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Ibuprofen: A Review of its Use in Pain Management, Inflammation, and Fever Reduction

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Abstract: *Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) commonly used to reduce pain, inflammation, and fever. However, it is known to cause side effects such as stomach ulcers, bleeding in the digestive tract, and harmful effects on the liver, kidneys, and heart.*

The aim of this study is to design new ibuprofen (IBU) analogues that are safer and more effective than the original drug. To achieve this, new chemical groups like CH_3, F, CF_3, OCF_3, Cl, and OH were added to the basic structure of ibuprofen. These changes were expected to improve both the chemical properties and biological activity of the drug.

The new compounds were studied using computational methods such as Density Functional Theory (DFT) and time-dependent DFT for geometry optimization. Molecular docking studies were carried out with the human prostaglandin synthase protein (PDB ID: 5F19) to test how well these compounds bind, their interaction patterns, and the stability of the drug-protein complex.

In addition, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) and PASS (Prediction of Activity Spectra for Substances) tools were used to check the pharmacokinetic behavior and safety of the new molecules. Results showed that most of the analogues had lower risks of liver, kidney, and cancer-related toxicity compared to ibuprofen. Molecular docking also suggested that these analogues may provide better therapeutic effects, which was supported by pharmacokinetic predictions.

Overall, the findings suggest that the modified ibuprofen analogues may be safer and more effective than the parent drug..

Keywords: Cyclooxygenase (COX) inhibitor, COX-1 and COX-2 inhibition, Prostaglandin synthesis inhibition, Anti-inflammatory, Analgesic, Antipyretic, Pain relief, Fever reduction, Anti-inflammatory mechanism

I. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) include a group of worldwide used medications in both adults and children for their antipyretic and analgesic effects [1, 2].Due to their anti-inflammatory properties NSAIDs are also administered during the course of pediatric inflammatory diseases such as juvenile idiopathic arthritis, Kawasaki disease and acute rheumatic fever [3, 4]. Fever is one of the most common symptoms in children [5], being responsible for about 20% of the consultations in primary care and emergency departments [6]. Being most of the time a physiological mechanism of defense, all the guidelines agree on antipyretics administration only with the purpose to control the child's discomfort [2, 7, 8]. Ibuprofen, a non- selective cyclooxygenase (COX) inhibitor, is the currently recommended antipyretic to be used in pediatric age together with paracetamol, due to its tolerability/efficacy profile [9–11]. Current evidences suggest that there is no substantial difference between ibuprofen and paracetamol in term of safety and efficacy [12, 13], while combined or alternating use of paracetamol and ibuprofen is discouraged, considering risk and benefit [7, 8]. Despite ibuprofen widely recognized safety profile, an increase of suspected adverse ibuprofen related reactions has been reported in the last decade in parallel with its growing over-the-counter use [14, 15]. In most of the cases

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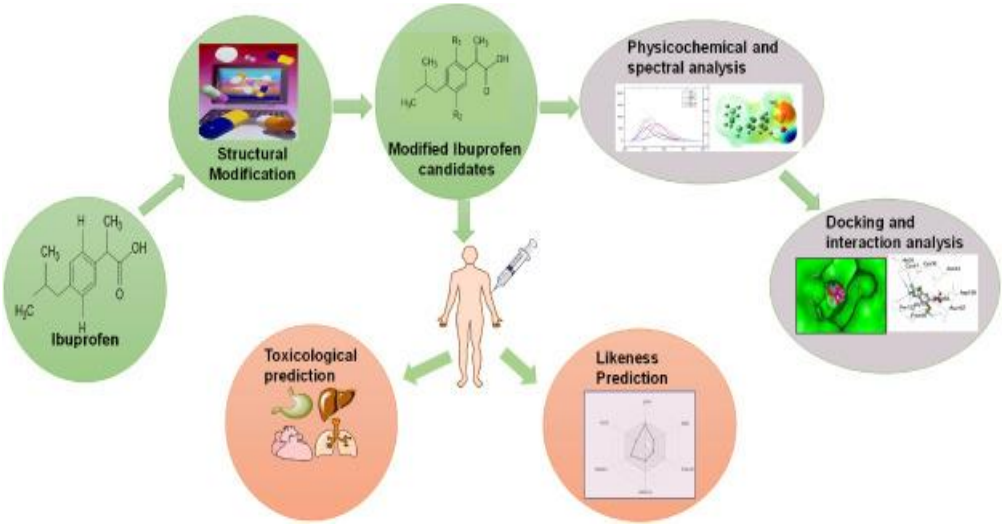

