Submitted: 19 July, 2021 Accepted: 25 August, 2021 Published: 08 November, 2021 DOI:10.22514/sv.2021.210

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REVIEW

Multimodal analgesia for postoperative pain in Asia: a review of evidence with clinical focus on dexketoprofen and tramadol/dexketoprofen fixed-dose combination

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Abstract

The majority of patients who have undergone surgery experience moderate-to-severe postoperative pain. Asian patients tend to under-report pain and are consequently under-treated. Poor postoperative pain management increases the risk of morbidity, prolonged opioid use, lower quality of life outcomes and the risk of chronic post-surgical pain. Multimodal analgesia is the cornerstone of postoperative pain management. Non-steroidal anti-inflammatory drugs are considered a core component of multimodal analgesia due to their anti-inflammatory and analgesic properties. Use of a consistent non-steroidal anti-inflammatory throughout the postoperative period can help to achieve and maintain adequate pain relief. This review investigates the use of multimodal analgesia in postoperative pain management in Asia, with a focus on clinicians' experience with dexketoprofen as a non-steroidal anti-inflammatory therapy throughout the postoperative period and its combination as fixed dose with Tramadol, a centrally acting synthetic opioid analgesic, in Asian patients, when necessary.

Keywords

Multimodal analgesia; Dexketoprofen; Tramadol; Fixed dose combination; Asia

1. Introduction

More than 80% of patients who undergo surgical procedures experience postoperative pain [1]. Of these, three-quarters experience moderate, severe or extreme pain [1]. Despite its high prevalence, less than half of patients who undergo surgery report adequate pain relief [1].

Among Asian patients, pain tends to be under-reported and under-treated [2]. Ethnocultural factors, such stoicism, may cause patients to be reluctant to ask for pain relief [3]. In addition, a lack of sufficient patient education about the importance of proactive postoperative pain management and a trend towards conservative pain management approaches may compound the issue [3, 4].

Inadequate postoperative pain management can have serious physical and psychological consequences [1, 5, 6]. Patients who experience poorly-controlled postoperative pain are at increased risk of morbidity, impaired physical functioning, prolonged opioid use, poorer quality of life outcomes and the risk of persistent or chronic postsurgical pain (CPSP) [1, 5–7]. Inadequate postoperative pain management can also result in an increased economic burden for health services, with longer length of hospital stay, more rehospitalizations and greater use of health resources [8, 9].

Here, we review the status of postoperative pain management in Asia, with a focus on the role of multimodal analgesia and clinicians' experience with dexketoprofen and a tramadol/dexketoprofen fixed-dose combination.

2. Guideline recommendations and acceptance of multimodal analgesia in Asia

The American Pain Society (APS) with input from the American Society of Anesthesiologists, and the Australian and New Zealand College of Anaesthetists (ANZCA) have both published broad evidence-based guidelines on analgesic strategies intended to optimize patient outcomes after surgery (Table 1, Ref. [1, 10]). These guidelines are endorsed in the region by Malaysian, Hong Kong, Thailand and Indonesian pain associations and societies [10]. In addition, the PROcedure-SPECific pain managemenT (PROSPECT) initiative provides evidence-based recommendations individualized to the patient and procedure [11, 12]. The recommendation to use multimodal analgesia as the cornerstone of postoperative pain management is common across these guidelines [1, 10, 11].

Multimodal analgesia is the use of more than one analgesic medication with different mechanisms of action to obtain additive or synergistic effects [1, 5, 9]. Combining analgesics that act by different mechanisms (e.g., peripherally vs centrally), and with differing pharmacokinetic profiles, provides a broader spectrum of pain relief while minimizing side effects

TABLE 1. International guideline recommendations on the treatment of postoperative pain [1, 10].

