported bioavailability of 94% for ibuprofen and 86% for paracetamol after oral administration of the combination pill[31]. Both ibuprofen and paracetamol are rapidly absorbed, reaching maximal concentrations within 1 to 2 hours of administration[34,35]. Indeed, one study suggested that co-administration of these two agents increased paracetamol absorption, potentially leading to earlier onset of pain relief compared with paracetamol alone[32].

Although paracetamol is considered one of the safest therapeutic options for treating acute pain, its propensity to cause hepatotoxicity continues to raise concerns among physicians. The metabolism of paracetamol produces N-acetyl-p-quinone imine (NAPQI), which is hepatotoxic[24], especially when glutathione levels are low, such as in undernourished patients or individuals who abuse ethanol, or when it is chronically administered. In general, daily doses of paracetamol should not exceed 4,000 mg[36]. The overall rate of drug-drug interactions of the ibuprofen/paracetamol combination with other over-the-counter analgesics, as well as the additive effect of other products that contain ibuprofen and paracetamol, is relatively low[37], and the two agents do not interact with one another.

Clinical efficacy

Systematic reviews and meta-analyses, including a Cochrane review, have shown that the combination of ibuprofen and paracetamol is more ef-

fective than placebo, and either drug used alone, for relieving postoperative pain and reducing the need for rescue analgesic medications[28,38,39].

The dose used is an important factor in the clinical effect. In the large-scale Paracetamol and NSAID (PANSAID) combination randomized trial (n = 556), the combination of ibuprofen 400 mg and paracetamol 1,000 mg was significantly more effective in relieving pain during mobilization 6 hours after hip arthroplasty compared with a lower-dose combination (ibuprofen 200 mg and paracetamol 500 mg; p=0.0006). The lower-dose combination was no more effective than paracetamol alone[40]. Additionally, the combination of ibuprofen 400 mg and paracetamol 1,000 mg was significantly more effective in relieving pain at rest 24 hours after surgery compared with paracetamol 1,000 mg alone (p=0.002), while the lower-dose combination was not[40]. In this study, patients in the group receiving the combination of ibuprofen 400 mg and paracetamol 1,000 mg had the lowest consumption of morphine rescue doses in the first 24 hours after surgery (the co-primary endpoint) compared with the other groups [median of 20 mg morphine for ibuprofen 400 mg and paracetamol 1,000 mg *vs.* 26 mg morphine for ibuprofen alone (p=0.002), 28 mg morphine for ibuprofen 200 mg and paracetamol 500 mg (p=0.005) and 36 mg morphine for paracetamol alone (p<0.001)][41]. When using Silverman's Integrated Approach (SIA), which combines rescue opioid use and pain scores, significantly lower scores (better outcomes) were observed during mobilization and at rest in the group receiving ibuprofen 400 mg and paracetamol 1,000 mg compared with the other treatment groups (ibuprofen 400 mg alone, paracetamol 1,000 mg alone, or ibuprofen 200 mg and paracetamol 500 mg; p=0.0001). Furthermore, 2 to 3 times more patients in the ibuprofen 400 mg and paracetamol 1,000 mg group achieved low SIA scores, indicating better pain relief (Figure 2)[40].

Similarly, a randomized trial in patients with knee pain found that the combination of ibuprofen 400 mg/paracetamol 1,000 mg was significantly more effective than paracetamol 1,000 mg alone for relieving pain at the first assessment (day 10; p=0.0012), whereas the lower-dose combination of ibuprofen 200 mg/paracetamol 500 mg was not (Figure 3)[42]. In the same study, ibuprofen 400 mg/paracetamol 1,000 mg was significantly more effective than either paracetamol 1,000 mg or ibuprofen 200 mg/paracetamol 500 mg for improving physical function scores on day 10, and for improving the functional sit-to-stand test at all timepoints during the 3-month study compared with all other comparators (ibuprofen 400 mg, paracetamol 1,000 mg, and ibuprofen 200 mg/paracetamol 500 mg) (p<0.05)[42].

