Review

Parenteral Ready-to-Use Fixed-Dose Combinations of NSAIDs for Multimodal Analgesia – An overview of approved products and challenges

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Review

Parenteral Ready-to-Use Fixed-Dose Combinations of NSAIDs for Multimodal Analgesia – An overview of Approved Products and Challenges

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Abstract: The combination of non-steroidal anti-inflammatory drugs (NSAIDs) with non-opioid analgesics is common in clinical practice for the treatment of acute pain conditions like post-operative and post-traumatic pain. Besides that, and despite the very satisfactory results achieved by oral analgesics, parenteral analgesia is a key tool in the treatment of painful conditions when the enteral routes are not convenient. The parenteral ready-to-use fixed-dose combinations of NSAIDs with non-opioid analgesics like paracetamol or metamizole could play a central role in the treatment of painful conditions since they are able to gather into only one formulation the advantages of multimodal and parenteral analgesia. Surprisingly, only very recently a parenteral ready-to-use fixed-dose combination of Ibuprofen/Paracetamol was launched to the market. This review aims to review the current availability of NSAID-based Parenteral Fixed-dose combinations with paracetamol and metamizole in the European and American markets, and how the combination of such drugs could play a central role in a multimodal analgesia strategy. Also, it is explored how the parenteral formulations of NSAIDs, paracetamol, and metamizole could serve as starting elements for the development of new parenteral ready-to-use fixed-dose combinations. With this review, we concluded that, despite the well-recognized utility of combining NSAIDs with non-opioid analgesics, there are in the literature several randomized clinical trial studies unable to demonstrate clear advantages concerning their efficacy and safety. In the future, it is deemed necessary to perform clinical trials specifically designed to assess the efficacy and safety of these fixed-dose formulations to generate solid evidence of their clinical advantages.

Keywords: fixed-dose combination; NSAID; ready-to-use; parenteral; multimodal analgesia; pain

1. Introduction

Severe acute pain remains a major problem associated with trauma-related injuries and surgery procedures. Acute pain is an unavoidable outcome and all efforts should be performed to manage the impact of painful conditions in the patients' recovery[1–3]. Besides the emotional impact, the suffering induced by untreated acute pain can result in effective physical problems, such as myocardial ischemia, impaired wound healing, delayed gastrointestinal (GI) motility, and poor

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respiratory effort[3,4]. At the same time, the last one can result in atelectasis, hypercarbia, or hypoxemia and thus contribute to a higher incidence of postoperative pneumonia[3].

Among analgesics, opioids are considered a gold standard for the treatment of painful conditions after surgery procedures, however, they present only moderate efficacy in relieving pain during movements and relevant side effects, such as nausea and vomiting and a high risk of addiction[4–6].

Multimodal pain management guidelines have been proposed for non-opioid analgesic procedures aiming to avoid opioid monotherapy strategies or at least to reduce the doses used to treat acute pain[7]. The combination of non-opioid analgesics (NOAs), mainly, paracetamol (APAP), with non-steroidal anti-inflammatory drugs (NSAIDs) is one of the most reported multimodal approaches used in clinical practice[2,8–10]. The practice guidelines for acute pain management issued by the American Society of Anaesthesiologists recognized the well-established use of NSAIDs and APAP (alone and in combination) with effective results in the management of several causes and types of pain[2,3,5,9,11,12]. Also, the Enhanced Recovery After Surgery (ERAS) Society guidelines, recommend a multimodal approach through the systemic administration of NSAIDs and APAP in combination[13,14]. The combination of APAP and NSAIDs has been a central focus of ERAS protocols since it is able to diminish pain and inflammation conditions reducing the need for opioid drugs and can be part of a multimodal analgesia strategy[2,7,9,11,15].

In general, fixed-dose combinations (FDCs) offer the opportunity to improve the therapeutic response in people with insufficient monotherapy[16]. Also, FDCs could contribute markedly to pain management in low-income countries since the availability of opioid drugs in these countries is extremely limited and both NSAIDs and NOAs are in general cheap. Indeed, in 2011 89% of globally available opioids were consumed by only the USA, Canada, the UK, and Australia[1].

Ibuprofen/Paracetamol FDC in tablets are available in the USA and some European markets as over-the-counter products. Also, in some countries of Europe but not in the USA are approved Ibuprofen/Paracetamol FDC for intravenous administration.

Since the parenteral administration of analgesic entities allows a rapid onset of action and pain management in patients that are unable to intake oral formulations[3,7], the parenteral FDCs of NSAIDs with NOAs may play a decisive role in the treatment of acute pain due to the possibility to solve at the same time some limitations related to monotherapy regimens[16].

This work aims to understand the role of ready-to-use parenteral FDCs composed by NSAIDs and NOAs (mainly Paracetamol and Metamizole) in the treatment of acute pain conditions and their increased value when used in multimodal analgesia regimens. Also, we explored the available literature to study the clinical evidence about the efficacy and safety of combining NSAIDs with NOAs to find out scientific results reporting the ability of these combinations to offer higher efficient analgesic capability when parenterally administrated.

2. Multimodal and parenteral analgesia

2.1. Multimodal analgesia

The pain pathway is a complex system where a noxious stimulus is converted into a neural signal resulting in a perception of an unpleasant experience. Beyond the obvious negative impact at the emotional level, acute pain turns deeply challenging the mobilization of the patients and could compromise for instance surgery outcomes [10].

Due to the complexity of pain physiology is not expectable to exist a single analgesic drug able to suppress completely pain perception. To accomplish this, more effective and satisfying results could be achieved by giving the use of multimodal analgesia (MMA) approaches[2–4,10].

MMA entails the administration of different medications with different mechanisms of action to obtain better analgesic outcomes than the administration of each drug alone. At the same time, due to the synergic relationship between the combined drugs, fewer side effects could be observed since the administration of reduced doses of each substance could be possible [2,3,12,17].

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MMA aims to avoid the use of opioids or at least reduce markedly the opiate doses[13]. In the literature, there are several studies supporting that multimodal analgesia is able to promote early mobilization and discharge of patients, lead to fewer readmission rates, and improve patient satisfaction[17]. Also, many works have been reporting that multimodal analgesia is a fundamental approach to minimize unnecessary opioid use and is relevant to manage the risk of opioid addiction[3,17]. In the clinical context, numerous guidelines about pain management procedures have been issued by numerous medical institutions such as the American Society of Anaesthesiologists (ASA), the American Academy of pain medicine (AAPM), Doctors Without Borders (MSF), Orthopaedic Trauma Association (OTA), among others. For instance, in 2015, a partnership between AAPM, ASA and the US Department of Veterans Health Administration, and the Department of Defence, resulted in the definition of new clinical practice guidelines for postoperative pain management[18]. There, the multimodal approach using NSAID combinations with paracetamol is presented as a strong recommendation with high-quality evidence[18]. Additionally, over the last few years, ERAS protocols are becoming the benchmark standards for enhancing postoperative recovery[14]. In these guidelines the essential role of the MMA in the treatment of acute pain conditions allowed to establish the MMA approach itself as the new gold standard of perioperative analgesic management[14].

Several classes of drugs can be used in combination. NOAs (such as APAP), NSAIDs, N-methyl-D-aspartate (NMDA)-receptor antagonists, gabapentinoids, α_2-receptor agonists, local anaesthetics, and SSRIs are some examples of drug classes that are being used as analgesic entities [2,4,7,10,12,14]. At this point, it is very interesting to note that some of these classes of drugs are not originally developed and are not approved to treat painful conditions but to treat other pathologic conditions such as depression, Alzheimer's disease, epilepsy, and hypertension. The reason why this heterogeneous group of pharmacological entities could exert potent analgesic outcomes is explained by the physiology of pain and its mechanisms of transmission[17]. Based on the type, location, and patient´s perception of the pain, one or more pain pathways can be targeted using analgesic combinations[17]. Roughly, the pain can be divided into nociceptive and neuropathic types. The first one has physiological proposes and is related to noxious stimuli and tissue damaging and the second one is precepted when the somatosensory system is damaged itself and is recognized as a pathological condition[17,19].

2.2. Parenteral analgesia

Parenteral administration of analgesics allows the administration of drugs when the other most convenient routes are not clinically available[3,7]. The most common parenteral routes of administration of analgesics are the intravenous (IV), intramuscular (IM), and subcutaneous (SC) routes[20]. Indeed, parenteral analgesia in one of the most common approaches used in the management of acute and post-operative pain substances is the IV route[14,21].

The IM and SC routes are commonly employed for the treatment of acute pain. However, after surgery, other routes are to be preferred because of the high risk of poor perfusion and thus the occurrence of inadequate analgesia or in late side effects due to the delayed distribution of the drugs[20]. Concerning IV administration, although IM and SC formulations may be appropriate for patients who are unable to receive oral medications and do not yet have IV access, IV administration is believed to provide the fastest relief[4]. However, it is important to keep in mind that, the costs of intravenous related to the use of IV forms are higher and with no benefit in terms of pain control when compared with other routes of administration[20].

Despite the evident advantages of the use of parenteral analgesics, their development and manufacture can be challenging and expensive[22]. For instance, it is the case of IBP where their very poor water solubility can result in the development of an unstable product and where the risk of crystallization following administration can lead to the formation of aggregates that can generate an embolus in blood vessels[22]. Also, the same occurs with the parenteral formulation of diclofenac sodium due to the poor solubility of diclofenac[23]. In contrast, Metamizole is very soluble in aqueous solutions however stability issues can be raised[24].

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Despite a large number of NOAs and NSAIDs available in the market, there is yet a lack of options concerning parenteral solutions. Until 2020, in the United States of America (USA), only parenteral formulations of paracetamol (APAP), ibuprofen (IBP), and ketorolac (KTLC) had been approved for postoperative pain management in monotherapy regimens [7]. Meanwhile, an intravenous formulation of meloxicam was also approved[25]. Concerning the European market, the number of approved parenteral NOAs and NSAIDs is larger however their availability is different between sovereign countries (Table 1).