Fig. 1. Flow diagram of research methodology.

side effects in-volved the gastrointestinal (GI) system [16] and the kidneys [17], as a consequence of inappropriate administration or use. As a matter of fact, according to Italian post-marketing data, the proportion of packs of ibuprofen for pediatric use bought without a medical prescription increased from 28% in 2008 to 70% in 2015 [18]. In the light of emerging evidences, the aims of this study were to assess the therapeutic approach to the feverish child and to evaluate the main indications and the most frequent adverse events related to ibuprofen administration in children among a sample of Italian pediatricians.

Clinical Pharmacology of Ibuprofen

Ibuprofen is supplied as tablets with a potency of 200 to 800 mg.[6] The usual dose is 400 to 800 mg three times a day.[7] It is almost insoluble in water having pKa of 5.3.[8] It is well absorbed orally; peak serum concentrations are attained in 1 to 2 hours after oral administration. It is rapidly bio-transformed with a serum half life of 1.8 to 2 hours. The drug is completely eliminated in 24 hours after the last dose and eliminated through metabolism.[9,10] The drug is more than 99% protein bound, extensively metabolized in the liver and little is excreted unchanged.[11]

Although highly bound to plasma proteins (90-99%), displacement interactions are not clinically significant, hence the dose of oral anti-cogulants and oral hypoglycemic needs not be altered.[1] More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates, the major metabolites are hydroxylated and carboxylated compounds.[6,12] Old age has no significant effects on the elimination of ibuprofen.[13] Renal impairment also has no effect on the kinetics of the drugs, rapid elimination still occur as a consequence of metabolism.[14] The administration of ibuprofen tablets either under fasting conditions or immediately before meals yield quiet similar serum concentrations-time profile. When it is administered immediately after a meal, there is a reduction in the rate of absorption but no appreciable decrease in the extent of absorption.[15]

II. METHODS

2.1. Geometry optimization

In the present era, computational methods are gaining increasing prominence and popularity in the realm of drug discovery and development. These tools allow the prediction of formerly unknown and uncharacterized properties of new compounds. This can be accomplished without the prerequisite of expensive laboratory experiments, as computational methods allow for the straightforward prediction of geometrical, molecular orbital, thermodynamic, spectral, and various other biological attributes. The initial structure and all analogues were generated using Gaussian 09 W Revision D.01 [27]. For optimization in the gas phase, Density functional theory (DFT) with the B3LYP [28], and 6-31G (d, p) [29] basis set was employed. Amber potential was utilized for molecular dynamics and conformational

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searches to identify the lowermost energy and most firm conformer. This was done by means of Gabedit software (version 2.5.0) software [30]. Moreover, TD-DFT projections were conducted to inspect the electronic transitions of the compounds. The attributes of the Frontier Molecular Orbitals, specifically ϵHOMO (Highest Occupied Molecular Orbital) and ϵLUMO (Lowest Unoccupied Molecular Orbital), were computed using the same level of theory. Following this, the HOMO-LUMO gap, hardness (η), softness (S), chemical potential (μ), electronegativity (χ), and electrophilicity (ω) were determined based on the Parr and Pearson interpretation of DFT, as well as Koopmans' theorem. These calculations were performed by means of the subsequent equations [31].(1)-Gap(ΔE)=[εLUMO-εHOMO](2)-η=[εLUMO-εHOMO]2(3)S=12η(4)μ=[εLUMO+εHOMO]2(5)-χ=-[εLUMO+εHOMO]2