Guideline recommendations in postoperative pain	Offer multimodal analgesia for the treatment of postoperative pain in children and adults	Use oral over IV administration of opioids for postoperative analgesia in patients who can use the oral route	Provide NSAIDs as part of multimodal analgesia for management of postoperative pain in patients without contraindication
As recommended by:			
American Pain Society	√	√	√
Australian and New Zealand College of Anaesthetists, and Endorsed by Malaysian, Hong Kong, Indonesian and Thailand Associations and Societies	√	√	√

associated with higher doses of multiple, single-drug analgesic interventions [13]. Patients receiving multimodal analgesia in the postoperative setting are likely to have lower overall opioid consumption compared with those managed using primarily intravenous (IV) opioid patient-controlled analgesia (PCA) [13].

Available literature suggests that multimodal analgesia is an accepted approach for the treatment of postoperative pain in Asian patients [14–16]. However, population-wide data on the use of multimodal analgesia or specific multimodal regimens employed in the postoperative setting are lacking.

A 2008 survey of the pain management practices of Filipino surgeons (n = 167) found the majority of surgeons (62%) administer a multimodal analgesic regimen from the immediate postoperative period [14]. Of these, almost 80% use the combination of a non-steroidal anti-inflammatory drug (NSAID) and a weak opioid, while the remainder opt for the combination of an NSAID and a strong opioid [14]. This study also identified a preference for administration of postoperative pain relief on schedule (87%) rather than as needed by the patient. While most respondents (83%) did not start oral pain medication in the recovery room, almost all respondents (98.8%) indicated that they start oral medication as soon as possible [14].

Patient benefits of multimodal analgesia were also reported in a 2017 retrospective review of opioid-related adverse events in 158 patients undergoing laparoscopic sleeve gastrectomy in a Singapore Hospital [15]. The implementation of a multimodal analgesic protocol resulted in a significant reduction in the incidence of opioid-related adverse events (33.3% to 8.8%, $p < 0.001$) and postoperative opioid use (23.7 mg to 0.7 mg, $p < 0.001$) [15].

A 2015 audit of acute pain services in Hong Kong investigated the evolution of pain management over two decades from 1992 to 2012. The audit identified an increasing emphasis on the implementation of multimodal analgesia and a shift towards procedure-specific management of postoperative pain [16]. The adoption of multimodal pain protocols in acute pain services in Hong Kong has been associated with reduced opioid consumption, reduced incidence of analgesia-related side effects, enhanced quality of life and satisfaction for postoperative patients [16].

The efficacy of a multimodal analgesic regimen for postoperative pain was compared with that of patient-controlled analgesia (PCA) in 100 patients undergoing posterior lumbar fusion in Korea [17]. Pain score, additional non-opioid consumption, side effects and patient subjective satisfaction scores were comparable between the two groups. However, compared with the PCA group, patients receiving multimodal analgesia had a shorter length of hospital stay (median (Interquartile range): 7 (5–8) days vs 8 (7–11) days; $p = 0.001$) and lower costs of pain control (70.6 ± 0.9 USD vs 173.4 ± 3.3, $p < 0.001$) [17].

The health resource benefits of multimodal analgesia were also noted in a 2019 cost-consequence analysis of a parecoxib plus opioid multimodal analgesia regimen in China [18]. The analysis found that multimodal analgesia was associated with fewer clinically meaningful adverse events compared with opioids alone in the 3-day postoperative period in Phase III clinical trials.

These findings suggest that the use of multimodal analgesia may be both a clinically relevant and cost-saving analgesic strategy. In fact, it has the potential to decrease hospital length of stay and physician and nurse time associated with the management of opioid-related clinically meaningful events [18].

While multimodal analgesia appears to be adopted throughout the region in a variety of surgical procedures, broader population-wide data are needed. This would provide a clearer picture of the general uptake of multimodal analgesia and the patient and clinician education required to optimize its use.

3. Optimizing postoperative pain management with multimodal analgesia

Postoperative pain is a complex experience involving both peripheral and central mechanisms [19]. It can be somatic or visceral, nociceptive or neuropathic, or (very frequently) a combination of these characteristics [5]. Nociceptive pain arises from tissue damage and is mediated by chemicals released within the damaged area. Neuropathic pain arises from damage or disease in the sensory neurons and is mediated by alterations in ion channel signaling. Centrally, both nociceptive and neuropathic pain are associated with changes in spinal cord and brain excitability [20].

