World Journal of Clinical Case Reports and Case Series

Case Series

The Efficacy and Tolerability of Dexketoprofen/Tramadol (DKP/TRAM) Fixed-Dose Combination for Post-operative and Non-Operative Management in Patients with Moderate-to-Severe Pain in Thailand: A Real World Multicenter Retrospective Case Series

Tiyaprasertkul W[1], Phornphutkul C[2], Chootip C[3], Suwanpramote P[4], Sarirasririd S[5], Niempoog S[6], Tangwiwat S[7], Kaewmano T[8] and Phorkhar T[9]*

[1]*Department of Anesthesiology, Bangkok Hospital Chiangmai, Chiangmai, Thailand*

[2]*Derpartment of Orthopaedics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

[3]*Department of Rehabilitation, Songkhla Hospital, Songkhla, Thailand*

[4]*Department of Orthopaedics, Faculty of Medicines, Ramathibodi Hospital, Bangkok, Thailand*

[5]*Department of Orthopaedics, Siriraj Piyamaharajkarun Hospital, Bangkok, Thailand*

[6]*Department of Orthopaedics, Faculty of Medicine, Thammasat University, Pathumthani, Thailand*

[7]*Department of Anesthesiology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand*

[8]*Department of Orthopaedics, Songkhla Hospital, Songkhla, Thailand*

[9]*Orthopaedics and Musculoskeletal Center, Chulabhorn Hospital, Bangkok, Thailand*

Abstract

Background: Early and effective management of pain is a vital component of patient care for minimizing pain severity and optimizing patient outcomes. Orally administered Dexketoprofen (DKP) 25 mg and Tramadol (TRAM) 75 mg in a Fixed Dose Combination (DKP/TRAM FDC) has demonstrated an analgesic efficacy greater than those of the single agents used alone.

Objectives: To describes clinicians' experience and outcomes of post-operative and non-operative management in patients with moderate-to-severe pain using a DKP/TRAM FDC in a real-world setting.

Methods: Clinicians compiled, shared and discussed their case studies using a DKP/TRAM FDC during four expert meetings. A total of 14 case studies were include in this study.

Results: All 14 patients achieved their pain relief with minimal adverse events. DKP/TRAM FDC is well tolerated by patients.

Conclusions: DKP/TRAM FDC is an effective and safe option for post-operative and non-operative management for patients with moderate-to-severe pain.

Keywords: Dexketoprofen; Tramadol; DKP/TRAM; Multimodal analgesia; Moderate-to-severe pain

Citation: Tiyaprasertkul W, Phornphutkul C, Chootip C, Suwanpramote P, Sarirasririd S, Niempoog S, et al. The Efficacy and Tolerability of Dexketoprofen/Tramadol (DKP/TRAM) Fixed-Dose Combination for Post-operative and Non-Operative Management in Patients with Moderate-to-Severe Pain in Thailand: A Real World Multicenter Retrospective Case Series. World J Clin Case Rep Case Ser. 2024;4(2):1028.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Sep 19th, 2024

***Corresponding author:** Tiyaprasertkul W, Bangkok Hospital Chiangmai, No. 88/8-9 Super Highway Road, Chiangmai, Thailand, 50000, Tel: +66-52089888

Abbreviations & Acronyms

DKP: Dexketoprofen Trometamol; TRAM: Tramadol Hydrochloride; DKP/TRAM FDC: Dexketoprofen Trometamol 25 mg and Tramadol Hydrochloride 75 mg in a Fixed Dose Combination; NSAID: Non-Steroidal Anti-Inflammatory drug; COX-1: Cyclo-Oxygenase 1; COX-2: Cyclo-Oxygenase 2; SNRI: Serotonin–Norepinephrine Reuptake Inhibitor; NRS: Numerical Rating Scale; TEAEs: Treatment-Emergent Adverse Events; CMC: Carpometacarpal; TFCC: Triangular Fibrocartilage Complex; ADL: Activities of Daily Living; ORIF: Open Reduction and Internal Fixation; WALANT: Wide-Awake Local Anesthesia and no Tourniquet; ICD: Intercostal Drainage; CSE: Combined Spinal–Epidural; MRM: Modified Radical Mastectomy; CMTY: Chemotherapy; RT: Radiotherapy; OPD: Outpatient Department;

Q6H: Quaque 6 Hora, every six hours; POD: Postoperative Day; PCA: Patient Controlled Analgesia; IV: Intravenous; OD: Once Daily; TID: Ter in Die, three times daily; BID: Bis in Die, two times daily; DKP/TRAM: Dexketoprofen 25 mg + Tramadol 75 mg; IM: Intramuscular; PRN: Pro re Nata, as needed; Q8H: Quaque 8 Hora, every eight hours; HS: Hora Somni, at bedtime; PO: Per Os, by mouth; PC: Post Cibum, after food; Q4H: Quaque 4 Hora, every four hours

Introduction

Pain, the most common symptom of disease, continues to be a major public health management problem as acute pain is a common reason for hospital visits [1]. Early and effective pain management is a vital component of patient care by optimizing patient outcomes [2]. Effective pain management reduces the risk of medical complications, increases patient satisfaction, improves physical ability, shortens hospital stays, leads to better quality of life outcomes and lowers the likelihood of progression to chronic pain [3-6]. Recent research has seen important advances in understanding multiple pathogenic pain pathways. Approaches using two or more pharmacological molecules simultaneously to target multiple pain pathways creates an opportunity to identify innovative agents able to modulate specific neuronal cell types and cellular mechanisms synergistically leading to the possible discovery of novel approaches for promising pain therapies [7,8].