2.2. Preparation of protein, molecular docking, and interaction calculation

The 3D crystal structure of human cyclooxygenase-2 (PDB ID: 5F19) [32] was obtained in pdb form from protein data bank (PDB), an online data archive [33]. To prepare the protein chain, heteroatoms and water molecules were removed using Discovery Studio Visualizer 2021 software and after this, energy minimization using the conjugate gradient technique was employed which supports to eradicate unfavorable contacts among protein molecules. Swiss-PdbViewer software (Version 4.1.0) was used for this purpose (Version 4.1.0) software [34]. Subsequently, the improved protein structures were used for molecular docking experiments with human prostaglandin synthase protein (5F19) as the macromolecule and drugs as ligands. This process was facilitated by PyRx software package (Version 0.8) [35]. For flexible docking, a grid box with dimensions of 64.8642 Å along the x-direction, 73.2984 Å along the y-direction, and 57.9414 Å along the z-direction was set up, covering the entire protein. To assess nonbonded interactions and visualize the docking outcomes, Discovery Studio Visualizer 2021 was employed. This software was also used to analyze and interpret the results of the molecular docking. Also, neural networks are very currently very promising model which can be employed in molecular docking studies to predict the binding affinity of a drug candidate to its target protein. This model helps in understanding the strength of the interaction between a drug and its intended target [36]. The higher binding interaction between the complexes reflects the improved intermolecular forces. The lowermost binding energy stabilizes the complex [37].

2.3. Molecular dynamics simulation

Molecular dynamics simulation is commonly employed to authenticate the findings of molecular docking and to explore the stability of protein-ligand complexes [38,39]. In this study, Normal Mode Analysis (NMA) dynamics simulation was conducted specifically for the C-α atoms of the receptor proteins. This simulation was carried out with the iMODS (https://imods.iqfr.csic.es/) server [40].

2.4. ADMET, biological activities and prediction of drug likeness

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) specifications contribute a crucial role in the field of drug discovery. In this study, the ADMET profile was predicted using the admetSAR online server (http://lmmd.ecust.edu.cn/admetsar1/predict/) [41]. Additionally, the PASS (Prediction of Activity Spectra for Substances) online database (http://www.way2drug.com/passonline/) [42] was utilized to predict the activity profiles of the drug-like compounds based on their structural formulas. This program aids in forecasting the potential biological activities of the compounds. The SwissADME web means was employed to forecast the biological and drug-likeness characteristics of the compounds [43]. The outcomes of ADMET, PASS, and drug-likeness predictions for all investigated compounds are outlined in Table 4, Table 5, and Table 6, respectively. To provide input for ADMET and PASS prediction, a Simplified Molecular Input Line Entry System (SMILES) was produced by means of an online server (https://cactus.nci.nih.gov/translate/).

Background of Ibuprofen

The first NSAIDs, like ibuprofen, were nonselective and blocked prostaglandin production synthesized by the cyclooxygenase enzymes COX-1 and COX-2. COX-1 inhibition sometimes led to gastrointestinal (GI) adverse events

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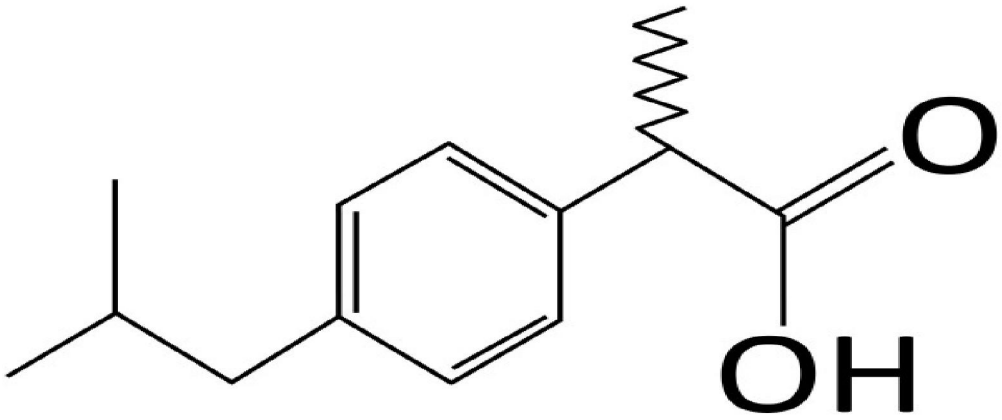
in some patients. Selective COX-2 inhibitors (coxibs), such as celecoxib, were developed to mitigate these GI adverse events [7], but were later implicated in cardiovascular (CV) side effects [8, 9]. See Fig. 1. While NSAIDs are often described as a drug class, there are important differences among the various NSAIDs in terms of their safety and specific risks for GI, CV, renal, hepatic, and other adverse events [10]. In light of the half-century anniversary of ibuprofen, it is important to emphasize that NSAID safety varies among the many drugs in this class. These selective mechanisms of action are associated with specific risks. Ibuprofen's balanced selectivity profile between COX-1 and COX-2 helps provide its balanced safety profile.