A severe or prolonged experience of postoperative pain can increase the risk of developing CPSP through central sensitization [5]. Early and optimal multimodal analgesia in the postoperative setting is needed to target the complex nature of pain and lessen the risk of CPSP [9].

Considering the unique characteristics of the different types of pain seen in the postoperative setting, multimodal analgesia needs to employ a combination of drugs with differing pharmacological actions. Ideally, this combination should include one drug that acts peripherally, such as a non-steroidal anti-inflammatory drug (NSAID), to stop pain where it starts, and one that modulates central transmission and integration of incoming pain signals, such as an opioid [21].

No specific combination of analgesics is recommended for multimodal postoperative pain management, as the efficacy of analgesics can differ between surgical settings. However, the APS does recommend the use of paracetamol or (better) NSAIDs as part of multimodal regimens [1].

Both NSAIDs and paracetamol have analgesic and antipyretic effects. However, paracetamol does not demonstrate anti-inflammatory properties [5, 22]. NSAIDs have an anti-inflammatory effect resulting in the relief of postoperative pain by reducing tissue swelling [5]. NSAID therapy should be preferred because of the extra anti-inflammatory action.

3.1 The role of non-steroidal anti-inflammatory drugs

NSAIDs are a heterogenous group of drugs, encompassing nonselective NSAIDs (nsNSAIDs) and COX-2 selective inhibitors (coxibs), which share the common property of COX inhibition [5, 22]. Inhibition of COX enzymes results in reduced prostaglandin synthesis, leading to a reduction in inflammation and pain. NSAIDs are also considered to have a secondary mechanism of action that influences basic cellular and neuronal processes, potentially reducing the perception of pain [21].

The ANZCA Faculty of Pain Medicine considers both nsNSAIDs and coxibs effective analgesics of similar efficacy and recommends both classes of NSAIDs in the management of acute postoperative pain [10]. While NSAIDs are common place in the postoperative setting, there has been some discussion in the past on the role of NSAIDs in the orthopedic surgical setting given evidence suggesting that NSAIDs may inhibit bone healing [23]. To date there are no sufficient data to advise against the use of NSAID in this setting. Optimal postoperative pain management individualizes the choice of NSAID and the multimodal regimen according to the patient characteristics and the type of procedure [21, 24].

Dexketoprofen is a traditional, non-selective NSAID and analgesic drug, inhibiting both COX-1 and COX-2 and subsequently reducing the production of prostaglandins [21]. It works both centrally and peripherally, reducing prostaglandins at the site of injury and also in the central nervous system to reduce pain response [21]. Inhibition of COX-1 is thought to contribute to a reduction in the risk of pain chronification through the inhibition of spinal glial cells that play a role on spinal sensitization [21].

As the S(+)-enantiomer of ketoprofen, dexketoprofen demonstrates equal analgesic activity with a faster onset of analgesia at half the dose of the racemic ketoprofen [21]. Formulated with tromethamine salt, it is highly soluble compared with the free acid form, enhancing its bioavailability and accelerating the onset of its therapeutic effect. Its fast absorption also lowers the potential for gastric ulceration, resulting in an improved tolerability profile compared with other NSAIDs [21].

The efficacy of single-dose oral dexketoprofen trometamol has been established in acute postoperative pain following dental surgery [25]. In a meta-analysis of five double-blind randomized controlled trials following dental surgery, approximately half of all patients treated with oral dexketoprofen 20 or 25 mg experienced at least 50% pain relief 4–6 hours after administration, compared with one in ten patients receiving placebo [25, 26]. Single-dose oral dexketoprofen 25 mg was more effective than ibuprofen 600 mg at preventing moderate-to-severe pain in the first hour of treatment after dental surgery [26].

Dexketoprofen has also been demonstrated to guarantee effective analgesia in randomized controlled trials of patients following hip arthroplasty and abdominal hysterectomy and has shown a similar degree of analgesia to diclofenac sodium 75 mg in patients undergoing uterine curettage [26–28].