Most studies[28,40,41] investigating the ibuprofen/paracetamol combination for acute pain have been

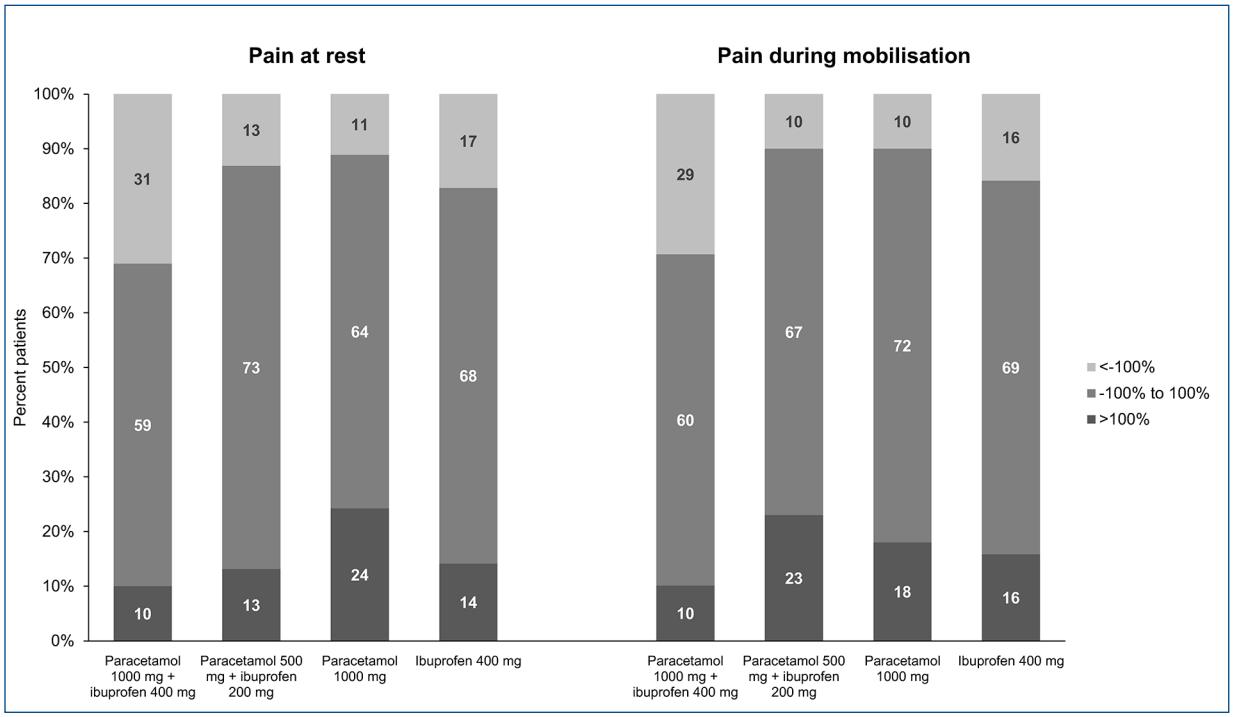


Figure 2. Proportion of patients achieving pain relief at rest and during mobilization in the days after hip arthroplasty in the PANSAID study, assessed using a SIA score that integrates pain severity scores with rescue morphine use[40]. SIA scores could range from –200% to +200%, with lower scores (< –100%) indicating greatest pain relief, higher scores (>100%) indicating least pain relief, and scores of –100% to +100% indicating intermediate pain relief. SIA, Silverman Integrated Analysis.