Multimodal analgesia involves combining analgesics with diverse modalities of action to obtain synergistic effects, yielding good pain relief, while minimizing adverse effects associated with higher doses of a single medication [9]. Compared with single-modality interventions, combining analgesics which act *via* different mechanisms potentially provides a broader spectrum of pain relief and enables individual analgesics to act with possible additive or synergistic actions [10]. Multimodal analgesia also offers a better compliance and efficacy/safety ratio. As a result, the use of multimodal analgesia in clinical practice has gained widespread acceptance as the cornerstone of effective pain treatment [11,12].

Several combinations of analgesics have been developed to offer convenient administration, reduced pill burden and improved patient adherence to treatment [13]. Orally administered Dexketoprofen Trometamol (DKP) 25 mg and Tramadol Hydrochloride (TRAM) 75 mg in a Fixed Dose Combination (DKP/TRAM FDC) has demonstrated an analgesic efficacy greater than those of single agents used alone [14]. DKP is a non-selective Non-Steroidal Anti-Inflammatory Drug (NSAID), which contains only the pure S-enantiomer of ketoprofen [15]. DKP shows analgesic and anti-inflammatory properties which inhibits Cyclo-Oxygenase 1 (COX-1) and COX-2 pathways to alleviate pain [16]. DKP rapid dissolution and absorption ensure rapid onset of analgesic activity within 15 minutes [17]. TRAM was the first synthetic opioid in its class with a dual analgesic mechanism through its action as a μ-opioid receptor agonist and as a Serotonin–Norepinephrine Reuptake Inhibitor (SNRI) [18]. TRAM provides a long duration of action and favorable safety profile over other opioids. Its analgesic effects take approximately an hour to be realized and lasts up to 6 hours [19]. On a dose-by-dose comparison, TRAM has about one-tenth the potency of morphine [20].

In 2016, DKP/TRAM FDC was approved in Europe, and is now available as a generic medication marketed under several trade names worldwide [21]. Leveraging the unique benefits of the two types of medication, TRAM/DKP FDC efficacy is complemented by rapid onset and long duration of action. A favorable safety and tolerability profile with a 25% reduction in the opioid dosage resulting in lower overall opioid consumption and drug addiction [22]. DKP/TRAM FDC has proven clinical efficacy in short-term symptomatic treatments of moderate-to-severe pain, including a wide range of post-operative [11,14,18,23] and non-surgical pain settings [9,14,22,24-27]. This case series report describes 14 patients' real-world experience to review the efficacy, safety and tolerability of DKP/TRAM FDC in the management of various origins of moderate-to-severe pain which may widen future possible applications of DKP/TRAM FDC.

Materials and Methods

Fourteen patients experiencing moderate to severe pain, defined as a pain intensity score ≥ 4 in an 11-point Numerical Rating Scale (NRS), were studied. The selected case studies were patients from multiple hospitals who had received a short course of Dexketoprofen (DKP) 25 mg/Tramadol (TRAM) 75 mg FDC for the treatment of surgical and non-surgical pain. Data on baseline characteristics, medical history, analgesic treatment regimen, presence of comorbidities, clinical outcomes and adverse events were compiled and discussed by physicians at 4 peer-to-peer expert meetings held in April, June, October and December 2022.

Patients selected for this case studies had been pre-assessed for possible contraindications to both opioid and NSAIDs, including renal impairment and history of gastrointestinal issues. Pre- and post- treatment pain were subjectively graded by each patient using NRS on a scale of 0 (no pain) to 10 (worst pain). Each patient's progress was assessed by direct interview and medical records review. Safety evaluation was based on the incidence, seriousness, intensity, and causal relationship of Treatment-Emergent Adverse Events (TEAEs). This study investigated retrospectively at outcomes of patients diagnosed and treated according to national guidelines and agreements, therefore, written informed consents were waived.

Results

Fourteen patients (9 females and 5 males) were included in this case series. The patients ranged in age from 20 to 70 years. Patients were stratified into two groups based on whether they had surgery or not. The surgical group consisted of cases 1-9, while the non-surgical group consisted of cases 10-14. Most of patients had nociceptive pain except cases 8, 9, 13 and 14 which had both nociceptive and neuropathic pain. These patients experienced various time courses of pain including acute, acute on chronic, and chronic pains at various sites of the body with different etiologies. Patient baseline data and individual classification of pain are summarized in Table 1.

Prior to treatment, 6 patients complained of moderate pain (4 ≤ NRS ≤ 6), whereas 8 patients complained of severe pain (NRS ≥ 7). All patients required strong analgesics for pain control. Clinical details for each case before DKP/TRAM initiation are summarized in Table 2.