Direct comparisons with COX-2 inhibitors are lacking; however, the efficacy and tolerability of single-dose dexketoprofen trometamol appears to be consistent with that seen with celecoxib, etoricoxib and parecoxib in the acute pain setting [26]. Dexketoprofen is available in an IV formulation, for use in the immediate postoperative period when patients are nil per oral. It is also available as an intramuscular (IM) formulation, and orally as a monotherapy or in a fixed-dose combination with tramadol 75 mg.

3.2 The role of fixed-dose combinations

Fixed-dose combinations can be used to deliver multimodal analgesia in an easy-to-administer formulation that reduces pill burden, enhancing the potential for patient adherence. Fixed-dose combinations carry all the advantages of multimodal therapy, including synergism achieved from peripheral and central analgesic actions and a better efficacy-to-safety ratio [21].

Several analgesic combinations have been trialed for the management of postoperative pain, including paracetamol with weak opioids such as codeine or tramadol [21]. While the paracetamol and weak opioid combinations produced sufficient pain relief, no studies found them to be superior to NSAIDs in controlling postoperative pain [21]. The combination of a weak opioid and an NSAID is considered a better alternative, due to the anti-inflammatory properties of NSAIDs and the additive analgesic activity provided by the opioid. NSAIDs target the chemical mediators of pain released during tissue damage. In addition, extensive evidence suggests that opioids have greater efficacy treating postoperative pain compared with normal pain states. Chemicals released during tissue damage and inflammation can lead to upregulation of opioid receptors [21].

Tramadol—a centrally acting μ-opioid receptor agonist and serotonin/norepinephrine reuptake-inhibitor (SNRI)—has been used effectively to treat moderate-to-severe pain since the 1970s and since that time has been shown to achieve comparable relief to equianalgesic doses of parenteral morphine or alfentanil [29]. It has a long duration of action and, unlike other opioids, has no clinically relevant effects on respiratory and cardiovascular parameters [29]. In a 2014 review of records in a hospital in Cebu, Philippines, tramadol was the most commonly utilized analgesic whether parenteral, oral, monotherapy or in combination with a non-opioid analgesic [30].

The tramadol 75 mg and dexketoprofen 25 mg fixed-dose combination (TRAM/DKP FDC) was introduced in Europe in 2016 and across the Asia Pacific region in 2018 to provide multimodal analgesia at lower and better tolerated doses than those of the single agents used alone [21, 31]. It is indicated for the relief of moderate-to-severe acute pain [21, 32].

A 2019 expert consensus on the use of TRAM/DKP FDC agreed that an orally administered fixed-dose combination of TRAM/DKP has shown an analgesic efficacy greater than that achieved by either component in monotherapy for dental pain, soft tissue surgery and joint replacement surgery [32]. This same concept was also highlighted by a Cochrane review [33].

4. Tramadol/dexketoprofen fixed-dose combination in postoperative pain management

In combination, dexketoprofen and tramadol target different peripheral and central sites, using complementary, synergistic mechanisms of action to deliver pain relief that is greater than the individual drugs alone [21, 32, 34–36]. The fast onset of action of dexketoprofen is complemented by the longer duration of analgesia typical of tramadol, to deliver both rapid and long-lasting analgesia. The anti-inflammatory activity of dexketoprofen and the central and peripheral analgesia of both dexketoprofen and tramadol makes TRAM/DKP FDC a flexible tool for the treatment of the mixed forms of pain seen in the postoperative setting [32].

As shown in clinical trials, the combination requires a lower dose of the individual agents to achieve analgesia, compared with tramadol and dexketoprofen monotherapy [21, 34–38]. The safety and tolerability of the combination is in line with that observed in previous clinical experience with tramadol and dexketoprofen monotherapy. The most frequently occurring adverse reactions included vomiting, nausea and dizziness, with most adverse reactions mild to moderate in intensity [21, 34–38]. The TRAM/DKP FDC consistently reported a lower incidence of opioid-related adverse effects in comparison to tramadol and dexketoprofen monotherapy, including the opioid-induced bowel dysfunction (OIBD) particularly important in abdominal surgery. It may lead to shorter hospital stays, improved recovery and return to function in patients treated with TRAM/DKP FDC [21].