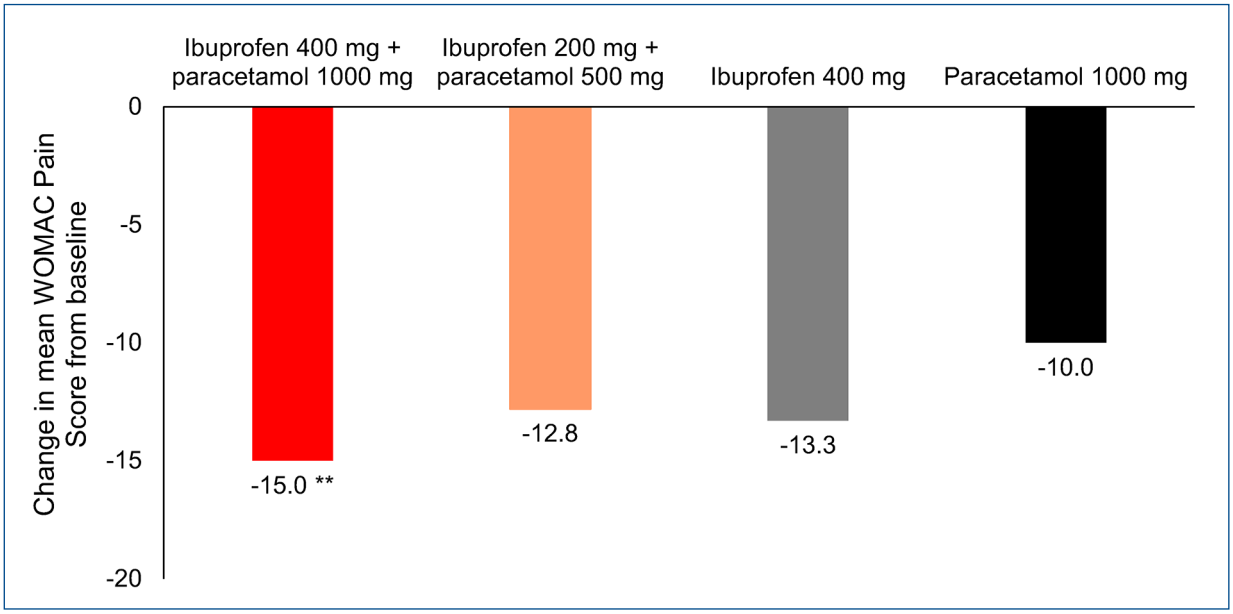


Figure 3. Mean change in WOMAC pain score from baseline to Day 10 after administration of a fixed-dose combination of paracetamol 500 mg/ibuprofen 200 mg (one or two tablets), ibuprofen alone or paracetamol alone in patients with knee pain associated with osteoarthritis[42]. The pain score was normalized to a 0–100 mm scale, where a lower score indicated less pain. WOMAC, Western Ontario McMaster Universities osteoarthritis index. ** $p<0.01$ *vs.* paracetamol 1,000 mg.

conducted in the postoperative setting. However, Chang et al[43] conducted a randomized controlled trial in patients presenting to the emergency department with acute pain in the extremities. The combination of ibuprofen 400 mg/paracetamol 1,000 mg was at least as effective as paracetamol 300-325 mg combined with an opioid (oxycodone, hydrocodone, or codeine) for relieving pain in the first 1 to 2 hours after administration (Figure 4)[43]. These data suggest that using an effective dose of ibuprofen and paracetamol can eliminate the need for opioids in the acute pain setting[43].

This is supported by data from a study[44] in patients undergoing third molar extraction, which showed that ibuprofen 400 mg/paracetamol 1,000 mg was more effective than paracetamol 1,000 mg/codeine 60 mg for relieving pain in the first 6 hours postoperatively. Another group received ibuprofen 400 mg/paracetamol 1,000 mg/codeine 60 mg, but this was no more effective than ibuprofen 400 mg/paracetamol 1,000 mg, indicating that adding codeine to the combination of ibuprofen and paracetamol did not significantly augment the analgesic effect[44]. These results support the hypothesis that NSAIDs play a key role in modulating inflammation and are a proven strategy for an opioid-sparing approach in postoperative pain management.

A randomized study of patients[45] with acute lower back pain showed that 3 days of treatment with a fixed-dose combination of ibuprofen/paracetamol 600/975 mg daily or 3 days of treatment with ibuprofen 1,200 mg/day were both effective in reducing pain. However, the intensity of pain on day 4 was significantly lower, and the proportion of patients with no or mild pain on day 10 was significantly higher in the group receiving the combination than in those receiving ibuprofen monotherapy ($p<0.05$)[45]. While both groups experienced significant improvements in function, patients receiving the combination of ibuprofen and paracetamol required less rescue medication, showed greater mobility (finger-to-floor distance), and reported higher treatment satisfaction than those in the ibuprofen monotherapy group[45].