Good pain relief was established in all patients. DKP/TRAM FDC, together with other drugs provided complete or near-complete pain control. The patients were able to continue with Activities of Daily Living (ADL), got back to work and went for further evaluation and treatment with less pain and discomfort. Neither TEAEs nor serious adverse reactions were observed during the change to the new drug protocol. Among the 14 cases, only 1 case (7.1%) showed mild symptoms, which was drowsiness in case 4. The level of pain intensity reduction in each case and the prevalence of adverse drug events are summarized in Table 3.

Table 1: Patient baseline data and classification of pain.

Case	Age	Sex	Classification of pain			
			Pathophysiology	Time course	Location	Etiology
Surgical group						
1	20	Male	Nociceptive	Acute	Hand	CMC dislocation
2	27	Male	Nociceptive	Acute	Joint	TFCC injury
3	27	Male	Nociceptive	Acute	Spine & rib	Spine dislocation & rib fracture
4	39	Male	Nociceptive	Acute	Anal canal	Hemorrhoid
5	40	Female	Nociceptive	Acute	Meniscus	Meniscus tear
6	57	Female	Nociceptive	Acute	Lumbar	Spinal canal stenosis
7	59	Male	Nociceptive	Chronic	Knee	Arthritis
8	23	Female	Nociceptive & neuropathic	Acute	Lumbar	Lumbar disc herniation at L4-5
9	40	Female	Nociceptive & neuropathic	Acute on chronic	Shoulder	Bone tumor
Non-surgical group						
10	53	Female	Nociceptive	Acute on chronic	Spine	Stenosis
11	60	Female	Nociceptive	Acute on chronic	Back	Scoliosis
12	70	Female	Nociceptive	Acute on chronic	Knee	Osteonecrosis
13	56	Female	Nociceptive & neuropathic	Acute on chronic	Acetabulum	Metastatic cancer
14	59	Female	Nociceptive & neuropathic	Acute on chronic	Foot	Complex regional pain syndrome

CMC: Carpometacarpal; TFCC: Triangular Fibrocartilage Complex

Table 2: Clinical details for each case before DKP/TRAM initiation.

Case	Operation	Pre-treatment (Prior to receive DKP/TRAM)	
		Medication	Pain score
1	ORIF with K wire under WALANT	1% Xylocaine with adrenaline 35 ml injection	7/10
2	Anthroscopic repair TFCC, capsular repair	None	4/10
3	Decompressive laminectomy	Fentanyl drip 50 mcg/hr for postoperative 9 days	7/10
4	Hemorrhoidectomy	None	10/10
5	Arthroscopic meniscectomy	Ibuprofen	5-6/10
6	Posterior decompression & posterolateral fusion	None	6/10
7	Total knee arthroplasty	Paracetamol 1000 mg Q6H Etoricoxib 90 mg Continuous epidural analgesia until POD2	9/10
8	Endoscopic lumbar discectomy	Etoricoxib 90 mg Gabapentin 400 mg	4/10
9	Total shoulder girdle resection and 2nd rib resection	Morphine PCA NSAIDs IV for 3 days	7/10
10	None	Etoricoxib 90 mg OD Combination of Paracetamol 450 mg and Orphenadrine 35 mg TID	7/10
11	None	NSAIDs Muscle relaxant	9/10
12	None	Steroids IV NSAIDs	8/10
13	None	COX-2 NSAIDs Paracetamol Tramadol	7/10
14	None	Tramadol 50 mg BID Pregabalin 150 mg BID Celecoxib 200 mg BID	4-5/10

ORIF: Open Reduction and Internal Fixation; WALANT: Wide-Awake Local Anesthesia and No Tourniquet; TFCC: Triangular Fibrocartilage Complex; Q6H: Quaque 6 Hora, Every Six Hours; POD: Postoperative Day; PCA: Patient Controlled Analgesia; NSAID: Non-Selective Non-Steroidal Anti-Inflammatory Drug; IV: Intravenous; OD: Once Daily; TID: Ter in Die, Three Times Daily; COX-2: Cyclo-Oxygenase 2; BID: Bis in Die, Two Times Daily

Case Presentation

Surgical group

Case 1: Case 1 was a 20-year-old male presenting with Carpometacarpal (CMC) dislocation of the second to fifth metacarpals. He was splinted for 6 weeks but stiffness and pain persisted. He underwent Open Reduction and Internal Fixation (ORIF) of metacarpal fractures using Wide-Awake Local Anesthesia and No Tourniquet (WALANT) with K wire. 1% xylocaine with adrenaline 35 ml was injected at the surgery area. The DKP/TRAM FDC was initiated immediate after surgery 1 tablet, after 2 hour the pain was reduced from 10/10 to 7/10 then pethidine 50 mg intramuscular was added. There was significant pain relief with pain intensity reduced from NRS 7/10 to 1/10 within 3 hours after surgery. by the next day only DKP/TRAM FDC was used, the patient reports the pain score was 1/10. No adverse events were observed.