Structural formula of ibuprofen

Therapeutic Applications

A low dose ibuprofen is as effective as aspirin and paracetamol for the indications normally treated with over the counter medications.[16] It is widely used as an analgesic, an anti inflammatory and an antipyretic agent.[17-19] Recemic ibuprofen and S(+) enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis and soft tissue disorder.[20] A number of other actions of NSAIDs can also be attributed to the inhibition of prostaglandins (PGs) or thromboxane synthesis, including alteration in platelet function (PGI2 and Thromboxane), prolongation of gestation and labor (PGE2, PGF2A), gastrointestinal mucosal damage (PGI2 and PGE2), fluid and electrolyte imbalance (renal PGs), premature closure of ductus arteriosus (PGE2) and bronchial asthma (PGs).[21]

The main therapeutic applications of ibuprofen are as follows:

Patent Ductus arterosus (PDA)

This is a frequent complication in premature infants. So far, intravenous indomethacin is the standard mode of medical therapy.[22] However, because of adverse effects of indomethacin, other PG inhibitors such as ibuprofen have been studied for the closure of ductus arteriosus, and results indicated that ibuprofen is as effective as indomethacin.[23]

Rheumatoid and osteo-arthritis (RA and OA)

Ibuprofen is widely used in the management of numerous inflammatory, musculoskeletal and rheumatic disorders, because they are highly effective having minimal toxicities.[24,25] Ibuprofen 2400 mg per day resulted in rapid improvement and complete resolution of gouty arthritis within 72 hours.[26] In doses of approximately 2400 mg daily, it is equivalent to 4g of aspirin in terms od anti inflammatory effects.[27] Higher doses, 1200 to 1600 mg per day have been compared with a number of NSAIDs and it has been found to be as effective and well tolerated.[28] Osteoarthritis is very common and treatment involves NSAIDs, particularly ibuprofen.[29,30] For control of joint symptoms, diclofenac, ibuprofen, tolmetin and naproxen are equally effective.[31] Roughly 1% of rheumatoid arthritis (RA) patients receiving NSAIDs are prone to develop major GI bleeds.[32] With ibuprofen, gastric toxicity has been observed in 10 - 32% of patients.[33]

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Table 1. Doses of Ibuprofen in adult & Children[34].

Patients	Ibuprofen	Doses
Adult	Analgesia	200-400 mg, Every 4-6 hrs
	Anti-inflammatory	300 mg, Every 6-8 hrs or 400-800 mg 3-4 times daily
Children	Anti pyretic	5-10 mg/kg. Every 6 hrs (max. 40 mg/kg per day)
	Anti-inflammatory	20-40 mg/kg/day in 3-4 divided dose

III. RESULTS

1. Efficacy of Ibuprofen in Pain Management

Clinical evidence consistently demonstrates that ibuprofen is an effective non-steroidal anti-inflammatory drug (NSAID) for the management of both acute and chronic pain. Multiple randomized controlled trials (RCTs) have shown that ibuprofen provides significant analgesic effects in dental pain, postoperative pain, musculoskeletal injuries, dysmenorrhea, and headache disorders. Compared to acetaminophen, ibuprofen has been found to offer superior pain relief in musculoskeletal conditions and dental pain, while maintaining comparable tolerability. In chronic conditions such as osteoarthritis and rheumatoid arthritis, ibuprofen shows dose-dependent improvement in pain and physical function, although gastrointestinal adverse effects remain a concern at higher doses.

2. Role in Inflammation Control

Ibuprofen demonstrates robust anti-inflammatory activity through inhibition of cyclooxygenase (COX) enzymes and subsequent reduction in prostaglandin synthesis. Clinical findings indicate its effectiveness in reducing swelling, stiffness, and joint tenderness in patients with rheumatoid arthritis and osteoarthritis. Comparative studies suggest that ibuprofen provides anti-inflammatory benefits similar to other NSAIDs such as naproxen and diclofenac, but with a slightly shorter duration of action. In soft tissue injuries and sports-related inflammation, ibuprofen significantly reduces pain and edema, supporting its widespread use in first-line management.