2.2.1. Paracetamol-based parenteral formulations

The mechanism of action of APAP is not completely known. However, it is probably mediated through the COX-inhibition in the central nervous system[13,26,27]. Some works have been suggesting that it acts inhibiting particularly COX inhibitor-3 which is a COX-1 isoenzyme but mainly expressed in the central nervous system [13,26]. Also, it has been reported that its analgesic mechanism could be related to the activation of descending serotonergic pathway, indirect activation of cannabinoid CB_1 receptors, and the inhibition of nitric oxide pathways in the central nervous system[3,17].

The APAP metabolite N-arachidonoylaminophenol (AM404) play also a very relevant role concerning analgesic activity. As in the case of paracetamol, its mechanism of action is not completely known, however, it seems to act in the blockade of neuronal uptake of anandamide and of neuronal sodium channels[27].

Peripherally, despite APAP exerts COX-1 and 2 inhibition in *in vitro* assays, the expected anti-inflammatory activity is not observed *in vivo* because, at sites of high peroxide concentration (such as sites of inflammation), APAP has reduced and very limited inhibitory activity of COX enzymes[3].

Intravenous administration of APAP and NSAIDs allows a faster onset of effect and a greater peak plasma concentration compared to oral administration[4,7,27]. Additionally, despite the mechanism of action of oral and intravenous (IV) APAP is the same, the IV administration seems to be less hepatotoxic than the oral route due to the absence of first-pass phenomena[4]. Surprisingly, no evidence of hepatotoxicity was observed with IV APAP after administration of 5 g across 24 hours in healthy subjects, a higher dosage than recommended[4].

APAP is the most common analgesic used in MMA since its regimen is well tolerated, with a minimal side effect profile[14]. In Europe and the USA, IV formulations of APAP are available in the market since later 2002 and November 2010, respectively [4,28,29]. The common formulation is 1,000 mg / 100 ml and the brands available are listed on the website of the FDA and on the list of nationally authorized medicinal products (PSUSA/00002311/201705) issued by EMA[30,31].

Despite there are numerous brands of intravenous forms of paracetamol available in the market, their development was always challenging due to the poor stability of paracetamol[32]. Indeed, during degradation, paracetamol is converted by hydrolysis to 4-aminophenol, which is rapidly converted to the hepatotoxic substance N-acetyl-*p*-benzoquinone imine (NAPQI). At the same time, oxidation reactions occur simultaneously. To avoid degradation, the production of the API and respective parenteral formulation should be performed under optimal pH values (range of 5-6) and low oxygen media (bubbling nitrogen)[32].

2.2.2. Metamizole-based parenteral formulations

Metamizole (or dipyrone) is a non-acidic analgesic like paracetamol but belongs to the group of phenazones[33]. As paracetamol, metamizole is a common analgesic and antipyretic but with little anti-inflammatory activity. It is generally well tolerated and is indicated to treat several pain conditions including postoperative pain, headache, migraine, neuropathic pain, cholic pain, and cancer pain[33–37]. In post-surgery proposes, metamizole is a more effective analgesic than paracetamol and at least as effective as NSAIDs[36].

In monotherapy and due to its presumably favorable safety profile, metamizole can be preferred over NSAIDs[33], however, metamizole has been related to some cases of severe neutropenia or agranulocytosis (myelotoxicity) and, due to this fact, it was banned from the market in some countries

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such as USA, UK, Sweden, Canada, Australia, Norway, and India[35–41]. Nevertheless, it continues available in some European and South American countries[33,36–38]. Interestingly, in Germany, its consumption has increasing significantly in recent years[35,36]. Indeed, the numbers about the incidence of metamizole-induced myelotoxicity are controversial and vary widely between studies. However, some studies point to a risk of around 1:1602 and a relative risk of 3.03[35,42]. Several studies have been performed to understand and quantify the real dimension of this risk, but conclusive results have not been obtained and several authors have reported differences in the magnitude of risk of adverse outcomes associated with metamizole use and often had small sample sizes and some other limitations that may have biased the results[40,43].

The mechanisms of action are not completely known however in the literature is suggested that metamizole is a prodrug where its metabolites (mainly act at peripheral and central levels[33,36,37]. 4-N-methyl-aminoantipyrine (4-MAA) is the major metabolite[36,44,45]. 4-MAA is biosynthesized non-enzymatically from metamizole in the GI tract and, due to this fact, the 4-MAA metabolite presents a bioavailability close to 100%, being the main metabolite in plasma [36,44,45].

Some authors reported that the main mechanism of action of metamizole metabolites could be related to the inhibition of COX activity, however, nowadays there is strong evidence that metamizole is not a NSAID since it seems to act directly blocking the hyperalgesia induced by the PGE2 and isoprenaline through a COX-independent mechanism[33,36,37]. Interestingly, as well as paracetamol, despite several studies have demonstrated that metamizole is able to inhibit COX activity (mainly COX-2 activity) however it exhibits a weak anti-inflammatory ability and low GI toxicity[37]. Recently, Gomes F. *et al.* hypothesized that the activation of the PI3Ky/AKT signaling pathway could occur through the agonism of opioid receptors[45]. Indeed, Gonçalves do Santos G. *et al.* have reported that 4-MAA anti-hyperalgesic effect depends on the k-opioid receptor activation, acting as a morphine-like drug[43,45–47]. Despite all of this, metamizole is yet classified as a NSAID by some authors[39].

The mechanism behind the agranulocytosis induction is not fully known, however, some authors excluded a direct toxic effect of metamizole, but it can be related to an immunoallergic reaction[39,42]. In the presence of heme iron, 4-MAA forms reactive electrophilic molecules that are toxic for granulocyte precursors mainly when depletion of the cellular ATP pool exists[36].

In contrast with paracetamol, metamizole is very soluble in water; however, it is a very unstable substance[24,48]. It is well known that metamizole is rapidly and non-enzymatically hydrolyzed to its active metabolite, 4-MAA. In the commercial parenteral formulations, very prolonged stability is achieved using high concentrations of metamizole since the concentration is the major factor in the hydrolysis of metamizole and an increasing concentration of metamizole decreases the hydrolysis rate[49].

In the European market, metamizole for parenteral use is commonly found in vials with 500 mg/1 ml, 1 g/2 ml, 2 g/5 ml for IV or IM use. The list of products available in European countries can be found in the list of nationally authorized medicinal products (PSUSA/00001997/202103) issued by EMA.

2.2.3. NSAID-based parenteral formulations

NSAIDs are the most consumed drugs worldwide and are the most common option available for the nonaddictive treatment of mild-to-moderate inflammatory pain[50]. The main and more well-known mechanism of action of NSAIDs is the inhibition of peripheral COX-1 and 2. These enzymes play a crucial function in the production of pro-inflammatory prostaglandins[2,26]. Other additional mechanisms in the central nervous are being proposed however they are based on *in vitro* and *in vivo* without clear evidence to occur in humans[11]. Indeed, the pharmacokinetic profile of NSAIDs, mainly their low distribution volume, may reveal slow or inadequate penetration of NSAIDs in the central nervous system (CNS) tissues[11].

As in the case of APAP, NSAIDs are also a key element in MMA since they are able to provide superior analgesia with opioid-sparing and present fewer side effects such as nausea, vomiting, and unwanted sedation[14].

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As cited previously, despite the large number of NSAIDs approved in the USA and Europe, they are not always available in parenteral formulations. Currently, there is a lack of IV NSAIDs available in the market and there is a clear need for the development of new IV NSAID formulations[25]. Until recently, in the USA, ibuprofen, and ketorolac were the only NSAIDs approved in IV regimen to treat post-operative related pain[7]. More recently, US FDA approved IV meloxicam for the management of moderate-to-severe pain. However, because of the delayed onset of analgesia, meloxicam alone is not recommended for cases when a rapid onset of analgesia is required.

In Table 1 are presented all the parenteral NSAIDs available in the USA and Europe. The number of NSAIDs authorized in Europe is larger; however, not all of the USA-approved products are approved in Europe. Ibuprofen, ketoprofen, and meloxicam are available for parenteral administration in Europe and in the USA, however, some differences exist. Concerning ibuprofen, in the USA there are available ampoules and flasks with 800 mg/8 ml and 800 mg/200 ml, respectively. In Europe, only large-volume formulations exist. The dose of ibuprofen is higher in the USA since the maximum dose found in Europe is 600 mg and, in the USA, Caldolor® has 800 mg of ibuprofen. As reported above, IV meloxicam was approved recently in the USA. The formulation presented in Anjeso® is 30 mg/1 ml and should be administrated in bolus without the need for reconstitution however the formulation available in some countries in Europe is formulated with half the dose of meloxicam (15 mg/1.5 ml) and must be administrated intramuscularly [51]. Also, there are small differences concerning the formulations of ketorolac approved by the US FDA and in Europe, however, in both cases, the drug can be administrated *via* IV or IM (Table 1). Aspegic® (acetylsalicylate), Xefo® (lornoxicam), Neo-Indusix® (tenoxicam), and Liometacen® (indomethacin) are only available as freeze-dried products. Despite the freeze-drying process is technically challenging, expensive, and yields a fragile and hygroscopic product, in the case of poorly soluble drugs such as indomethacin, tenoxicam, and lornoxicam, it can avoid the undesired crystallization of drugs during their storage[52–54]. Concerning acetylsalicylate, despite its salts are commonly soluble in water, freeze-drying is useful due to the extensive hydrolysis of salicylic salts in aqueous media[55].

Despite the most NSAIDs share the same therapeutic indications, some of them are recommended predominantly for specific painful conditions. Thus, according to Table 1, the listed NSAIDs may be sorted into three groups: the NSAIDs indicated predominantly for the treatment of musculoskeletal system-related pain, the NSAIDs indicated in the treatment of postoperative pain/post-traumatic related pain and the group of NSAIDs indicated to the treatment of unclear painful conditions. Nevertheless, in the case of piroxicam and meloxicam, their therapeutic indications seem to be more restricted since in the SPCs (Summary of Product Characteristics) of Feldene® (piroxicam) and Movalis® (meloxicam) the first line use of this products in the treatment of acute pain is discouraged due their safe profiles[56,57].

Since all conventional NSAIDs are weak acids, when taken orally, the drug molecules tend to be uncharged due to the strongly acidic environment of the stomach, even when they are taken with food[58,59]. The uncharged state of the molecules allows their rapid absorption through the gastric surface epithelium[58]. Due to this fact, NSAIDs generally have high bioavailability after oral administration and, in some NSAIDs, SPCs recommend the use of the parenteral route only when less invasive routes are not available[60–62]. Indeed, there is not clear evidence of superior efficacy and safety of NSAIDs parenterally administered[61,62].