Case 2: Case 2 was a 27-year-old male presenting with Triangular Fibrocartilage Complex (TFCC) partial tear type 1B. He experienced pain on the left wrist for 2 weeks due to weight training injury. He was treated with short arm slab and pain control medication without improvement. Physical examination was done, on left wrist. A positive ulnar fovea sign elicited tenderness in the ulnar-sided wrist. He underwent arthroscopic capsular repair for TFCC tear under intraoperative brachial plexus block. DKP/TRAM FDC was initiated on the day of surgery two times daily, along with 50 mg intravenous pethidine as needed. Thereafter, patient received only DKP/TRAM FDC two times daily for three more days. Good pain control was achieved with pain intensity reduced from NRS 4/10 to 1/10. No adverse events were observed.

Case 3: Case 3 was a 27-year-old male presenting with spinal dislocation and rib fractures. He experienced a traumatic incident resulting in a fracture dislocation of T9-T10 with incomplete cord injury. He also received fractures of the right 4th-8th ribs and the left 6th rib. He underwent decompressive laminectomy with Intercostal Drainage (ICD) at the right chest under general anesthesia. After surgery, he received fentanyl drip 50 mcg/hr for 9 days, DKP/TRAM FDC was initiated at POD9 after operation every eight hours, together with gabapentin 300 mg three times daily. IV fentanyl could be held and IV patient-controlled analgesia with morphine was prescribed instead. Only DKP/TRAM FDC was continued for 5 days together with IV PCA morphine 12 mg within 3 days. Excellent pain control was achieved with pain intensity reduced from NRS 7/10 to 3/10. No

Table 3: Post-treatment medication, level of pain intensity reduction and adverse drug events.

Case	Day of treatment	Post-treatment		Adverse reaction
		Medication	Pain score	
1	POD0	DKP/TRAM 1 tab Pethidine 50 mg IM	1/10	None
2	POD0	**POD0:** DKP/TRAM 1 tab BID Pethidine 50 mg IV PRN **POD1-3:** DKP/TRAM 1 tab BID	1/10	None
3	POD9	DKP/TRAM 1-tab Q8H, 5 days Gabapentin 300 mg TID IV PCA morphine 12 mg for POD9-11	3/10	None
4	POD1	DKP/TRAM Q8H Morphine IV PRN	1-2/10	Drowsiness at Day 1.
5	POD1	DKP/TRAM 1-tab TID, 5 days Lorazepam 0.5 mg, Ondansetron IV PRN	0/10	None
6	POD0	**POD0:** Morphine IV 1 mg/hr DKP/TRAM TID Paracetamol 500 mg Q6H **POD1:** Morphine IV 3 mg PRN DKP/TRAM TID Paracetamol 500 mg Q6H	3/10	None
7	POD2	Paracetamol 4 mg/day x 3 days DKP/TRAM Q8H x 3 days Pregabalin 25 mg hs	1/10	None
8	POD0	**POD0:** Morphine IV 3 mg PRN DKP/TRAM TID Paracetamol 500 mg Q6H **POD1-2:** DKP/TRAM TID Paracetamol 500 mg Q6H	2/10	None
9	POD3	**POD 3-7:** DKP/TRAM 1-tab Q8H Pregabalin 75 mg 1 tab OD Morphine IV PRN	3/10	None
10	OPD1	DKP/TRAM 1-tab TID Pregabalin 75 mg HS Eperisone TID Vit. B1-6-12 forte OD	3/10	None
11	OPD1	DKP/TRAM TID Eperisone 50 mg 1 tab PO TID PC	3/10	None
12	OPD1	DKP/TRAM TID Paracetamol 650 mg 2 tabs PO Q8H PRN Perskindol™ spray PRN pain	3/10	None
13	OPD1	DKP/TRAM 1-tab Q8H Paracetamol 500 mg 1 tab PO Q4H	3-4/10	None
14	OPD1	DKP/TRAM Q8H, 5 days Pregabalin 150 mg BID, 5 days	2/10	None

POD: Postoperative Day; DKP/TRAM: Dexketoprofen 25 mg + Tramadol 75 mg; IM: Intramuscular; BID: Bis in Die, two times daily; IV: Intravenous; PRN: Pro re nata, as Needed; Q8H: Quaque 8 Hora, every eight hours; TID: Ter in Die, three times daily; PCA: Patient-Controlled Analgesia; Q6H: Quaque 6 Hora, every six hours; OD: Once Daily; OPD: Outpatient Department; HS: Hora Somni, at bedtime; PO: Per Os, by mouth; PC: Post Cibum, after food; Q4H: Quaque 4 Hora, every four hours

adverse events were observed.

Case 4: Case 4 was a 39-year-old male presenting with hemorrhoid and morbid obesity. He underwent hemorrhoidectomy with spinal anesthesia. DKP/TRAM FDC was initiated the day after surgery every eight hours, together with intravenous morphine as needed. Excellent pain control was achieved with pain intensity reduced from NRS 10/10 to 1-2/10. Drowsiness was observed on the first day of post-operative treatment.

Case 5: Case 5 was a 40-year-old female presenting with meniscus tear. She experienced right knee pain for 6 months, especially in bending position. Conservative treatment and NSAIDs (Ibuprofen) were periodically used with no good response. She underwent arthroscopic meniscectomy under local anesthesia. DKP/TRAM FDC was initiated the day after surgery three times daily, along with lorazepam 0.5 mg and intravenous ondansetron as needed. Only DKP/TRAM FDC was continued for 5 days. Excellent pain control was achieved with pain intensity reduced from NRS 5-6/10 to 0/10. Patient was able to walk the next day after surgery. No adverse events were observed.