Recently, a series of 13 case studies was published detailing the use of TRAM/DKP FDC in the postoperative pain management of Asian patients undergoing orthopedic, soft tissue or laparoscopic surgery [31]. All cases reported well-tolerated postoperative pain management with good pain relief with TRAM/DKP FDC. No patients discontinued TRAM/DKP FDC during the prescribed treatment period [31].

The efficacy of the TRAM/DKP FDC has been demonstrated in randomized trials involving 1853 patients [34–36]. In addition, one *post-hoc* analysis and one head-to-head clinical trial have also been undertaken [37, 38].

In a Phase II dose-finding trial involving 606 patients, dexketoprofen alone, or in combination with tramadol, demonstrated rapid onset of pain relief that was superior to placebo. The addition of tramadol to dexketoprofen resulted in a greater peak pain relief and greater relief over the long-term [36]. Patients receiving a fixed combination of TRAM/DKP required less rescue medication overall compared with patients receiving monotherapy or placebo [36].

Abdominal hysterectomy is a recognized model of moderate-to-severe acute pain frequently used in the clinical evaluation of analgesic drugs [35]. A Phase III, randomized, double-blind, placebo and active-controlled study of 606 patients was conducted to evaluate the analgesic efficacy and safety of TRAM/DKP FDC in comparison with the single components in moderate-to-severe pain following abdominal hysterectomy [35]. The TRAM/DKP FDC demonstrated statistically superior analgesia compared with dexketoprofen 25 mg and tramadol 100 mg as monotherapy ($p < 0.001$ for both comparisons) after both single-dose (8-hours post-dose) and multiple-dose (6 subsequent doses) phases [35]. There was also evidence of a longer time to first use of rescue medication and significantly lower overall use of rescue medications in patients receiving TRAM/DKP FDC compared with dexketoprofen 25 mg and tramadol 100 mg as monotherapy [35].

Total hip replacement is a major orthopedic surgery and is considered a clinically relevant model of moderate-to-severe acute nociceptive somatic pain [34]. The superior analgesic efficacy and safety of the TRAM/DKP FDC was assessed in 641 patients experiencing at least moderate intensity pain on the day after total hip replacement surgery [34]. Analgesic efficacy was assessed in single-dose (8-hours post-dose) and multiple-dose (12 subsequent doses, each one administered every 8 hours) phases [34]. The TRAM/DKP FDC demonstrated statistically superior pain control in the single-dose phase (measured as mean sum of pain intensity difference over 8 hours after first dose) compared with dexketoprofen 25 mg ($p = 0.019$; 95% CI 6.4–73) and tramadol 100 mg ($p = 0.012$; 95% CI 9.5–76) monotherapy. Superior analgesic effect was sustained throughout 48 hours of the multiple-dose phase [34].

The duration of the TRAM/DKP FDC analgesic effect was analyzed in a *post-hoc* analysis of two previously described studies [38]. The TRAM/DKP FDC was demonstrated to provide superior long-duration analgesia compared with dexketoprofen 25 mg or tramadol 100 mg alone. TRAM/DKP FDC patients had significantly lower mean pain scores compared with monotherapy and placebo at all time points over a 56-hour period ($p < 0.0001$) [38].

The superiority of TRAM/DKP FDC has also been assessed in one head-to-head randomized, double-blind single-dose trial versus a tramadol 75 mg plus paracetamol 650 mg (TRAM/PARA) combination or placebo, in dental pain