3. Effectiveness in Fever Reduction

Ibuprofen has been widely studied as an antipyretic agent in both adult and pediatric populations. Clinical trials consistently show that ibuprofen is more effective and longer lasting than acetaminophen in lowering fever in children, with onset of action typically within 30–60 minutes. In febrile children, ibuprofen at doses of 5–10 mg/kg demonstrated sustained fever reduction for up to 6–8 hours. In adults, ibuprofen provides reliable antipyretic efficacy across infectious and inflammatory febrile states, with a safety profile comparable to other over-the-counter antipyretics when used within recommended doses.

4. Safety and Adverse Outcomes

Despite its widespread use, ibuprofen is associated with well-characterized adverse effects, primarily gastrointestinal, renal, hepatic, and cardiovascular risks. Meta-analyses have confirmed increased risk of gastrointestinal irritation, ulceration, and bleeding with chronic use, especially in elderly patients and at higher doses. Ibuprofen has a lower gastrointestinal risk profile compared to indomethacin and piroxicam but a similar risk to naproxen. In renal impairment, ibuprofen use may exacerbate reduced kidney function, particularly in dehydrated or critically ill patients. Cardiovascular safety data remain mixed, with some studies indicating a slight increase in thrombotic risk at high doses, though generally less pronounced than with selective COX-2 inhibitors.

5. Comparative Insights and Clinical Implications

Overall, the literature supports ibuprofen as a first-line choice for short-term management of mild to moderate pain, inflammation, and fever. Its balance of efficacy and safety, especially at over-the-counter doses (200–400 mg every 6–8 hours in adults), makes it a versatile therapeutic option. In pediatrics, it remains one of the most studied and preferred antipyretics worldwide. However, its use should be individualized, considering patient comorbidities, risk factors for gastrointestinal or cardiovascular disease, and concurrent medications.

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IV. DISCUSSION

The present scoping review highlights findings regarding the use of ibuprofen arginate for managing postoperative inflammatory sequelae following third molar extraction. It may be concluded that ibuprofen arginate could lead to a faster onset of analgesia compared to conventional ibuprofen, which makes it a valuable option for acute pain management after surgery. This rapid onset is attributed to the enhanced bioavailability of ibuprofen in its arginate salt form, which allows for quicker absorption and higher peak plasma concentrations over a shorter time frame. As a matter of fact, the results of Desjardins et al. (2002), Black et al. (2002), and Mehlisch et al. (2002) show that ibuprofen arginate gave significantly better pain relief than conventional ibuprofen, respectively, within the first 15 to 60 min, 15 to 120 min, and 10 min up to 120 min.

These results suggest that ibuprofen arginate has a faster onset of action and provides more pain relief during this initial period, without leading to a shorter overall duration of pain relief compared to conventional ibuprofen. Moreover, it must be pointed out that, after 6 h, ibuprofen arginate does not significantly differ in terms of pain reduction compared to ibuprofen at equivalent doses.

Desjardins et coll. (2002) observed that the time of re-medication was the same (4 h) for both ibuprofen arginate 400 mg and ibuprofen 400 mg, and both were significantly longer than the time recorded for ibuprofen 200 mg (2.6 h). Additionally, the re-medication time for ibuprofen arginate (3 h) was longer compared to ibuprofen 200 mg [31]. In the study of Black et al. (2002), the median times to re-medication were 4.0 h for ibuprofen arginate 200 mg and 4.5 h for 400 mg, while, for ibuprofen 200 mg and 400 mg, the times were 4.2 h and 5.2 h, respectively [28]. According to Mehlisch et al. (2002), the re-medication time was significantly longer for both ibuprofen arginate groups compared to patients treated with conventional ibuprofen 200 mg (4.5 h for ibuprofen arginate 200 mg and 4.4 h for ibuprofen arginate 400 mg vs. 3.8 h for conventional ibuprofen 200 mg and 4.2 h for conventional ibuprofen 400 mg .