Case 6: Case 6 was a 57-year-old female presenting with spinal canal stenosis. She experienced back pain for 2 years, which was aggravated by walking but slightly relieved at rest. She was subjected to nonoperative management, but pain remained and disrupted her daily routines and activities. She underwent posterior decompression and posterolateral fusion using pedicle screw from L2 to S1 under general anesthesia. DKP/TRAM FDC was initiated on the day of surgery three times daily, along with 1 mg intravenous morphine per hour and paracetamol 500 mg every six hours. The day after, she received DKP/TRAM FDC three times daily along with 3 mg intravenous morphine as needed and paracetamol 500 mg every six hours. Good pain control was achieved with pain intensity reduced from NRS 6/10 to 3/10. No adverse events were observed.

Case 7: Case 7 was a 59-year-old male presenting with bilateral osteoarthritis of the knees with pain more on the left (9/10) than the right side (0/10). He is allergic to sulfa and has a long-standing history of hypertension (>10 years), diabetes mellitus (4 years), dyslipidemia (5 years), obstructive sleep apnea (10 years), and benign prostatic hyperplasia (6 years). He was prescribed paracetamol 1,000 mg orally 1.5 hour before surgery. He underwent total knee arthroplasty with Combined Spinal Epidural (CSE) anesthesia, followed by bilateral adductor canal block. He received etoricoxib 90 mg on the next day. The DKP/TRAM FDC was initiated two days after surgery every 8 hours, together with paracetamol 4,000 mg per day and pregabalin 25 mg at bed time for 3 days, due to assumed severe pain following bilateral TKA. There was excellent pain relief with pain intensity from 9/10 to 1/10. The adverse events include nausea and dizziness did not occur after intake of DKP/TRAM.

Case 8: Case 8 was a 23-year-old female presenting with lumbar L4-L5 disc herniation. She experienced left sciatica pain for 2 months with a positive straight leg raise test. She underwent endoscopic lumbar discectomy for L4-L5 disc herniation under general anesthesia. Prior to surgery, she received etoricoxib 90 mg and gabapentin 400 mg. DKP/TRAM FDC was initiated on the day of surgery three times daily, along with 3 mg intravenous morphine as needed and paracetamol 500 mg every six hours. Thereafter, she was adjusted to DKP/TRAM FDC three times daily and paracetamol 500 mg every six hours for 2 days. Good pain control was achieved with pain intensity reduced from NRS 4/10 to 2/10. No adverse events were observed.

Case 9: Case 9 was a 40-year-old female presenting with underlying breast cancer. She had been treated with Modified Radical Mastectomy (MRM), Chemotherapy (CMTY), and Radiotherapy (RT) for 7 years. Four months prior to surgery, a growing mass was found at the right shoulder resulting in limited range of motion and moderate pain. Fibroblastic osteosarcoma (radiation-induced sarcoma) was found in pathologic report. She underwent total shoulder girdle resection, including total scapulectomy, distal claviculectomy, proximal humeral resection, and 2nd rib resection under general anesthesia. Pectoralis and latissimus dorsi muscles were incised while the axilla and brachial plexus were dissected. After surgery, she received PCA morphine and intravenous NSAIDs for breakthrough pain for 3 days. DKP/TRAM FDC was initiated 3 days after surgery 1 tablet every eight hours, along with pregabalin 75 mg once daily and intravenous morphine as needed for 5 days. Good pain control was achieved with pain intensity reduced from NRS 7/10 to 3/10. No adverse events were observed.

Non-surgical group

Case 10: Case 10 was a 53-year-old female OPD patient presenting with spinal stenosis. She is obese with a weight of 120 kg. Her chief complaint was sciatic back pain on the left side starting 5 days prior, especially during prolonged walking. Previously, she received etoricoxib 90 mg once daily and the combination of Paracetamol 450 mg and Orphenadrine 35 mg three times daily without improvement. Conservative treatment using medication and physical therapy was planned. DKP/TRAM FDC was prescribed 1 tablet three times daily, along with pregabalin 75 mg at bedtime, eperisone three times daily and Vit. B1-6-12 forte once daily. At 1-week follow-up, good pain control was achieved with pain intensity reduced from NRS 7/10 to 3/10. No adverse events were observed.

Case 11: Case 11 was a 60-year-old female OPD patient presenting with back scoliosis. She experienced severe back pain radiating to the left leg and was unable to walk for 6 days. The condition was not improved with NSAIDs and muscle relaxant which was taken for 5 days. After consultation, she received DKP/TRAM 1 tablet three times daily and Eperisone 1 tablet three times daily after meal. At 1-week follow-up, patient's condition was well improved with pain intensity reduced from NRS 9/10 to 3/10. No adverse events were observed.