Table 1. Parenteral NSAIDs approved in the USA and in Europe.

NSAID	Formulations	Route of administration	Indications	Brands[1]	Countries with marketing authorization[4]
Ibuprofen	800 mg/8 ml 800 mg/200 ml	IV	Management of mild to moderate pain and moderate to severe pain in adults. Also, it is indicated	Caldolor®	US

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NSAID	Formulations	Route of administration	Indications	Brands[1]	Countries with marketing authorization[4]
			for the reduction of fever in adults[63].		
Ketorolac	15 mg/1 ml 30 mg/1 ml	IV/IM	Short-term management of moderate to severe acute pain, including pain following operative procedures[64].	Toradol®[2]	US
Meloxicam	30 mg/1 ml	IV	Management of moderate-to-severe pain, alone or in combination with non-NSAID analgesics in adults[51].	Anjeso®	US
Acetylsalicylate	500 mg/5 ml (freeze-dried)	IM/IV	Symptomatic treatment of pain, in rheumatology, traumatology, oncology, surgery and anaesthesiology, post-operatively, and in preparation for exams. Also used in the symptomatic treatment of fever[65].	Aspegic®	BE, HU, and PT
Dexketoprofen	50 mg/2 ml 25 mg/2 ml	IM/IV	Symptomatic treatment of acute pain of moderate to severe intensity when oral administration is not appropriate, such as post-operative pain, renal colic, and low back pain[66,67].	Ketesse® Keral® Auxilen® Dekenor® Morsadex®	DE, AT, SK, SI, ES, EE, FI, FR, GR, NL, HU, IE, LV, LT, MT, PL, CZ, and RW
	50 mg/100 ml	IV		Dexketoprofen B. Braun®	ES
Diclofenac	75 mg/3 ml[3] 50 mg/1 ml 25 mg/1 ml	IV/IM	IM use is effective in acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and post-operative pain. In IV use, it is indicated for the treatment or prevention of post-operative pain in the hospital setting[68].	Voltaren® Voltarol® Fenil-V® Akis® plus Dicloin® Diclac® Almiral®	DE, AT, BE, BG, SK, SI, ES, EE, FR, FI, GR, NL, HU, IE, IT, LV, LT, MT, PL, PT, GB, CZ, RW, and SE

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NSAID	Formulations	Route of administration	Indications	Brands[1]	Countries with marketing authorization[4]
Etofenamate	1,000 mg/2 ml	IM	Indicated in painful and acute inflammatory situations in rheumatology, traumatology, and post-operatively [69].	Rheumon® Traumon®	DE, AT, GR, HU, PT, and RW
Ibuprofen	600 mg/100 ml[3] 400 mg/100 ml 200 mg/50 ml	IV	Indicated in adults for the short-term symptomatic treatment of acute moderate pain, and for the short-term symptomatic treatment of fever. IV route is clinically justified when other routes of administration is not possible[70].	Ibuprofen B. Braun® Solibu®	DE, AT, BE, BG, DK, SK, SI, ES, EE, FI, NL, HU, IE, LV, LT, PL, PT, GB, CZ, RW, and SE
Indomethacin	50 mg/2 ml 25 mg/2 ml (freeze-dried)	IV	Indicated to reduce (acute) pain due to inflammation of the muscles and muscles joints (musculoskeletal system)[71].	Liometacen®	IT
Ketoprofen	100 mg/2 ml[3]	IM	Indicated for Rheumatoid arthritis. Osteoarthritis ankylosing spondylitis. An acute episode of gout. The injectable form is especially indicated in the treatment of acute attacks with predominance of pain[72].	Profenid® Rofenid® Ketonal® Orudis®	BE, SK, SI, ES, FR, IT, LV, LT, PL, PT, CZ, and RW
Ketorolac	50 mg/5 ml 30 mg/1 ml[3] 10 mg/1 ml	IM/IV	It is indicated for the short-term management of moderate to severe acute post-operative pain. Treatment should only be initiated in hospitals. The maximum duration of treatment is two days[73].	Toradol® Taradyl®	BE, DK, ES, EE, FI, GR, IS, IT, LV, LT, PT, GB, RW, and SE
Lornoxicam	8 mg/2 ml (freeze-dried)	IM/IV	Short-term relief of acute mild to moderate pain[74].	Xefo®	SK, GR, HU, and RW
Meloxicam	15 mg/1.5 ml	IM	Short-term treatment of symptomatic acute exacerbations of rheumatoid arthritis and ankylosing spondylitis when other routes of administration are not appropriate[57].	Movalis® Melox® Mobic®	SK, EE, FR, GR, HU, IT, LV, LT, MT, PL, PT, and RW
Piroxicam	20 mg/1 ml	IM	Indicated for symptomatic relief of osteoarthritis,	Feldene® Flexase®	DE, BE, ES, FR, HU, PL, and PT

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NSAID	Formulations	Route of administration	Indications	Brands[1]	Countries with marketing authorization[4]
			rheumatoid arthritis, and ankylosing spondylitis[56].		
Tenoxicam	20 mg/3 ml[3] (freeze-dried)	IM/IV	Indicated for patients considered unable to take oral tenoxicam for the relief of pain and inflammation in osteoarthritis and rheumatoid arthritis and for the short-term management of acute musculoskeletal disorders including strains, sprains, and other soft-tissue injuries[75].	Neo-Indusix®	GR, GB, and RW

Abbreviations: IM- intramuscular**, IV-** Intravenous**, IM/IV-** Intramuscular and Intravenous. [1]Here are presented only the main brands found during the research. However, in many cases there are available in the market other products with other brand names; [2]According to the data obtained from the FDA website, Toradol® is no more available in the USA. Instead, generic products are sold in the USA. Toradol® is presented in the table due this is the brand most cited in the literature when ketorolac formulations are mentioned; [3]There are available in the market identical products, where the drug dosage is the same, but the liquid volumes differ slightly. Despite this, the product characteristics are not impacted; [4] Based on the information available in the databases consulted on the websites of the Health Authority of each European country. The countries are listed in a two-letter country code.

3. Parenteral Fixed-dose Combinations

The combination of analgesic entities is a common practice. As reported previously, due to the complexity of pain physiology, it is not expectable that only one drug is always capable to induce satisfactory analgesia in all painful conditions.

When administrated in monotherapy, NSAIDs have been related to cardiovascular (CV), GI, and renal adverse effects[50]. Unfortunately, even the selective COX-2 NSAIDs are related to the occurrence of markable CV and renal AEs once after their development, and the unexpected physiologic role of COX-2 in the vasculature and in the kidney was discovered[50]. Considering that even in short term, NSAIDs could increase the risk of the occurrence of severe AEs in a dose-dependent manner, the combination of NSAIDs with paracetamol or metamizole could lead to the development of safer analgesic products due to the possibility to reduce the effective doses of NSAIDs [76,77].

Combinations of NSAIDs with paracetamol have presented greater antinociceptive effect compared with the respective drugs alone and have superior morphine-sparing effect when compared with corticosteroids, tramadol, nefopam, corticosteroids, and metamizole alone[5]. This effect could be related to synergic interactions between the dissimilar mechanisms of action of analgesic entities[78]. In a very interesting study, Miranda H. *et al.*[78] demonstrated the synergic relationship between paracetamol and NSAIDs by isobolographic analysis in the acetic acid abdominal constriction test of mice (writhing test). The authors concluded that the results validate the clinical use of APAP/NSAID combinations in the treatment of pain conditions[78].

Considering the considerable number of drugs available to be administrated in MMA context, it would be expectable to be viable for the pharmaceutical development of numerous analgesic FDCs. Instead, in the American and European markets, the unique parenteral analgesic FDC approved at this moment is paracetamol with ibuprofen. Bellow, we reported the results of complete research

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performed in the literature to review all information available about the development of parenteral FDCs of NSAIDs with NOAs.

In subchapter 3.3, a literature search about randomized clinical trials (RCTs) testing the utility of combining NSAIDs with paracetamol/propacetamol and metamizole for clinical proposes is reported. However, applying the inclusion and exclusion criteria described there, paracetamol/propacetamol but not metamizole combinations with NSAIDs were found.

3.1. Paracetamol-based Parenteral Fixed-dose Combinations

Paracetamol and ibuprofen are among of the most consumed analgesics. Usually, they are widely available even without a medical prescription[79]. As reported previously, at this moment, the combination of paracetamol with ibuprofen is the unique parenteral analgesic FDC available in the American and European markets. Even when taken orally, the combination of APAP/IBP (paracetamol/ibuprofen) has been demonstrated to be an effective alternative to opioid-based analgesia[80]. However, there are a limited number of studies comparing the efficacy of the intravenous (IV) formulations of these drugs mainly about their combination[3].

As reported previously, the use of combinations of some NSAIDs with paracetamol and metamizole is widely established in clinical practice. Still, the procedures related to the introduction of ready-to-use FDCs of these drugs in the European and USA markets are not easy at all. Moreover, the market of analgesic FDCs in Europe and the USA is very recent. Indeed, only in 2015, Vale Pharmaceuticals Ltd submitted to the United Kingdom (UK) a marketing authorization application under the three decentralized procedures (DCPs) (UK/H/6034/001/DC, UK/H/6035/001/DC and UK/H/6176/001/DC) for an oral FDC APAP (500 mg)/IBP (150 mg) (tablets form)[81]. In this process, the United Kingdom (UK) was defined as the Reference Member State (RMS) and Austria, Germany, Croatia, Ireland, Luxembourg, France, Belgium, Netherlands, Portugal, and Spain were involved as Concerned Member States (CMS). During the process, Germany, France, Netherlands, and Spain raised major issues regarding efficacy and safety data. According to these countries, the clinical trials presented during the submission were not able to demonstrate the additional benefit for the new FDC when compared to the mono-components concerning the efficacy and safety profiles. After that, in the absence of an agreement at the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), the matter was referred to The Agency's Committee for Medicinal Products for Human Use (CHMP) for arbitration. With this, in 2017 the European Medicines Agency completed the assessment regarding the authorization of the medicine APAP/IBP 500 mg/150 mg film-coated tablets. The CHMP concluded that the benefits of APAP/IBP 500 mg/150 mg film-coated tablets outweigh its risks and reported that this combination was more effective than the individual components, while its safety profile was similar[82]. The clinical aspects of this application were supported by five clinical studies sponsored by AFT pharmaceuticals Ltd (AFT-MX-1, AFT-MX-3, AFT-MX-4, AFT-MX-6, and AFT-MX-6E) to demonstrate the efficacy and safety of the oral FDC[81,83,84].