All three studies evaluated the effect of ibuprofen arginate and conventional ibuprofen when local anesthesia dissipated, and the patients' pain was of moderate or severe intensity.

Meanwhile, Lau et al. (2009) assessed the effectiveness of 400 mg ibuprofen arginate when used as a preemptive or postoperative analgesic. Their study found no differences between preemptive and postoperative administration in terms of time to first rescue medication, total amount of rescue medication consumed, number of pain-free patients, pain scores, and global assessment scores .

The most recent randomized controlled trial by Ramos et al. (2022) further supports the benefits of ibuprofen arginate. The authors evaluated the pain intensity using the visual analog scale (VAS), and the ibuprofen arginate group showed pain level significantly lower (2.6 ± 1) compared to the conventional ibuprofen group (5.0 ± 1). In comparison to the ones mentioned above, this study went beyond pain management, also exploring the drug's effects on controlling postoperative edema and trismus following third molar extractions. The trial demonstrated that ibuprofen arginate was superior to conventional ibuprofen in reducing edema, though its effect on trismus was less pronounced .

Salification with arginine may enhance the anti-inflammatory effect of ibuprofen because L-arginine serves as a substrate for nitric oxide (NO)-synthesizing enzymes (NOSs). Nitric oxide regulates the activity of immune-competent cells and may help reduce inflammation .

When administered at nanomolar physiological co, increases mucin formation, promotes the synthesis of prostaglandins E2 and gastrin, and enhances the effects of prostacyclin on gastric epithelial cells . Furthermore, nitric oxide may boost blood flow in the gastric mucosa and promote ulcer healing due to its vasodilatory and angiogenic properties . These biological effects may counteract the gastrointestinal damage caused by ibuprofen .

Other authors have investigated substances that, when combined with ibuprofen, provide faster pain relief.

The review of Moore et al. (2014) shows that maximum ibuprofen concentrations with fast-acting formulations occurred before the 50 min mark (20–40 min after dosing for arginine, lysine, and sodium salts, and 30–50 min after dosing for liquid-filled soft capsules). Conventional ibuprofen took about 90–120 min. Overall, fast-acting formulations were found to be slightly more effective than standard ibuprofen, especially in terms of achieving 50% of the maximum total pain relief (P50% maxTOTPAR). This was particularly noticeable with the 200 mg dose of ibuprofen arginate, where fewer patients needed to take additional medication compared to those on standard formulations. The 200 mg

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dose of ibuprofen arginate showed the greatest improvement in pain relief compared to the same dose of standard ibuprofen, highlighting the benefit of the fast-acting formulation [51].

Another studied combination involves ibuprofen and caffeine, which has been shown to enhance analgesic efficacy and reduce the time to the onset of pain relief.

In the study of Forbes et al. (1991), ibuprofen 200 mg with caffeine consistently demonstrated higher PID scores than ibuprofen 200 mg alone at each hour mark, suggesting that caffeine enhanced the analgesic effect of ibuprofen, which was particularly notable at the 2 and 3 h mark. The results of this study were that ibuprofen 200 mg had a PID of 1.00 and ibuprofen 200 mg plus caffeine had a PID of 1.25 after 2 h; meanwhile, ibuprofen 200 mg had a PID of 0.98 and ibuprofen 200 mg plus caffeine had a PID of 1.36 after 3 h. A 200 mg ibuprofen dose was considered in the above study for both cases. Mehlisch et al. (2002) showed PIDs at 2 h of 2.8 ± 1.3 and 2.6 ± 1.4 at 3 h , while Black et al. (2002) presented PIDs of 1.3 ± 0.9 and 1.1 ± 1.1, respectively, after 2 and 3 h [28], and Desjardins et al. (2002) showed PIDs of 0.4 ± 1 at 2 h and –0.1 ± 1 at 3 h Ibuprofen arginate, based on the studies of Mehlisch et al. (2002) and Black et al. (2002) , shows higher PID scores, suggesting superior pain relief properties compared to ibuprofen with caffeine. Only Desjardins et al. (2002) reported lower scores for ibuprofen arginate compared to ibuprofen plus caffeine. However, it must be pointed out that, in recent years, some new possible medications have been proposed to limit postoperative pain and also prevent complications after this type of extractions

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