Case 12: Case 12 was a 70-year-old female Outpatient Department (OPD) patient presenting with osteonecrosis of right knee. She had a history of minor trauma on the right knee, causing pain and limping. Previously, she received IV steroids and NSAIDs with no improvement in pain. Unicondylar knee replacement is planned. DKP/TRAM FDC was prescribed 1 tablet three times daily, along with Paracetamol 650 mg 2 tablets every eight hours as needed and cool spray as needed. At 1-week follow-up, excellent pain control was achieved with pain intensity reduced from NRS 8/10 to 3/10. No adverse events were observed.

Case 13: Case 13 was a 56-year-old female OPD patient presenting with metastatic breast cancer with impending fracture at right acetabulum. She had modified radical mastectomy, along with combination chemoradiotherapy for 2 years. Three months earlier, patient developed progressive continuous right hip pain and was unable to walk without gait aid. Bone scan showed multiple uptakes. Radiograph showed impending fracture of the right acetabulum. Cox-2 NSAIDs, paracetamol/tramadol were prescribed to the patient from a previous consultation with another doctor but pain persisted. She also received zoledronate 4 mg IV monthly, as well as hormonal and radiation therapy. The new regimen for symptomatic treatment was DKP/TRAM FDC 1 tablet every eight hours and paracetamol 500 mg 1 tablet every four hours. At 2-weeks follow-up, good pain control was achieved with pain intensity reduced from NRS 7/10 to 3-4/10. No adverse events were observed.

Case 14: Case 14 was a 59-year-old female OPD patient presenting with complex regional pain syndrome. She had right hip arthroplasty with pain present at the right foot (NRS 2-3/10) for 6 months. Later on, patient fell down causing severe pain (NRS 10/10). Before consultation, patient was unable to walk and had also taken too many tablets of her pain control medication. Her previous medicines were tramadol 50 mg 2 tablets two times daily, pregabalin 150 mg 2 tablets two times daily and celecoxib 200 mg two times daily. Her medication was switched to DKP/TRAM every eight hours and pregabalin 150 mg two times daily for 5 days. At 1-week follow-up, patient was able to ambulate again. Pain was well controlled and reduced from NRS 4-5/10 to 2/10, with no adverse events observed.

Discussion

The efficacy and safety of the DKP/TRAM have been well

reported in moderate-to-severe pain management studies. The DKP/TRAM demonstrated a better pain relief compared with placebo, and Dexketoprofen or Tramadol monotherapy in postoperative pain setting, such as abdominal hysterectomy [18], total hip arthroplasty [23], and third molar extraction [25]. Recently, the DKP/TRAM is also proven to be used in acute low back pain [28] and acute cancer pain [29].

In this study, DKP/TRAM FDC was prescribed to patients with various types of operations to cure (1) chronic disease, e.g., knee arthritis (2) acute illness, e.g., CMC dislocation, TFCC injury, spine dislocation together with rib fracture, hemorrhoid, meniscus tear, spinal canal stenosis, and lumbar disc herniation (3) acute flares on top of chronic condition with mixed nociceptive and neuropathic pain, e.g., bone tumor. Moreover, DKP/TRAM FDC was also prescribed to non-operative patients with acute flares on top of chronic inflammation, e.g., stenosis, scoliosis, osteonecrosis, metastatic cancer, and complex regional pain syndrome. All patients had significant pain reduction with DKP/TRAM FDC, indicating a potential for wider use of DKP/TRAM FDC in pain management regimens.

The results obtained from these cases confirmed the pain control efficacy and tolerability of DKP/TRAM FDC in terms of effectiveness, rapidity of onset, and duration of analgesia in patients with moderate-to-severe pain at baseline. In terms of effectiveness, DKP/TRAM FDC targets both central and peripheral sites in the descending pain pathway through complementary mechanisms and synergistic action. Dexketoprofen exhibits an anti-inflammatory effect, whereas tramadol acts on μ-opioid receptors and inhibits serotonin and norepinephrine reuptake in the pain pathway leading to better pain relief [11,14,13]. DKP/TRAM FDC demonstrated superior pain relief compared with tramadol 100 mg and dexketoprofen 25 mg monotherapy [18,23,24]. The DKP/TRAM FDC was also proven to be superior to a tramadol plus paracetamol combination over 6 hours [25]. This made it possible for patients to rapidly recover and return to ADLs and work. In terms of rapidity, the DKP/TRAM FDC demonstrated fast analgesic activity within 15 minutes due to the property of dexketoprofen, a traditional NSAID that acts centrally and peripherally to reduce pain response [11,17]. In the Phase II dose-finding trial, the DKP/TRAM FDC resulted in the fastest onset of action and the greatest pain relief peak [24]. In terms of duration of analgesia, the post-hoc analysis of the Phase III and Phase IIIb trials showed that DKP/TRAM FDC provides superior analgesia for extended periods of time, up to 56 hours, compared with tramadol 100 mg or dexketoprofen 25 mg monotherapy [30].

For safety and tolerability, the mild adverse events, drowsiness, was presented only in case 4 on the first day of post-operative treatment. The result was fully in line with the 2 previously reported case studies in postoperative pain [31] and acute non-surgical pain [32] patients. The common reported adverse events in these 2 case studies were nausea, vomiting, and dizziness that resolved in each of these cases within a short period of time. However, the absence of serious adverse events could not be taken as an absence of risk, due to small study population.