In 2020 was approved in Europe the intravenous ready-to-use FDC IBP/APAP 10 mg/ml + 3 mg/ml of Vale Pharmaceuticals Ltd (also named Comboval® or Combofusiv®). According to the Public Assessment report of the product (PAR SE/H/1948/01/DC) this product was developed to extend the therapeutic advantage of the FDC tablets to patients when administered by the intravenous route is clinically justified by an urgent need to treat pain and/or when other routes of administration are not possible[83]. In 2021, it was approved the FDC (Maxigesic® of the AFT Pharmaceuticals (PAR SE/H/2093/001/DC)[84]. In both applications, beyond the supportive studies with paracetamol/ibuprofen FDC in tablets cited in the previous paragraph, AFT-MXIV-01, AFT-MXIV-06, and AFT-MXIV-07 were considered[81–84].

Regarding the North American market, only very recently (2020), FDA approved the first oral analgesic FDC (IBP 125 mg plus APAP 250 mg) for acute pain[85]. In contrast to the European market, no parenteral combination of IBP/APAP was approved in EUA, however, US FDA accepted New Drug Application for the parenteral FDC Maxigesic® IV (also named Combogesic®) in October 2021[86].

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The clinical trials presented in the marketing authorization applications of Vale pharma and AFT Pharmaceuticals were performed to support the safety and efficacy of APAP/IBP FDC and were sponsored by AFT Pharmaceuticals Ltd itself. In total were performed, ten phase I, four phase II/III and one long-term exposure (phase II) clinical trials[80]. A summary of all the clinical trials performed was published by Aitken et al.[80] In this work, the authors concluded that results show the excellent tolerability and safety of multiple FDC APAP/IBP oral tablet doses over 24–48 hours. Also, they reported that the FDC did not increase the incidence of AEs [80] and that the FDC provided an even greater opioid-sparing effect, with significantly fewer patients requiring rescue medication when compared with APAP monotherapy[80].

More recently, a meta-analysis aiming to assess the efficacy and safety of IBP/APAP FDC for the treatment of acute postoperative pain in adults was performed by Abushanab D. & Al-Badriyeh D.[85] Despite in this study no restrictions about the formulation (oral, intravenous) were performed, the authors concluded that IBP/APAP FDCs is effective analgesic against the placebo in acute postoperative, moderate to severe pain in adults[85]. In this meta-analysis seven double-blind, randomized controlled trials with 2,947 participants were included and three FDC dose levels were considered: 75–100 mg IBP/250 mg APAP, 150–200 mg IBP/500 mg APAP (FDA-approved dose level), and 292.5–400 mg IBP/975–1,000 mg APAP[85]. The authors concluded that the ≥ 50% pain relief outcome was more achieved with the FDC compared to placebo (risk ratio [RR] 2.60, 95% confidence interval [CI] 2.11–3.20, $p < 0.00001$) and as was reduced the need for rescue medications (RR 0.51, 95% CI 0.37–0.71, $p < 0.0001$). However, the authors reported that safety outcomes were inconclusive and warned of the need for future studies to confirm its safety and benefits against other marketed analgesics in postoperative pain[85].

3.2. Metamizole-based Parenteral Fixed-dose Combinations

As reported previously, like paracetamol, metamizole is a very popular analgesic entity. However, nowadays, it was banned from several countries since its consumption is allegedly related to an increased risk induce a rare side effect of neutropenia and even agranulocytosis[40,43]. Metamizole is banned from the USA, UK, Canada, Australia, Japan, Sweden, Denmark, and India, however, in some European countries, Latin America, Israel, and Russia, metamizole is the most popular non-opioid used as a first-line analgesic and sometimes available as over-the-counter medication. Indeed, it has been largely consumed in one of the most relevant European countries, Germany[40,43,87]. There, the prescription volumes of metamizole increased more than 8-fold reaching a total of 204 million defined daily doses (DDD) in 2016, which equals 2.9 DDD per person and year[40]. Surprisingly, despite the high consumption of Metamizole in Germany, there, all metamizole-containing combinations were withdrawn and banned from the market in 1987[42].

According to our research, there are in the market some PFDCs of Metamizole with antispasmodics, muscular relaxants, antihistamines, Vitamin B_{12} and corticosteroids, penicillin, and expectorants, but not with NSAIDs. Since the number of parenteral Metamizole FDCs in Europe is very scare and non-existent in the USA, a larger search was performed to present the FDCs with metamizole available in the worldwide market. For this, all metamizole combinations found in Vademecum.es, Drugs.com, PubMed, Web of Science, Google scholar, and Clinicaltrials.com were included in the table below (Table 2).

According to the information obtained and presented in Table 2, it was not found any parenteral FDC of metamizole and NSAIDs. Recently, a Randomized Clinical Trial (RCT) assessing the potential benefit of the combination of metamizole and ibuprofen after third lower molar extraction was concluded (NCT02686021). According to the information available on the clinicaltrails.gov website, the route of administration of the combined drugs is unknown and there is not reported the use of FDC but only the use of metamizole and ibuprofen in combination.

Meanwhile, there were not found in the literature other opened or completed RCTs assessing the therapeutic potential of metamizole/NSAID combinations. It could be, in the future, an interesting scientific and clinical matter to be explored since, despite metamizole is banned in several countries, it is extensively consumed worldwide[88].

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Table 2. Fixed-dose combinations with Paracetamol and Metamizole available in the market.

Combination	Strengths	Route of administration	Indications	Brands[1]	Countries with marketing authorization[2]
Paracetamol + Ibuprofen	1000mg+ 300mg/ 100 mL	IV	Short-term symptomatic treatment of moderate acute pain in adults, when intravenous administration is considered clinically necessary and/or when other routes of administration are not possible[89].	Combofusiv® Comboval® Combogesic®	AT, CZ, DE, EE, IE, HR, HU, LT, MT, NL, PT, SI, SE, and UK
Metamizole + Scopolamine (or Butilscopolamine)	2,500 mg + 20 mg/5 ml	IM/IV	Post-surgical pain, post-trauma pain, or colicky pain[90].	Buscapina® compositum	AR, BR, CL, ES, and MX
Metamizole + Pitofenone	2,500 mg + 10 mg/5 ml	IM/IV	Treatment of pain conditions in the digestive tract and in the bile and urinary tract[91].	Litalgin®	FI
Metamizole + Pitofenone + Fenpiverinium	2,500 mg + 10 mg + 0.1 mg/5 ml	IM/IV	Treatment of pain conditions in the digestive tract and in the bile and urinary tract and dysmenorrhea[92].	Analgin® Spasmalgon®	CZ, LV, and PL
Metamizole + Adiphenine + Promethazine	750 mg + 25 mg + 25 mg/2 ml	IM	General painful conditions [93].	Dorilen®	BR
Metamizole + Hydroxocobalamin + Dexamethasone	500 mg + 5 mg + 2 mg/1 ml	IM	Processes of acute joint inflammation processes such as arthritis, periarthritis, bursitis, gout, ankylosing spondylitis, in degenerative processes that go along with pain, such as arthrosis and intervertebral disc disorders; in neuralgia and in back and neck pain[94].	Dexalgen®	BR
Metamizole + Pargeverine	2,000 mg + 5 mg/4 ml	IV	Treatment of all acute pain accompanied by muscle spasms in any portion of the digestive tract or the hepatobiliary, urinary, or female genital[95].	Viadil® Compuesto	CL
Metamizole + Ampicillin + Guaifenesin + Lidocaine + Chlorphenamine	500 mg + 500 mg + 100 mg + 30 mg + 4 mg/3 ml	IM	Unknown[3]	Ampigrin®	MX
Metamizole + Procaine Penicillin G	400,000 U.I. + 500 mg/5 ml	IM	Unknown[3]	Respicil®	MX
Metamizole + Chlorphenamine	Unknown[3]	Unknown [b)]	Unknown[3]	Singril® iny	MX

Abbreviations: IM- intramuscular**, IV-** Intravenous**, IM/IV-** Intramuscular and Intravenous. [1]Here are presented only the main brands found during the research. However, in many cases there are available in the market other products with other brand names; [2]The countries are listed in two-letter country code; [3]Information about these products is vary scare and only available on commercial websites. The summary of product characteristics of these products was not found.

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3.3. Other NSAID-based Combinations

Since the unique ready-to-use parenteral NOA/NSAID FDC available on the European and American markets are the paracetamol/ibuprofen developed by the AFT pharmaceuticals, a literature search was performed to study the clinical evidence about the efficacy and safety of combining other NSAIDs with paracetamol or metamizole. This research was performed using PubMed, Google Scholar, and web of knowledge to identify the RCTs published since ever.

The literature search included keywords such as NSAID, paracetamol, propacetamol, metamizole, dipyrone, combination, fixed-dose, ready-to-use, NSAID and the exact search string used was "NSAID OR acetam* OR paracet* OR proparacet*) AND (fixed* OR FDC OR ready* OR combin* OR multimodal OR analg*) AND (surgery OR oper* OR acute OR post* OR pain) AND adults" and resulted in the discovery of more than 8,000 references. The titles and the abstracts were analysed for relevance and included to be reviewed according to the inclusion and exclusion conditions.

The published papers were reviewed if they reported (RCTs) that were performed in adult humans and aimed to compare the efficacy and/or safety profiles of combinations of NSAIDs with paracetamol or metamizole administrated simultaneously and by the same route through the use of FDC formulations or not. Due to the well-known similarity between paracetamol and propacetamol (PPCM), studies using combinations with PPCM instead APAP were also included. Due to the lack of RCTs about parenteral FDCs, all types of pain, all systemic routes of administration (enteral and parenteral), and dose regimens were considered. On the other hand, were excluded studies where the combination was administrated via spinal and intra-articular since in these cases, the action of the drugs is local and not systemic. Also, studies with opioid analgesics as comparators, studies with pediatric enrolment, and other trials where the aim is not to treat painful conditions (e.g. Ductus arteriosus) were excluded.