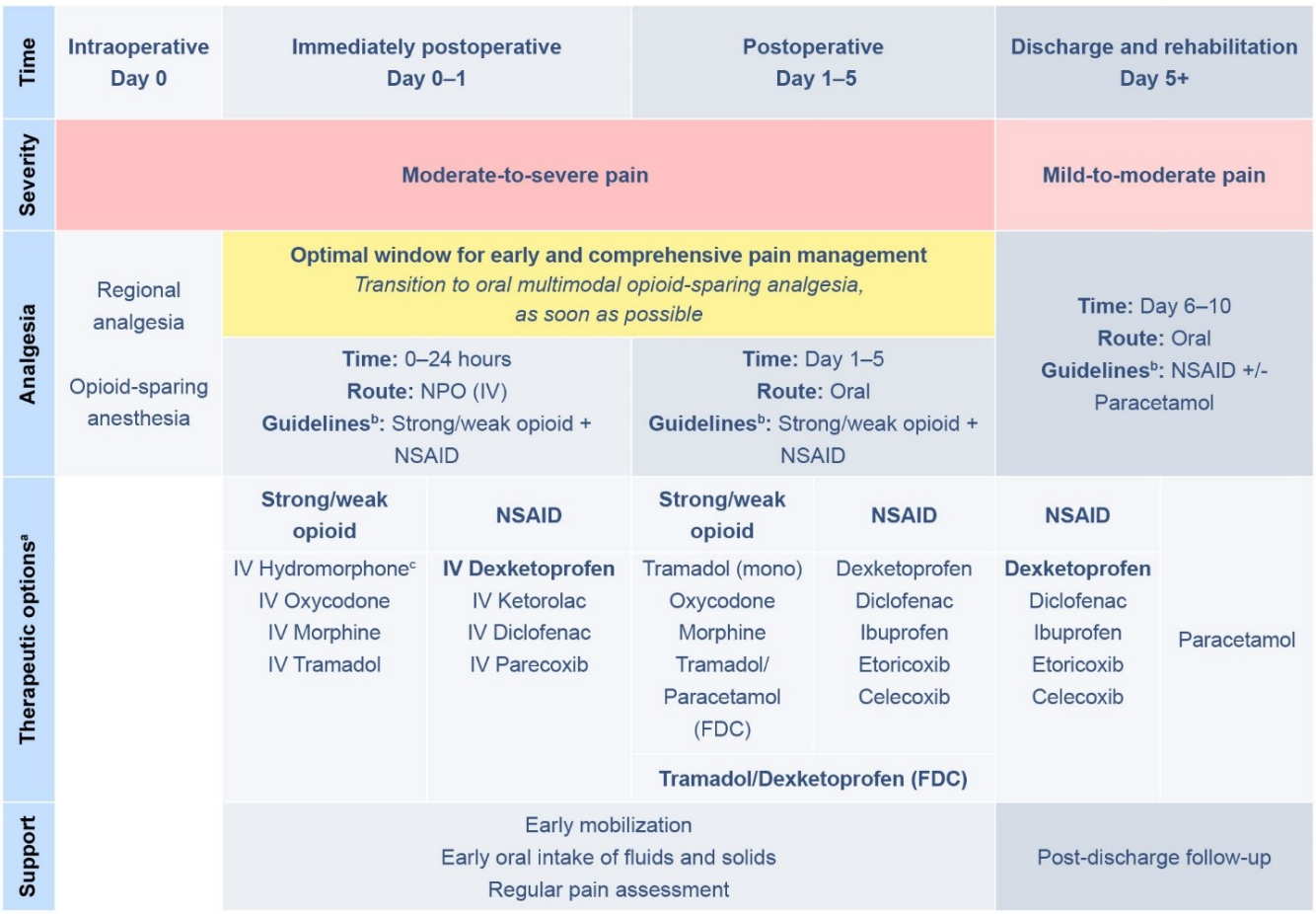

FIGURE 1. Proposed overview of postoperative pain management transition. [a] Lists do not represent all available molecules within a therapeutic class. [b] Adapted from American Pain Society (APS), the Australian and New Zealand College of Anaesthetists (ANZCA) and the PROcedure-SPECific pain managemenT (PROSPECT) initiative. [c] IV Hydromorphone is not available in the Philippines and similarly the mentioned drugs may not be available in all countries.