Gastrointestinal (GI) disorders are the most common adverse events have been reported with all NSAID therapies. However, dexketoprofen is generally well-tolerated with a lower risk of upper gastrointestinal bleeding compared with other traditional NSAIDs, such as meloxicam, rofecoxib, and ketorolac [33]. It has also been reported as having a lower risk of heart failure. Additionally, dexketoprofen had the second lowest risk of heart failure compared with other NSAIDs in an analysis of NSAID use in heart failure patients admitted to hospital [34]. Likewise, tramadol has no clinically relevant negative effects on respiratory or cardiovascular parameters. The most commonly reported adverse reactions due to tramadol are nausea and dizziness, both occurring in more than 10% of patients [35].

In the DKP/TRAM FDC, the dose of tramadol is reduced from 100 mg to 75 mg, resulting in a lower incidence of adverse reactions. In clinical studies the most commonly observed adverse reactions due to DKP/TRAM FDC were vomiting, nausea and dizziness (2.9%, 2.7% and 1.1% of patients, respectively) [37]. The DKP/TRAM FDC presented a lower incidence of gastrointestinal disorder (6.4%) in comparison with the dexketoprofen 25 mg (8.4%) and tramadol 100 mg (10%) groups [18]. Moreover, gastrointestinal disorders including nausea, vomiting, abdominal discomfort and diarrhoea were reported with a trend towards improved tolerability in patients receiving DKP/TRAM, as compared with paracetamol/TRAM group [25].

Six of the 14 cases presented in this study received the standard dose of DKP/TRAM FDC three times daily. Patient-specific conditions influence analgesic medication choice, thus each patient got different combinations of medication. The elderly people (those ≥ 60 years of age) are at a higher risk of adverse drug events. There were 2 elderly people in this case report (case 13 and case 14). Both patients received DKP/TRAM FDC three times daily with no observed adverse drug events, supporting the tolerability of using DKP/TRAM FDC in elderly patients.

Chronic pain can be challenging to treat due to its multifactorial etiologies and accordant complexity of management. Since the development of tolerance and physical dependence are pervasive limitations of using opioid analgesics, DKP/TRAM FDC are not the standard of care for treating chronic pain in clinical practice. However, it has proven efficacy in breakthrough acute on chronic pain such as arthritis [34] or cancer pain [31]. Effective and safe regimens for the use of DKP/TRAM FDC in patients with chronic pain awaits further study.

Conclusion

DKP/TRAM FDC is an effective and safe option for post-operative and non-operative management for patients with moderate-to-severe pain.

Funding

This report is supported by a research grant from A. Menarini (Thailand) Ltd.

References

1. Gregory J, McGowan L. An examination of the prevalence of acute pain for hospitalised adult patients: a systematic review. J Clin Nurs. 2016;25(5-6):583-98.

2. Berry P, Chapman CR, Covington EC, et al. Pain: Current understanding of assessment, management and treatments. Glenview IL, USA: National Pharmaceutical Council, INC; 2004.

3. Garimella V, Cellini C. Postoperative pain control. Clin Colon Rectal Surg. 2013;26(3):191-6.

4. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: A clinical practice guideline from the American pain society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17(2):131-57.

5. Gan TJ. Poorly controlled postoperative pain: Prevalence, consequences, and prevention. J Pain Res. 2017;10:2287-98.

6. Kuusniemi K, Pöyhiä R. Present-day challenges and future solutions in postoperative pain management: Results from pain forum 2014. J Pain Res. 2016;9:25-36.

7. Dubois MY, Gallagher RM, Lippe PM. Pain medicine position paper. Pain Med. 2009;10(6):972-1000.

8. Stucky CL, Gold MS, Zhang X. Mechanisms of pain. Proc Natl Acad Sci USA. 2001;98(21):11845-6.

9. Bhatia A, Buvanendran A. Anesthesia and postoperative pain control - multimodal anesthesia protocol. J Spine Surg. 2019;5(Suppl 2):160-5.

10. Raffa RB, Tallarida RJ, Taylor R, Pergolizzi JV. Fixed-dose combinations for emerging treatment of pain. Expert Opin Pharmacother. 2012;13(9):1261-70.

11. Varrassi G, Hanna M, Macheras G, Montero A, Montes Perez A, Meissner W, et al. Multimodal analgesia in moderate-to-severe pain: a role for a new fixed combination of dexketoprofen and tramadol. Curr Med Res Opin. 2017;33(6):1165-73.

12. International Association for the Study of Pain. Management of postsurgical pain in adults. IASP.2017.

13. Santos MD, Oh KS, Varrassi G, Nagrale D. 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.

14. Varrassi G, Coaccioli S, De-Andrés J, Hanna M, Macheras G, Montero A, et al. Expert Consensus on Clinical Use of an Orally Administered Dexketoprofen Plus Tramadol Fixed-Dose Combination in Moderate-To-Severe Acute Pain: A Delphi Study. Adv Ther. 2019;36(11):3174-85.

15. Mauleón D, Artigas R, García ML, Carganico G. Preclinical and clinical development of dexketoprofen. Drugs. 1996;52(Suppl 5):24-45.