Applying the inclusion and exclusion criteria described above, 18 references were considered in this review. These works are presented in further detail in Table 3 and reported the clinical assessment of the efficacy of paracetamol/propacetamol combinations with diclofenac, ketoprofen, ketorolac and piroxicam since there were not found any published RCTs about the assessment of combinations of metamizole with NSAIDs. As reported previously, no metamizole combinations were included after the application of our inclusion and exclusion criteria.

Table 3 is sorted primarily by NSAID used in the combination and after by year of publication of the paper. There are ten RCTs about diclofenac combinations, five RCTs assessing the efficacy of ketoprofen combinations, two reporting results about the efficacy of ketorolac combinations, and a last one assessing the efficacy of the combination of piroxicam/paracetamol.

The vast majority of the RCTs presented in Table 3 were randomized, parallel, double-blind, and controlled trials. However, there are some exceptions. Montgomery *et al.*[96] assessed the analgesic efficacy of paracetamol alone and in combination with diclofenac in an open-label study. Also, Romundstad *et al.*[97] designed a crossover trial instead a parallel one. There, according to the authors, the patients were randomized in blocks of four in a complete crossover manner, according to a balanced, reduced Latin square design. Yet recently Msolli *et al.*[98] opted to explore the possible benefits of combining piroxicam with paracetamol in a single-blinded study instead the typical double-blind approach. In this case, the randomization was performed by a blinded study investigator.

Table 3. Published Randomized clinical trials about NSAIDs combinations with Paracetamol or Propacetamol.

Author, year	Trial Design (N)	Pain Model	Study Objetives	Treatment details (Drug; Dosage; Regimen; Route; Frequency; Duration)	Primary Outcomes	Conclusions
Diclofenac + Paracetamol (or Propacetamol)						
Montgomery et al.,1996[96]	Randomized, parallel, open-label, and controlled trial (60)	Elective abdominal gynecological surgery	Assess the analgesic efficacy of paracetamol alone and in combination with diclofenac.	1. APAP 1,500 mg 2. DCF 100 mg 3. APAP 1,500 mg + DCF 100 mg Single rectal dose given before the surgery with 24 hours of observation..	• Opioid consumption after the operative procedure	**Efficacy:** Combination reduced the amount of morphine consumed. **Safety:** No difference in the incidence of side effects between the groups
Breivik et al.,1999[99]	Randomized, parallel, double-blind, and controlled trial (120)	Surgical removal of third molars	Assess the analgesic effect of combining diclofenac with paracetamol and with codeine.	1. APAP 1,000 mg 2. DCF 100 mg. 3. APAP 1,000 mg + DCF 100 mg 4. APAP 1,000 mg + DCF 100 mg + CDN 60 mg 5. APAP 100 mg + CDN 60 mg Single oral dose was given after the surgery with 8 hours of observation.	• Pain intensity (VAS score)	**Efficacy:** Combination of drugs is superior to diclofenac or paracetamol alone. **Safety:** No difference in the incidence of side effects between the groups
Beck et al.,2000[100]	Randomized, parallel, double-blind, and controlled trial (70)	Hysterectomy	Assess the pharmacokinetics of rectal paracetamol in women and compare their analgesic efficacy with diclofenac combination	1. APAP 20 mg/kg (small-dose) 2. APAP 40 mg/kg (large-dose) 3. APAP 20 mg/kg + DCF 100 mg Single rectal dose was given before the surgery within 24 h of observation.	• Opioid consumption • Pain intensity (VAS score).	**Efficacy: O**nly lower VAS scores after APAP + DCF at 4 h. **Safety:** Not addressed by the authors.

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Author, year	Trial Design (N)	Pain Model	Study Objetives	Treatment details (Drug; Dosage; Regimen; Route; Frequency; Duration)	Primary Outcomes	Conclusions
Siddik et al., 2001[101]	Randomized, parallel, double-blind, and controlled trial (80)	Caesarean	Assess the postoperative analgesic effects of propacetamol in combination with diclofenac	1. Placebo 2. DCF 100 mg 3. PPCM 2 g 4. PPCM 2 g + DCF 100 mg; Propacetamol Intravenously q.i.d and Diclofenac rectally t.i.d during 24 h after surgery.	• Opioid consumption • Pain intensity (VAS at rest and on coughing) • Patients' Satisfaction	**Efficacy: N**o statistical difference between the groups **Safety:** No difference in the incidence of side effects between the groups.
Man et al., 2004[102]	Randomized, parallel, double-blind, and controlled trial (50)	Painful soft tissue injuries	Asses the efficacy and safety of oral paracetamol compared with NSAIDs or combination therapy	1. DCF 25 mg 2. APAP 1,000 mg 3. APAP 1,000 mg + DCF 25 mg 4. IND 25 mg Orally administration of Diclofenac t.i.d, paracetamol q.i.d, and indomethacin t.i.d with observation during 120 min (stage 1) and 3 days (stage 2).	• Pain intensity (VAS score) at rest and with movement	**Efficacy:** No statistical difference between the groups **Safety:** No difference in the incidence of side effects between the groups.
Hiller et al., 2004[103]	Randomized, parallel, double-blind, and controlled trial (71)	Elective tonsillectomy	Assess the analgesic efficacy between the combination of Paracetamol with Diclofenac and either drug alone.	1. PPCM 2,000 mg 2. DCF 75 mg 3. PPCM 2,000 mg + DCF 75 mg Single IV dose administrated after anaesthetic induction and postoperatively, propacetamol was administered twice and diclofenac once.	• Pain intensity (VRS and VAS scores) at rest and on swallowing	**Efficacy:** No statistical difference between the groups. **Safety:** No difference in the incidence of side effects between the groups.
Woo et al., 2005[104]	Randomized, parallel double-blind, and controlled trial (300)	Musculoskeletal Injury	Assess the efficacy safety of oral paracetamol compared with oral nonsteroidal anti-	1. DCF 25 mg 2. IND 25 mg (+ APAP placebo) 3. APAP 1,000 mg (+ IND placebo)	Pain intensity (VAS) at rest and with limb movement	**Efficacy:** The analgesic benefits of oral combination is small and of doubtful clinical significance.

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Author, year	Trial Design (N)	Pain Model	Study Objetives	Treatment details (Drug; Dosage; Regimen; Route; Frequency; Duration)	Primary Outcomes	Conclusions
			inflammatory drugs or combination therapy.	4. APAP 1,000 mg + DCF 25 mg Stage 1 - Single oral dose with 2 hours of observation. Stage 2 - Outside the hospital, the same therapy with three days of observation (paracetamol q.i.d and diclofenac or indomethacin t.i.d)		**Safety:** No difference in the incidence of side effects between the groups.
Legeby et al., 2005[105]	Randomized, parallel, double-blind, and controlled trial (50)	Mastectomy with immediate breast reconstruction	Assess the analgesic efficacy of diclofenac, in combination with paracetamol and opioids.	1. APAP 1000mg 3.APAP 1,000 mg + DCF 50 mg Diclofenac was administrated rectally t.i.d and Paracetamol was administrated orally t.i.d with 64 hours of observation.	•Pain intensity (VAS score)	**Efficacy:** The combination reduced the opioid consumption and improved pain relief during the first 20 h **Safety:** Post-operative bleeding was significantly higher with diclofenac than with placebo ($P < 0.01$).
Munishankar et al., 2008[106]	Randomized, parallel, double-blind, and controlled trial (78)	Elective caesarean section	Assess the efficacy of the combination of diclofenac and paracetamol used for pain relief after major surgery.	1. APAP 1,000 mg 2. DCF 100 mg 3. APAP 1,000 mg + DCF 100 mg Study drugs were given as a suppository at the end of surgery and then orally for 24 h. Paracetamol q.i.d and diclofenac t.i.d with 24 hours of observation.	• Opioid consuption	**Efficacy:** Patients given a combination of diclofenac and paracetamol used 38% less morphine compared to patients given paracetamol. **Safety: N**ot addressed by the authors.
Ridderikhof et al., 2018[107]	Randomized, multicenter, parallel, double-blind, and controlled trial (547)	Acute Musculoskeletal Trauma	Assess efficacy of paracetamol and diclofenac alone or in combination.	1. APAP 1,000 mg 2. DCF 50 mg 3. APAP 1,000 mg + DCF 50 mg Diclofenac and paracetamol were administrated orally t.i.d and q.i.d respectively with 3 days of observation.	Pain intensity (NRS pain score) at rest and with movement	**Efficacy:** No statistical difference between the groups. **Safety:** No difference in the incidence of side effects between the groups.