resulting from third molar extraction [37]. The TRAM/DKP FDC demonstrated superior total pain relief over 6 hours (TOTPAR6) compared with TRAM/PARA (mean TOTPAR6, 13 TRAM/DKP FDC vs 9.2 TRAM/PARA and 1.9 placebo; $p < 0.0001$). Significantly more patients treated with the TRAM/DKP FDC noted pain relief within 30 minutes of taking a dose, compared with patients treated with TRAM/PARA. Significantly more patients in the TRAM/DKP FDC arm (80.8%) rated the study medication as 'good', 'very good' or 'excellent', than in the TRAM/PARA (56.6%) and placebo (15.3%) arms. The incidence of adverse events was comparable between the groups [37].

5. Experts' clinical opinion on treatment transitions in postoperative pain management

Multimodal analgesia is the cornerstone of all stages of post-operative pain management in Asian clinical settings, and internationally. The use of an oral FDC is considered an optimal choice when transitioning out of regional anesthesia. Including an NSAID as part of this combination is deemed to contribute significantly to the repression of the effects of the consequent release of sensitizing substances during tissue injury, thereby limiting peripheral sensitization of nociceptors. This has an important clinical implication for the prevention of CPSP, as it has been noted that deeper tissue injury is likely to produce a powerful sensitization of pain pathways.

When selecting NSAID options in the postoperative setting, clinicians should consider individual differences in sensitivity and tolerability. When an NSAID is found to be well-tolerated and effective in a patient, there should be no need to alter that NSAID background for the entirety of the postoperative pain management journey. Dexketoprofen has greater gastric tolerability when compared to racemic ketoprofen [21].

In addition to tolerability, the dexketoprofen component of the TRAM/DKP FDC also has the advantage of being available in IV and IM formulations, enabling continuity and consistency of analgesia throughout the postoperative period. Maintaining an NSAID background as the chief component of a multimodal analgesia regimen is pertinent in the face of the noxious inflammatory cascade. Patients can be initiated on the well-tolerated IV dexketoprofen in the immediate postoperative period when they are nil per oral. At the earliest possibility—ideally within the initial 24–48 hours after surgery—patients can be transitioned onto the oral

TRAM/DKP FDC without altering the NSAID background of their postoperative analgesia treatment plan. Once the patient completes the TRAM/DKP FDC treatment, they can be transitioned onto oral dexketoprofen if they require pharmacological support for any mild-moderate residual pain (Fig. 1).

6. Conclusions

Multimodal analgesia is the cornerstone of postoperative pain management and is well adopted throughout Asia, and globally. A continuous and consistent NSAID background as part of a multimodal analgesic regimen may provide a consistency of care that optimizes postoperative pain relief.

Dexketoprofen in monotherapy or in FDC with tramadol offers a comprehensive postoperative multimodal analgesia management due to its demonstrated safety and efficacy. Its availability in IV, IM and oral formulations, and in a FDC with tramadol means that patients can receive consistent management with dexketoprofen at all stages of the postoperative treatment period and into recovery. Real-world experience with TRAM/DKP FDC in Asian patients indicates it is effective and well-tolerated, making it an optimal oral analgesic option for Asian patients with moderate-to-severe postoperative pain.

AUTHOR CONTRIBUTIONS

MDS contributed to the planning, development and editing of the manuscript, including reading and approving the final manuscript. KSO contributed to the development and editing of the manuscript, including reading and approving the final manuscript. GV contributed to the development and editing of the manuscript, including reading and approving the final manuscript. DN contributed to the planning, development and editing of the manuscript, including reading and approving the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

The services of a medical writer were funded by A. Menarini Asia Pacific Pte Ltd.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Giustino Varrassi is the member of Editor Board of this journal, given his/her role as Editor Board, had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

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How to cite this article: Maria Dolma Santos, Kim Soon Oh, Giustino Varrassi, Dinesh Nagrale. Multimodal analgesia for postoperative pain in Asia: a review of evidence with clinical focus on dexketoprofen and tramadol/dexketoprofen fixed-dose combination. Signa Vitae. 2021;17(6):1-7. doi:10.22514/sv.2021.210.