In addition to relieving pain in the acute setting, there is evidence that ibuprofen/paracetamol reduces the incidence of persistent pain, which may help decrease the number of patients transitioning from acute to chronic pain[46]. An analysis of primary care data from Italy showed that, among 102,216 patients prescribed analgesics for acute musculoskeletal pain, the risk of developing persistent pain (lasting ≥3 months) was significantly lower in patients who received ibuprofen/paracetamol than in those receiving other systemic analgesics (adjusted hazard ratio 0.72, 95% confidence interval 0.61-0.85)[46].

Safety

Both ibuprofen and paracetamol are generally well tolerated with a low incidence of adverse effects[24,35]. Although inhibition of COX-1 has antiplatelet effects, NSAIDs do not significantly increase the risk of postoperative bleeding complications[47]. The spectrum and severity of adverse effects seen during treatment with the combination are similar

to those seen with monotherapy, with common adverse effects including nausea, vomiting, and dizziness[48]. In the PANSAID study, there was no significant difference in the incidence of adverse effects between the groups receiving ibuprofen 400 mg and paracetamol 1,000 mg (15%), ibuprofen 200 mg and paracetamol 500 mg (14%), ibuprofen alone (16%), or paracetamol alone (16%)[41]. Notably, the risk of nausea at 24 hours was significantly lower in the group receiving ibuprofen 400 mg and paracetamol 1,000 mg than in all the other groups ($p \leq 0.04$), and the risk of dizziness at 6 hours was significantly lower than in the paracetamol-only group ($p=0.02$) or the ibuprofen 200 mg and paracetamol 500 mg group ($p=0.04$)[41]. These findings are supported by data from systematic reviews and meta-analyses, which suggest that the incidence of adverse effects with the ibuprofen/paracetamol combination is similar to, or even lower than, that with placebo or either drug given as monotherapy[28,39,48]. According to a meta-analysis of randomized controlled trials[38], the risk of treatment discontinuation due to adverse effects is no higher with the ibuprofen/paracetamol combination than with placebo, regardless of dose.

Some of the differences in adverse effect rates between the treatment arms in studies of acute pain can be attributed to the lack of symptom control or the use of rescue medication (e.g., opioid analgesics), which likely explains the high rate of adverse effects in the placebo arms of these studies[48]. Additionally, adverse effect rates with the combination of ibuprofen/paracetamol do not appear to be dose-dependent[48].

Indications

The combination of NSAIDs and paracetamol is recommended as part of a multimodal approach to postoperative pain management in Italy and helps to reduce the need for opioids in this setting[49]. Similarly, European guidelines recommend multimodal analgesia including paracetamol and NSAIDs for the treatment of acute pain, with a preference for drugs that reduce opioid use[50].

Based on the available evidence[28,40,41], the ibuprofen/paracetamol combination can be considered for any adult patient experiencing acute pain, since the combination of an NSAID and a centrally acting analgesic may provide adequate acute pain relief by targeting both inflammation and nociceptive signals. It is the logical starting point for patients with mild to moderate acute pain; more severe pain or pain that is not relieved by this combination may require a combination with a more potent analgesic such as an opioid.

Treatment choices and dosages need to be individualized based on the patient's phenotype, as outlined later in the text. Regardless of the treatment choice, it is advisable to start treatment as soon as possible after acute pain develops, limit the amplification and perpetuation of pain, and follow the World Health Organization principles of admini-