16. Hanna M, Montero A, Perrot S, Varrassi G. Tramadol/dexketoprofen analgesic efficacy compared with tramadol/paracetamol in moderate to severe postoperative acute pain: subgroup analysis of a randomized, double-blind, parallel group trial - DAVID study. Pain Ther. 2021;10(1):485-503.

17. Walczak JS. Analgesic properties of dexketoprofen trometamol. Pain Manag. 2011;1(5):409-16.

18. Moore RA, McQuay HJ, Tomaszewski J, Raba G, Tutunaru D, Lietuviete N, et al. Dexketoprofen/tramadol 25 mg/75 mg: randomised double-blind trial in moderate-to-severe acute pain after abdominal hysterectomy. BMC Anesthesiol. 2016;16:9.

19. Scott LJ, Perry CM. Tramadol a review of its use in perioperative pain. Drugs. 2000;60(1):139-76.

20. Lee CR, McTavish D, Sorkin EM. "Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states". Drugs. 1993;46(2):313-40.

21. International Association for the Study of Pain. Acute pain. April 28, 2024.

22. Barra M, Remák E, Liu DD, Xie L, Abraham L, Sadosky AB. A cost-consequence analysis of parecoxib and opioids vs opioids alone for postoperative pain: Chinese perspective. Clinicoecon Outcomes Res. 2019;11:169-77.

23. McQuay HJ, Moore RA, Berta A, Gainutdinovs O, Fülesdi B, Porvaneckas N, et al. Randomized clinical trial of dexketoprofen/tramadol 25 mg/75 mg in moderate-to-severe pain after total hip arthroplasty. Br J Anaesth. 2016;116(2):269-76.

24. Moore RA, Gay-Escoda C, Figueiredo R, Tóth-Bagi Z, Dietrich T, Milleri S, et al. Dexketoprofen/tramadol: randomised double-blind trial and confirmation of empirical theory of combination analgesics in acute pain. J Headache Pain. 2015;16:541.

25. Gay-Escoda C, Hanna M, Montero A, Dietrich T, Milleri S, Giergiel E, et al. Tramadol/dexketoprofen (TRAM/DKP) compared with tramadol/paracetamol in moderate to severe acute pain: results of a randomised, double-blind, placebo and active-controlled, parallel group trial in the impacted third molar extraction pain model (DAVID study). BMJ Open. 2019;9(2):e023715.

26. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J. Acute pain management: Scientific evidence, fourth edition 2015. Med J Aust. 2015;204(8):315-7.

27. Meloncelli S, Divizia M, Germani G. Efficacy and tolerability of orally administered tramadol/dexketoprofen fixed-dose combination compared to diclofenac/thiocolchicoside in acute low back pain: experience from an Italian, single-centre, observational study. Curr Med Res Opin. 2020;36(10):1687-93.

28. Varrassi G, Hanna M, Coaccioli S, Suada M, Perrot S. DANTE Study: The First Randomized, Double-Blind, Placebo and Active-Controlled, Parallel Arm Group Study Evaluating the Analgesic Efficacy and Safety of Dexketoprofen TrometAmol aNd Tramadol Hydrochloride Oral FixEd Dose Combination on Moderate to Severe Acute Pain in Patients with Acute Low Back Pain-Rationale and Design. Pain Ther. 2022;11(3):1055-70.

29. Tuan J, Wang EH, De Leon JRC, Mendoza MJ, Varrassi G. Management of Acute Cancer Pain in Asia: An Expert Opinion on the Role of Tramadol/Dexketoprofen Fixed-Dose Combination. Cureus. 2023;15(3):e35770.

30. Matamala AM, Bertolotti M, Contini MP, Guerrero Bayón C, Nizzardo A. Tramadol hydrochloride 75 mg/dexketoprofen 25 mg oral fixed-dose combination in moderate-to-severe acute pain: Sustained analgesic effect over a 56-h period in the postoperative setting. Drugs Today. 2017;53(6):339-47.

31. Kok Yuen H, Edward HW, Jose Antonio S, Chi Wai C, Ferdinand Sy, Keen Wai C. Real-world experience with tramadol plus dexketoprofen fixed-dose combination in postoperative pain management: A series of case studies from Asia. Clin Case Rep Rev. 2020;6(4):1-7.

32. Tantavisut S, Ho KY, Arandia EF, Cheng SC, Eiamtanasate S, Jarayabhand R, et al. Real-World Evidence on the Efficacy and Tolerability of Tramadol/Dexketoprofen (TRAM/DKP) Fixed-Dose Combination for the Management of Acute Non-surgical Pain in Asian Patients: A Multicentre Retrospective Case Series. Cureus. 2023;15(6):e41156.

33. Laporte JR, Ibáñez L, Vidal X, Vendrell L, Leone R. Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. Drug Saf. 2004;27(6):411-20.

34. Arfè A, Scotti L, Varas-Lorenzo C, Nicotra F, Zambon A, Kollhorst B, et al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study. BMJ. 2016;354:i4857.

35. Skudexa 75 mg/25 mg summary of product characteristics. Accessed 10 January 2024.