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Author, year	Trial Design (N)	Pain Model	Study Objetives	Treatment details (Drug; Dosage; Regimen; Route; Frequency; Duration)	Primary Outcomes	Conclusions
Ketoprofen + Paracetamol (or Propacetamol)						
Fletcher et al., 1997[108]	Randomized, parallel, double-blind, and controlled trial (60)	Disc surgery	Assess the effect of combining propacetamol with ketoprofen	1. PPCM 2,000 mg 2. KTPF 50 mg 3. PPCM 2,000 mg.+ KTPF 50 mg 4. Placebo All drugs were given q.i.d and intravenously for 2 days after the surgery. The observation occurred during the same period	Pain intensity (VAS score)	**Efficacy:** The combination reduced pain scores both at rest and on movement. **Safety:** No difference in the incidence of side effects between the groups.
Aubrun et al., 2000[109]	Randomized, parallel, double-blind, and controlled trial (50)	Spinal fusion surgery	Assess the efficacy of ketoprofen in patients receiving propacetamol.	1. PPCM 2,000 mg 2. PPCM 2,000 mg + KTPF 100 mg ketoprofen and propacetamol were administrated intravenously t.i.d and q.i.d respectively during 24h after the surgery. The observation occurred during the same period.	Pain intensity (VAS score)	**Efficacy:** The combination reduced morphine requirements and improved postoperative analgesia. **Safety:** No difference in the incidence of side effects between the groups.
Fourcade et al., 2005[110]	Randomized, parallel, double-blind, and controlled trial (97)	Thyroidectomy	Compare the efficacy of propacetamol and ketoprofen, alone or in combination.	1. PPCM 2,000 mg 2. KTPF 100 mg 3. PPCM 2,000 mg + KTPF 100 mg Propacetamol and Ketoprofen were administrated intravenously 30 min before the end of surgery and 6 and 12 h after the surgery. The observation occurred during the same period.	Pain intensity (VAS score)	**Efficacy:** No statistical difference between the groups. **Safety: N**ot addressed by the authors.
Akural et al., 2009[111]	Randomized, parallel, double-blind, and controlled trial (76)	Postoperative Dental Pain	Assess the efficacy of combining paracetamol with ketoprofen.	1. APAP 1,000 mg. 2. KTPF 100 mg	Pain Intensity difference (PID), sum of PID (SPID),	**Efficacy:** The combination provided significantly more

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Author, year	Trial Design (N)	Pain Model	Study Objetives	Treatment details (Drug; Dosage; Regimen; Route; Frequency; Duration)	Primary Outcomes	Conclusions
				3. APAP 1,000 mg + KTPF 100 mg 4. Placebo Ketoprofen and paracetamol were administrated orally in a single dose. The observation was performed every 15 minutes for 10 hours.	and NRS score at rest and on dry swallowing.	rapid onset of analgesia than either drug alone. **Safety:** No difference in the incidence of side effects between the groups.
Salonen et al., 2009[112]	Randomized, parallel, double-blind, and controlled trial (116)	Tonsillectomy	Evaluate whether co-administration of intravenous paracetamol with ketoprofen.	1. KTPF 1 mg/kg 2. APAP 1,000 mg + KTPF 1 mg/kg 3. APAP 2,000 mg + KTPF 1 mg/kg Both ketoprofen and paracetamol were administrated intravenously in a single dose after the surgery.	The proportion of patients requiring rescue analgesia	**Efficacy:** In the combination groups the number of opioid doses was reduced. **Safety:** No difference in the incidence of side effects between the groups.
Ketorolac + Paracetamol (or Propacetamol)						
Romundstad et al., 2006[97]	Randomized, crossover, double-blind, and Controlled trial (16)	Pressure algometry	Evaluate the effect of propacetamol 2 g and ketorolac 30 mg, individually and in combination.	1. PPCM 2,000 mg 2. KTLC 30 mg 3. PPCM 2,000 mg + KTLC 30 mg 4. Placebo The crossover study had a Latin square design. The drugs were administrated intravenously in a single dose and the observation was performed for 165 minutes.	Pressure pain tolerance threshold (PPTT)	**Efficacy:** Combining paracetamol with ketorolac increased the PPTT. **Safety:** No difference in the incidence of side effects between the groups.
Iorno et al., 2013[113]	Randomized, parallel, patient-blinded, and controlled trial (60)	Voluntary ambulatory abortion	Assess the efficacy and safety of oral paracetamol with IV ketorolac	1. KTLC 30 mg. 2. APAP 1,000 mg + KTLC 30 mg Ketorolac was administrated intravenously o.d and paracetamol was administrated orally t.i.d. The patients were observed until the next day morning.	Pain intensity (NRS score)	**Efficacy:** The studied was effective and well tolerated in the control of postoperative pain.

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Author, year	Trial Design (N)	Pain Model	Study Objetives	Treatment details (Drug; Dosage; Regimen; Route; Frequency; Duration)	Primary Outcomes	Conclusions
						Safety: No difference in the incidence of side effects between the groups.
Ketoprofen + Paracetamol (or Propacetamol)						
Msolli et al., 2021[98]	Randomized, parallel, single-blinded, and controlled trial (1632)	Traumatic injury	Explore the possible benefits of combining piroxicam with paracetamol.	1. APAP 1,000 mg 2. PRX 20 mg 3. Paracetamol 1,000 mg + PRX 20 mg Paracetamol and Piroxicam were administrated orally t.i.d and b.i.d, respectively. Each patient was re-evaluated on the 3rd and 7th day.	Need for additional oral analgesics	**Efficacy:** The combination does not increase the analgesic effect compared to paracetamol alone. **Safety:** The occurrence of adverse events was significantly more frequent in the PRX alone and combination groups.

Abbreviations: APAP- Paracetamol**, CDN-** codeine**, DCF-** Diclofenac**, FDC**- Fixed-dose combination, **IND**- Indomethacin, **IM-** intramuscular**, IV-** Intravenous**, IM/IV-** Intramuscular and Intravenous, **KTLC**- Ketorolac, **KTPF**- Ketoprofen, **NRS-** Numeric rating scale, **NSAID-** Non-steroidal anti-inflammatory drug, **o.d-** Once a day, **q.i.d-** Four times a day, **t.i.d-** Three times a day, **PID-** Pain Intensity difference, **PPCM**- Propacetamol, **PPTT-** Pressure pain tolerance threshold, **PRX**- Piroxicam, **SPID-** Sum of pain Intensity difference, **VAS-**Visual analog scale, **VRS-** Verbal rating scale.

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Concerning the pain models, all except one study used real clinical painful conditions to assess the analgesic combinations. The study performed by Romundstad *et al.*[97] used an artificial approach to generate a painful stimulus in healthy volunteers. The most common primary outcomes used in the studies to quantify the impact of the intervention were the measure of pain intensity with the Visual Analog Scale (VAS) approach and the measure of opioid drug consumption during a time interval.

Concerning Table 3, all studies reported the same analgesic dosages and routes of administration that are commonly used and authorized when the drugs are used in monotherapy. In other words, none of these studies considered the use of sub-therapeutic dosages to study the synergic relation of the analgesics nor suggested alternative routes using new formulations. Anyway, Beck *et al.*[100] published results where two different doses of APAP were introduced in two parallel arms of the trial to compare their efficacy with a diclofenac combination. There, the efficacy and pharmacokinetics of smaller (20 mg/kg) and larger (40 mg/kg) doses of APAP (both administrated rectally) were compared with the analgesic capability performed by the combined administration of diclofenac (100 mg) with APAP (20 mg/kg)[100].

Despite the reviewed RCTs aimed to assess the efficacy and safety profiles of combinations of NSAIDs with APAP or PPCM, not in all studies the combining drugs were administrated by the same route and/or at the same time. These studies are not the best to assess the potential value for the development of new analgesic FDCs however, at the least, they could be used as a very preliminary proof-of-concept to display the therapeutic utility of combining analgesics in a FDC formulation. At this point, it is important to underscore that these studies were not designed to assess the efficacy nor the safety profiles of FDCs but were performed to assess the benefits of the use of analgesic combinations for the treatment of painful conditions comparing the combining procedure with monotherapy interventions. Indeed, in two studies the route of administration of the combined drugs was not the same. Siddik *et al.*[101] designed a trial where the administration of the PPCM was performed intravenously while diclofenac was used rectally. Also, in the work published by Iorno *et al.*[113] ketorolac was administrated intravenously and APAP orally in the same enrolled patients. At the same time, despite the reviewed RCTs aimed to assess the analgesic efficacy of combining certain NSAIDs with APAP or PPCM, in some cases, their protocols defined the asynchronous administration of the drugs and not in simultaneous administration as is achieved with FDC formulations. Indeed, Siddik *et al.*[101] reported a trial protocol where 100 mg of diclofenac was administrated rectally every 8 hours and 2 g of propacetamol intravenously every 6 hours. In the same manner, Man *et al.*[102], Woo *et al.*[104] and Ridderikhof *et al.*[107] reported the combination of diclofenac with paracetamol in tablets based on t.i.d and q.i.d regimens, respectively. Yet, Munishankar *et al.*[106] administrated diclofenac t.i.d and paracetamol q.i.d, however in this case they used 50 mg diclofenac and 1,000 mg paracetamol rectally at the end of the surgery and then orally during the patients' recover[106]. Also, combining ketoprofen and propacetamol, Aubrun *et al.*[109] administrated the NSAID every 8 hours and propacetamol every 6 hours. However, in this case, the drugs were both administrated intravenously. Concerning the clinical trial performed by Iorno *et al.*[113] Ketorolac was used orally and intravenously based on an o.d regimen and paracetamol every 8 hours. Very recently, in the RCT published by Msolli *et al.*[98], the authors conducted a trial combining piroxicam b.i.d and paracetamol every 8 hours[98].

In some trials, despite the combining drugs were both administrated simultaneously and through the same route of administration none of the authors claimed the intention to develop or at least assess the possibility to propose the development of FDCs. Despite all this, and focusing attention on parenteral FDCs, some studies presented in Table 3 could be useful to understand the clinical impact of the development of new Parenteral Fixed-Dose combinations (PFDCs). Concerning, the trials about diclofenac combinations, Montgomery *et al.*[96] and Beck *et al.*[100] reported the simultaneous administration of the combination as a single rectal dose given before the surgery procedure. Breivik *et al.*[99], also reported the administration of a single rectal dose but after the surgery procedure. In the same way, in the trial published by Legeby *et al.*[105], diclofenac and paracetamol were administrated simultaneously but rectally and orally respectively. Yet, in the work

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published by Hiller *et al.*[103] the first dose of combined drugs was administrated simultaneously intravenously right before the surgery procedure, however postoperatively, according to the planned procedure the administration of the combination was not always performed simultaneously. In the case of ketoprofen combinations, only in the work published by Aubrun *et al.*[109] the administration of combining drugs was not performed simultaneously.

Concerning the ketoprofen RCTs presented in Table 3, the most common route of administration of the drugs in the trial's arms was intravenous. Indeed, only the study performed by Akural *et al.*[111] reported the administration of ketoprofen combinations orally. Additionally, in this study, the administration regimen was a single dose with an observation period of 10 hours. Also, Salonen *et al.*[112] administrated simultaneously ketoprofen with propacetamol intravenously in a single-dose regimen but in this study, the patients received the drugs intravenously. Fletcher *et al.*[108] reported the simultaneous administration of the combination every 6 hours intravenously for two days after surgery. In the same way, in the study performed by Fourcade *et al.*[110] the patients received the combined drugs every 6 but only for 12 hours.