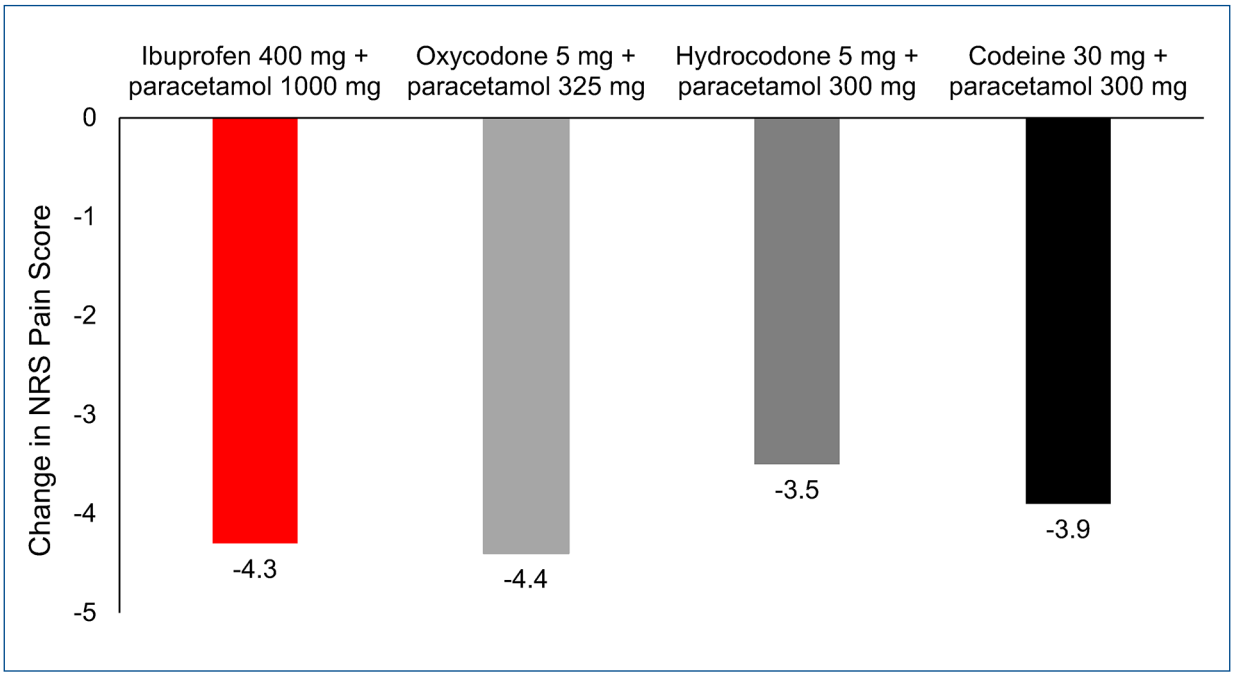


Figure 4. Pain reduction (measured by the change in NRS Pain Score) 2 hours after administration of paracetamol combined with ibuprofen, oxycodone, hydrocodone, or codeine in patients who presented to the emergency department with acute moderate-to-severe pain in the extremities[43]. Pain was rated on an 11-point NRS, where a score of 0 indicated no pain and a score of 11 indicated the worst possible pain. NRS, numerical rating scale.

stering treatment regularly 'by the clock' to ensure optimal analgesia throughout the 24-hour period.

Individualized treatment

While both ibuprofen and paracetamol are well tolerated, certain individuals may need to be considered when prescribing these agents based on age, blood pressure, and concomitant medications. Additionally, older patients may be more susceptible to adverse effects with NSAIDs, particularly if they have compromised renal function[51].

NSAIDs and paracetamol may increase blood pressure by up to ~5 mmHg in hypertensive individuals during continued use[52-54]; the effect of NSAIDs is more marked in patients taking antihypertensive therapy[53], although NSAIDs do not appear to affect the likelihood of a hypertensive individual reaching blood pressure goals[44]. Short-term (≤8 days) administration of ibuprofen does not significantly affect blood pressure in hypertensive patients on diuretic therapy, even at a high dose (3,200 mg/day)[55] or in elderly patients with mild renal impairment[56]. Overall, the evidence suggests that patients taking antihypertensive therapy may safely take the ibuprofen/paracetamol combination for short periods to manage acute pain, provided that appropriate blood pressure monitoring is performed.

Many patients take low-dose aspirin for cardioprotection, and there is a risk that NSAIDs may reduce the antiplatelet effects of aspirin (by competing for COX-1) or worsen the risk of gastrointestinal adverse effects[57]. The risk of an interaction with aspirin is highest when ibuprofen is taken chronically[58], whereas the risk is lower when it is taken occasionally for acute pain. The effect of ibuprofen on the antiplatelet activity of aspirin is time-dependent[59]; therefore, patients can minimize this risk by adhering to specific dosing times, as outlined above.

Both ibuprofen and warfarin are highly protein-bound; however, these drugs allosterically bind to different sites on human serum albumin[60]. Research suggests that ibuprofen stabilizes the warfarin-albumin interaction, reducing the rate of warfarin dissociation from plasma protein, whereas salicylic acid promotes warfarin dissociation[61]. Nonetheless, the clinical significance of this interaction remains unclear. There is evidence that ibuprofen increases bleeding time in patients taking warfarin, even during short-term use, but the risk of clinically significant bleeding is low[62].