In the case of ketorolac combinations, in the literature were found two RCTs where ketorolac was combined with paracetamol or propacetamol (Table 3). In a trial performed by Romundstad *et al.*[97] both ketorolac and propacetamol were used intravenously in a single dose. In the case of Iorno *et al.*[113] ketorolac was administered only at the end of the surgical intervention, intravenously while paracetamol was administered 15 minutes before surgery, on discharge from the hospital (mean 6 hours after surgery) and in the morning the day after surgery.

Yet, was published very recently a study where piroxicam was combined with paracetamol to explore the possible benefits of combining piroxicam with paracetamol. In this study both drugs where administrated orally but not with the same dosage frequency.

Regarding the efficacy and safety results and considering the works presented in table 3, some authors were able to demonstrate superior analgesia using combining drugs that either alone. However, there are also many cases where the studies were no able to demonstrate superior clinical outcomes.

3.3.1. Paracetamol-based Combinations with Diclofenac

The mechanisms of action of NSAIDs are different when compared with other NOAs like paracetamol and propacetamol. Due to this fact, it is expectable to occur a synergic activity of the drugs regarding their analgesic effect.

Montgomery et al.[96] designed a RCT (n=60) aiming to compare the analgesic efficacy of the combination of diclofenac plus APAP comparing it with the efficacy of both drugs alone. The outcome used in this trial where the amount of morphine consumes by the patients. The authors concluded that the use of the combination reduced significantly the amount of morphine consumed when compared with the paracetamol group (p<0.01). Comparing with the diclofenac group the amount of morphine consumed by the combination group was also reduced however it was not significantly different. Breivik *et al.*[99] (n=120) investigated the enhanced analgesic effect of a diclofenac/APAP combination against the pain induced by removing the third molars. The primary efficacy measure was pain intensity and it was concluded that concomitant oral administration of diclofenac and paracetamol is superior to diclofenac or paracetamol alone (p<0.05). The study performed by Beck *et al.*[100] (n=70) was a little different from the others since its main objective was not to assess the efficacy of a diclofenac/APAP combination in the treatment of painful conditions related to gynaecological surgery but mainly to study the pharmacokinetics of two doses of paracetamol. In other words, in this trial, the authors mainly investigated the analgesic paracetamol plasma concentrations since until then it had not been defined. Due to this, that study had not a comparator group with diclofenac alone but in any case, the results achieved by authors about the efficacy of the combination were in general inconclusive. There, VAS scores achieved in the combination group were significantly lower (p<0.05) compared with the paracetamol group. Siddik *et al.*[101] (n=80) evaluated the analgesic capability of the combination of diclofenac/PPCM in women after caesarean delivery. Based on the VAS score values obtained in this study, some points of

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observation resulted in favourable and significant results for the use of the combination group, but the authors were not able to demonstrate the evident improvement of analgesic effect using the combination as an alternative to the drugs alone. The authors concluded this study was unable to show a significant morphine-sparing effect using the combination of diclofenac/PPCM. Concerning safety, the authors did not find any difference regarding the incidence of adverse events between the assessed groups. Man *et al.*[102] (n=50) also designed a trial to investigate the efficacy and safety of a synergic effect of combining diclofenac with APAP to treat pain related to soft pain injuries treated in an emergency department. In this study, beyond the groups of the combination and respective drugs alone, the authors inserted another trial arm where the patients received indomethacin alone. Based on the results obtained using VAS score as efficacy outcome, the authors reported no statistical difference among all arms of the study concerning both the efficacy and incidence of adverse events. Same way, Woo *et al.*[104] designed an identical study but with more patients enrolled (n=300). Also, in this study, the authors concluded that the benefit of using the diclofenac/APAP combination resulted in a small and doubtful clinical utility. Hiller *et al.*[103] (n=71) also tested the analgesic capability of diclofenac and PPCM in combination for the treatment of postoperative pain induced after elective tonsillectomy in adults. At 9 p.m. the incidence of pain at rest was significantly lower in the propacetamol group than in the diclofenac group (p<0.05) but not significant comparing the combination group with both drugs alone. In this work was reported that the combination of diclofenac offers only a minor advantage concerning postoperative analgesia or the incidence of side effects, without clear clinical advantages in adult tonsillectomy patients. Legeby *et al.*[105] (n=50) performed a RCT to evaluate the combination of diclofenac with paracetamol. The trial was constituted of two arms, one testing the analgesic activity of a combination of diclofenac with APAP and other with APAP alone. In this work, was not included a trial arm with diclofenac alone since the authors treated the inclusion of diclofenac in the combination group as an added agent to be compared to the control group (paracetamol alone). Anyway, the authors reported lower VAS scores in the combination group when compared to the control group (p<0.05) at the first 20 hours of observation, but not between 21 and 64 hours of observation. The authors concluded that adding diclofenac to paracetamol reduced opioid consumption and improved pain relief during the first 20 hours at rest but was not effective during the patient's mobilization. Munishankar *et al.*[106] (n=78) tested the efficacy of a combination of diclofenac/APAP in the pain control of women subjected to elective caesarean section. As the main endpoint, the investigators quantified the consumption of morphine for the first 24 hours after the medical procedure. The authors concluded that the consumption of morphine was reduced by 38% in the group who was given the diclofenac/APAP combination compared to the group of paracetamol alone. The same was not observed when the combination group was compared to the diclofenac group. Concerning the incidence of adverse events, the authors suggest that the combination may be associated with more side effects, however larger studies are required. In a larger study, Ridderikhof *et al.*[107] (n=547), assessed the efficacy and safety of diclofenac/APAP combination with a RCT for the treatment of acute musculoskeletal traumatic pain. This study aimed to assess that paracetamol was not inferior to nonsteroidal anti-inflammatory drugs or to the combination of both drugs in the treatment of pain produced by minor musculoskeletal trauma. They concluded that analgesic treatment with paracetamol was not inferior to the analgesia induced by diclofenac or by the combination of diclofenac/APAP. Indeed, the Intention-to-treat analysis revealed mean NRS reduction in rest -1.23 (95% confidence interval [CI] -1.50 to -0.95) and -1.72 (95% CI -2.01 to -1.44) with movement, both for paracetamol at 90 minutes compared with baseline. Pairwise comparison in rest with diclofenac showed a difference of -0.027 (97.5% CI -0.45 to 0.39) and -0.052 (97.5% CI -0.46 to 0.36) for combination treatment. With movement, these numbers were -0.20 (97.5% CI -0.64 to 0.23) and -0.39 (97.5% CI -0.80 to 0.018), respectively.

Concerning the efficacy, from the ten studies presented in Table 3 about diclofenac combinations, only the study published by Breivik *et al.*[99]was able to report that concomitant oral administration of diclofenac and paracetamol is superior to diclofenac or paracetamol alone. Montgomery *et al.*[96] reported that combination reduced significantly the amount of morphine consumed by the combination group when compared with paracetamol but not when compared to the diclofenac

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group. Interestingly, Munishankar *et al.*[106] also reported that the combination was able to demonstrate a superior opioid-sparing effect when compared with the paracetamol group but not with the diclofenac group. In the rest of the studies, the authors were not able to demonstrate clear advantages of using diclofenac combinations.

Regarding safety, in general, all the studies that published results reported no statistical significance between the groups receiving combination drugs groups and those where the diclofenac or paracetamol was prescribed alone.

3.3.2. Paracetamol-based Combinations with Ketoprofen

As with diclofenac combinations, some authors had assessed the possibility to improve the analgesia outcomes by combining ketoprofen with paracetamol or propacetamol.

The clinical study performed by Fletcher *et al.*[108] (n=60) aimed to evaluate the effect of the combination of propacetamol (Prodafalgan®) and ketoprofen (Profenid®) after surgery of patients with herniated disc of the lumbar spine. The authors began with the principle that a combination of analgesic drugs may enhance analgesia and reduce side effects after surgery. The VAS scores obtained from the enrolled patients after the analgesic treatment were used as the primary endpoint of the study and were lower in the combination group than in groups of propacetamol, ketoprofen, and placebo at rest (p<0.05) and on movement (p<0.01). The authors concluded the combination of propacetamol and ketoprofen reduced effectively pain scores both at rest and on movement but were not able to reduce the morphine consumption and incidence of side effects. Aubrun *et al.*[109] (n=50), also assessed the analgesic effects of ketoprofen in patients undergoing spinal fusion surgery and receiving propacetamol. As like in the work performed by Legeby *et al.*[105] for the diclofenac combination, also in this case, the NSAID was handed as an addition to the propacetamol treatment. The pain intensity was assessed using the VAS scale, and the authors concluded that combining ketoprofen with propacetamol significantly reduced morphine consumption (25±17 *vs* 38±20 mg, p=0.04) and VAS score (p=0.002). Indeed, the total postoperative morphine consumption was significantly (33%) reduced with ketoprofen. Meanwhile, Fourcade *et al.*[110] (n=97) compared the efficacy of ketoprofen and propacetamol alone and in combination in adult patients after being subjected to thyroidectomy. The authors began to explain that despite the combination of NSAIDs with NOAs are widely used in clinical context, this practice has been poorly assessed. The results achieved in this study revealed that despite pain scores were significantly higher with propacetamol compared with ketoprofen and the combination at 2 h after surgery (35±3.7, 21±2.6, respectively; p<0.01), the concomitant use of propacetamol and ketoprofen does not improve analgesia compared with ketoprofen alone. Akural *et al.*[111] (n=76) experimented the use of ketoprofen plus paracetamol in the treatment of dental pain in a single-dose regimen. Once more the authors based on the concept that a combination of analgesic drugs with different pharmacologic properties may be more effective, with fewer adverse events, than either agent used alone. With this, the authors reported that at 1.5 hours Sum of Pain Intensity Difference (SPID) at rest and on swallowing was significantly greater in the combination group than in the paracetamol, ketoprofen, and placebo groups (all, p<0.05). Also, the authors reported that the mean time to onset of pain relief at rest and on swallowing was significantly less in the combination group than among the other groups (all, p<0.05) and the median time to use of rescue medication were significantly longer in the combination group than in the paracetamol group (p=0.006) and the placebo group (p<0.001). Concerning the side effects, the prevalence of trismus, bleeding, and edema was not significantly different between the study groups. With these results, the authors concluded that the obtained results support the clinical practice of combining ketoprofen with paracetamol for the management of acute pain. Also, Salomen *et al.*[112] (n=114) evaluated whether the co-administration of IV paracetamol could enhance the analgesic efficacy of ketoprofen in patients undergoing a tonsillectomy. Taking into account the primary outcome of this study, despite no difference was detected in the proportion of patients receiving oxycodone between the three groups, significantly fewer doses of rescue analgesia were provided in the combination groups compared with the ketoprofen-alone group (p=0.005). Indeed, 27% less oxycodone was required in the combination group with paracetamol 1g (p=0.023) and 38% less in the

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combination group where paracetamol 2 g was used (p=0.002) when both groups were compared with the ketoprofen-alone group. With these results, the authors concluded that combining intravenous paracetamol with ketoprofen at the end of tonsillectomy did not reduce the proportion of the patients requiring rescue analgesia, but the number of opioid doses was less in the add-on groups.

In summary, as can be consulted in Table 3, as with the diclofenac combinations, not all published works were able to demonstrate increased analgesia capability by combining ketoprofen with paracetamol or propacetamol. Also, concerning the safety aspects of combining ketoprofen with APAP or PROPAP reported by some studies reinforce that combining these kinds of drugs does not impact significantly the incidence of the occurrence of adverse events.

3.3.3. Paracetamol-based Combinations with Ketorolac

Ketorolac was the first parenteral NSAID commercialized in the USA in 1990[114]. Due to their long presence in the market, the very lack of clinical trials assessing the analgesia efficacy of ketorolac combinations with APAP or PROPAP is surprising. Concerning the number of studies about the combination of ketorolac with APAP, our results are in accordance with the results obtained in another study published in 2010 by Cliff *et al.*[115] where the authors performed a qualitative systematic review of analgesic efficacy of combinations of NSAIDs with paracetamol for the treatment of acute postoperative pain. In this study, only one RCT with ketorolac was reported by the authors.

Romundstad *et al.*[97] (n=16) assessed the analgesic ability to combine ketorolac with propacetamol in healthy patients. To this, the authors applied a pressure stimulus on the base of a fingernail until the pressure pain tolerance threshold was reached. Indeed, it was the unique study reported in Table 3 where the painful conditions were induced artificially instead of using real clinical scenarios. For the total observation period, only in the combination group was observed a significant increase in the pressure pain tolerance threshold (PPTT) when compared with baseline (p<0.04), and PPTT decreased significantly after placebo (p< 0.01). Also, the combination and ketorolac alone increased PPTT compared with the placebo (p<0.001) and with propacetamol (p< 0.001). Additionally, the combination was significantly better than ketorolac alone (p< 0.04) but not with propacetamol alone since after propacetamol 2 g, PPTT did not change significantly neither compared with placebo or baseline. With these results, the authors concluded that their findings support to be advantageous to combine paracetamol with an NSAID for the relief of acute pain. Also, Iorno *et al.*[113] (n=60) tested the analgesic efficacy and safety profile of combining ketorolac with paracetamol enrolling women undergoing voluntary abortion. The authors achieved interesting results where significant differences in pain levels at T0 (NRS 0.92 and 2.08; p<0.01), at T2 (in the morning after surgery; data collected by phone interview) and, following administration of the next dose of paracetamol (1.58 vs. 1.98; p=0.01). Only at T1 there were no significant differences between NRS scores in the two groups (3.7 *vs* 3.5, respectively, p=0.3453). Concerning the adverse events, only a case of dizziness was reported in the combination group, and no other unexpected adverse events were recorded. With these results, this small study suggests that oral paracetamol t.i.d. in combination with IV ketorolac o.d. is effective and well tolerated in the control of postoperative pain after ambulatory uterine evacuation.

Both studies available assessing the efficacy and the safety of combining ketorolac with APAP/PROPAP are very small to achieve any conclusive results. Despite all this, both assays present favorable evidence for the use of ketorolac in combination with paracetamol or propacetamol.

3.3.4. Paracetamol-based Combinations with Piroxicam

Piroxicam is indicated for symptomatic relief of osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis. However, due to its safety profile, piroxicam should not be a first-line option[56]. The very long half-life of oxicams like piroxicam has been related to increased GI toxicity when compared with other traditional NSAIDs[116]. Probably due to this fact, the number of published works about this NSAID is very limited.

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During our literature research, only one study assessing the combination of piroxicam plus paracetamol where found. In the RCT performed by Msolli *et al.*[98] (n=1504) the authors proposed to explore the benefits of combining an NSAID with paracetamol compared to paracetamol alone, or NSAID alone, in the treatment of post-traumatic pain. The primary outcome was the need for additional oral analgesics. The need for additional oral analgesics was comparable between the paracetamol-NSAID combination group (9.8%) and the paracetamol group (11.4%; p=0.43). Also, the ED readmission rate was similar between the two groups at 5.6 and 5.8%, respectively (p=0.86). In contrast, the need for new analgesics and ED revisit rates were both more frequent in the piroxicam group where the frequency of dissatisfaction was higher. Concerning the safety profile, side effects were more frequent in the piroxicam and combination groups. With this, the authors concluded that the combination of piroxicam with paracetamol does not increase the analgesic effect compared to paracetamol alone. Also, they reported that paracetamol alone is superior to piroxicam alone for posttraumatic extremity pain.

Discussion

The combination of NSAIDs with NOAs is not something new. In clinical practice, the multimodal approach is actually very common. Indeed, the combination of analgesic entities has been demonstrated to be able to improve analgesia outcomes through synergic mechanisms and is commonly recommended by medical guidelines for pain management [13].

Due to the well-known efficacy and safety profiles of paracetamol and NSAIDs, their combination is one of the most recommended multimodal strategies in several clinical guidelines for pain management[7,10]. Metamizole is an alternative to paracetamol with very satisfactory efficacy performance however, it is banned from some countries due to its doubtful safety profile. Despite all this, metamizole is also a good NOA to be considered in the development of new FDC products since are already several parenteral FDCs with metamizole available in the market (section 3.2)

Since the combination of NSAIDs with NOAs is common in clinical practice and several combinations of NSAIDs with paracetamol or metamizole are possible, it was expected to find FDCs available in the market. However, it is surprising that only the FDC of paracetamol with ibuprofen is available. This ready-to-use FCD is available in tablets and in solution for intravenous administration but even these products have been both introduced in the market very recently (section 3.1).

Even though the evident clinical and economic advantages that a parenteral ready-to-use FDC can provide, their development and marketing authorization could be very challenging. During the development, must be ensured that the mixture of APIs does not change the pharmacokinetics and pharmacodynamics of both drugs. Also, a formulation that allows the stability of both APIs at the same time must be found[117]. During the marketing authorization application, very clear clinical evidence should be demonstrated that the new FDC provides advantageous efficacy and safety profiles when compared with already medicinal products[82–84,117,118].

Taking into account that parenteral formulations of paracetamol, metamizole, and some NSAIDs are available in the market (sections 2.2.1, 2.2.2, and 2.2.3), it is possible, at least conceptually, to develop parenteral ready-to-use FCDs with these drugs. However, to achieve the market, these products must be assessed by well-designed RCTs. Since the efficacy and safety profiles of these drugs alone are already well established, it is only necessary to demonstrate the safety and efficacy of the combination. For this, based on the marketing applications submitted to EMA for the market introduction of the Comboval® and Maxigesic® IV the non-clinical aspects submitted can be based just on a literature review. However, for the clinical aspects, well-designed RCTs are mandatory to study not only the efficacy and safety profiles of the new combination, but also to prove that the combination does not alter the pharmacokinetics of the combining drugs[83,84].

In the literature, there is a lack of RCTs available to study the potential utility of NSAID combinations (section 3.3). According to our review, some authors designed RCTs to assess the efficacy and the safety of combining NSAIDs with paracetamol (or propacetamol), however, several of them were unable to demonstrate clear advantages in the use of such combinations. Focusing on the design of the studies, we see that they have severe limitations that could impact deeply the results.

For instance, in some studies, the drugs were not administrated simultaneously, and/or by the same route. Since these studies were not designed to assess the efficacy nor the safety profiles of FDCs they are not enough to prove the efficacy of NSAID combinations however they could serve as proof-of-concept concerning the safety requests.

Conclusions

The combination of NSAIDs with NOAs is not something new and is very well-established in clinical practice due to the synergic relationship established between their different mechanisms of action of the drugs.

Despite the clear advantages of using analgesic combinations, there are in literature several works unable to report clear clinical advantages in real clinical contexts. In several works, some conditions like the different routes of administration of the combined drugs and their non-simultaneous administration could be the reason for the achievement of such results.

Since there are already available in the market parenteral formulations of paracetamol, metamizole, and NSAIDs the development of several parenteral ready-to-use FDCs is conceptually possible. However, at this moment, only the ibuprofen/paracetamol combination is available in the market. Surprisingly, their marketing introduction is very recent. Indeed, with well-designed studies, the marketing authorization applicants were able to demonstrate satisfactory results about the efficacy and safety of this ready-to-use FDC.

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Abbreviations

AAPM	American Academy of pain medicine
AE	Adverse event
APAP	Paracetamol
ASA	American Society of Anaesthesiologists
b.i.d	Two times a day
CHMP	Committee for Medicinal Products for Human Use
COX	Cyclooxygenase
CV	Cardiovascular
ERAS	Enhanced Recovery After Surgery
FDA	Food and Drugs Administration
FDC	Fixed-dose combination
GI	Gastrointestinal
IBP	Ibuprofen

IM	Intramuscular
IV	Intravenous
KTLC	Ketorolac
MMA	Multimodal analgesia
MSF	Doctors without frontiers
NAPQI	N-acetyl-p-benzoquinone imine
NMDA	N-Methyl-D-aspartic acid
NOA	Non-opioid analgesic
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
o.d	Once a day
PFDC	Parenteral fixed-dose combination
PPCM	Propacetamol
q.i.d	Four times a day
PID	Pain Intensity difference
PPTT	Pressure pain tolerance threshold
SPID	Sum of pain Intensity difference
SSRI	Selective serotonin reuptake inhibitor
t.i.d	Three times a day
USA	United States of America
VAS	Visual analogue scale
VRS	Verbal Rating Scale

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