These considerations highlight the need for tailored analgesic strategies, focused on the individual patient profile. Currently, the role of personalized medicine, including pharmacogenetic predictors of adverse events in the perioperative period, remains under investigation[63]. In the future, precision medicine will enable personalized analgesic treatments, based not only on clinical observations of comorbidities and concomitant medications, but also on the genetic variability of individuals.

Dosage

Two oral formulations of ibuprofen/paracetamol combinations are available in Italy; one contains ibuprofen 150 mg/paracetamol 500 mg per tablet, and the other ibuprofen 200 mg/paracetamol 500 mg per tablet. The recommended dose of both combinations is 1 to 2 tablets every 6 hours, with a maximum dose of 6 tablets in a 24-hour period. Therefore, the two formulations differ only in the amount of ibuprofen, which may reach 900 mg or 1,200 mg daily, respectively. The double dose of ibuprofen 200 mg/paracetamol 500 mg has been tested in the PANSAID study[40] and other comparative studies described above[42-44]. Although both formulations have not been compared in a direct head-to-head clinical trial, based on the dose-response effect of ibuprofen, the formulation containing 200 mg of ibuprofen would be expected to have a greater anti-inflammatory and analgesic effect than those containing lower doses[64]. It has been suggested that 200 mg represents the smallest clinically useful dose of ibuprofen[65].

All NSAID/paracetamol combinations have dose-dependent antinociceptive effects[66], and should be administered at the lowest dose that achieves effective analgesia and for the shortest time necessary, to minimize adverse effects[49,50]. For paracetamol, the risk of cardiovascular, gastric, or renal adverse effects, and mortality, is lower when the drug is taken for short periods (rather than continuously) and/or at low doses[67]. At maximal doses of the combinations available in Italy, the risk of paracetamol-induced hepatotoxicity is low because the total daily paracetamol dose is ≤ 4,000 mg[68]. Importantly, the addition of ibuprofen to augment the analgesic efficacy of paracetamol can be helpful in limiting the paracetamol dose necessary to achieve adequate analgesia.

Patient counselling

Paracetamol or ibuprofen are common choices as first-line monotherapy for pain conditions, such as headaches or other acute pain episodes. However, paracetamol or NSAID alone is less effective than the combination for acute pain, and patients should be advised that the combination targets both inflammatory and pain pathways to speed up recovery. In acute pain conditions, the additive effect of paracetamol and ibuprofen in combination may alleviate pain more effectively.

The synergy between paracetamol and ibuprofen is essential for reducing the amount of the NSAID required to provide effective analgesia. According to pharmacokinetic data, patients should be advised to take the combination on an empty stomach[33]. Those taking low-dose aspirin should

take ibuprofen-containing products at least 30 minutes after or 8 hours before taking immediate-release aspirin, in order to avoid a reduction in the antiplatelet activity of aspirin, especially in patients under secondary prevention[69]. Patients should also be advised not to augment combination therapy with additional doses of over-the-counter paracetamol, as this may lead to accidental overdose.

CONCLUSIONS

The single pill combination of ibuprofen/paracetamol is an effective and well-tolerated analgesic with a rapid onset of action (within 2 hours of administration), which is suitable for use in the acute pain setting. This combination may be as effective as those containing codeine and hydrocodone and, therefore, has the potential to limit the use of opioids for acute pain. Both paracetamol and ibuprofen are well tolerated, and the use of the two drugs in combination provides a well-tolerated and useful alternative to traditional multimodal analgesia. This approach has the potential to optimize pain control and reduce the doses of each agent used as monotherapy. There are a few safety concerns when this combination is used occasionally for acute pain, provided that patients are appropriately counselled on how to take this treatment.

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Conflict of Interest
FC and PR declare that they have served as consultants for Sandoz. PTL, DP and RP have no conflict of interest to disclose.

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Authors' Contributions
Conceptualization: FC; methodology: FC and PR; investigation: FC, PTL, DP, RP, PR; supervision: FC; writing - original draft: FC, PTL, DP, RP, PR; writing - review and editing FC and PR.

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Data Availability
Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Ethics Approval and Informed Consent
Not applicable.

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