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Original Research Paper

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COMPARISON ANALGESIC: TRAMADOL WITH ACETAMINOPHEN VS TRAMADOL WITH DICLOFENAC IN POST-OPERATIVE PAIN MANAGEMENT

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ABSTRACT

Background: Post-operative pain management is a critical aspect of patient care following surgical procedures. Effective pain management not only alleviates discomfort also promotes faster recovery, reduces the risk of complications, enhances overall patient satisfaction and well-being. The goal of post-operative pain management is to provide adequate analgesia while minimizing adverse effects and ensuring patient safety. **Methods:** This is a prospective cross-sectional observational study conducted among the participants visiting tertiary care teaching hospital located in the southern rural part of India for duration of 4 months. The data was collected using questionnaire and analysed using appropriate statistical tool to conclude the results. **Results:** The findings suggests that most participants were administered with tramadol 100mg at frequency of two times per day in intramuscular route of administration (85.7%). The adjuvant analgesics used include acetaminophen (77.1%) and diclofenac (22.9%). 57.1% of patients experienced side effects and 42.9% patients did not experience any side effects. Overall efficacy of tramadol with acetaminophen and diclofenac has been established. **Conclusion:** In summary, tramadol with acetaminophen had lower incidence of side effects and preferred over tramadol with diclofenac in post operative pain management due to its safety profile.

KEYWORDS : Post-operative pain management, tramadol, acetaminophen, diclofenac, side effects.

INTRODUCTION

Post-operative pain management is crucial for patient satisfaction and recovery, with tailored treatment plans enhancing patient satisfaction and overall outcomes post-surgery.

Tramadol is a synthetic opioid analgesic and SNRI, similar to codeine and morphine. It is considered a lower-risk option for moderate to severe pain due to its good tolerability and multimodal mechanism of action. Tramadol is a Step 2 option on the World Health Organization's pain ladder and has about 1/10th of the potency of morphine. Though it is similar to morphine, development of drug dependence is comparatively low, it differs from other opioids by modulating the effects of neurotransmitters like serotonin and norepinephrine, activating descending pain inhibitory pathways, similar to other SNRI antidepressants like duloxetine and venlafaxine.

Numerous pain conditions, such as neuropathic pain, osteoarthritis, fibromyalgia, lower back pain, labour pain, and cancer, can be effectively treated with tramadol. Anxiolytic, antidepressant, and anti-shivering benefits are also provided by its SNRI action which are common comorbidities with pain. Tramadol is a viable therapy option since it addresses a wide range of pain and inflammatory targets.

Acetaminophen, belonging to pharmacological class of NSAIDs, is the most widely used analgesic globally and is recommended as first-line therapy for pain conditions by the World Health Organization. Unlike other NSAIDs such as ibuprofen or aspirin, acetaminophen has minimal anti-inflammatory properties. It is available in various dosage forms, including syrup, tablets, injections, and suppository. It is often combined with other drugs in over 600 over-the-counter (OTC) allergy, cold, sleep, and pain relievers. One of the key advantages of acetaminophen is its relatively low incidence of gastrointestinal side effects compared to other NSAIDs.

Diclofenac is a phenylacetic acid derivative and NSAID that inhibits COX-1 and-2, the enzyme responsible for producing prostaglandins (PGs), which contribute to inflammation and pain signalling. It is commonly used as first line therapy for acute pain, chronic pain and inflammation. Diclofenac was designed based on phenylbutazone, mefenamic acid, and indomethacin structure.

Table 1-Pharmacokinetics and pharmacodynamics of tramadol, acetaminophen and diclofenac

PHARMACOKINETICS & PHARMACODYNAMICS		
Tramadol	Acetaminophen	Diclofenac
1. Tramadol is administered orally or through injection. 2. Tramadol is metabolized in the liver by CYP2D6 and CYP3A4 enzymes. 3. Formation of O-desmethyltramadol (M1) and N-desmethyltramadol (M2) metabolites. 4. O-desmethyltramadol (M1) has high affinity for mu-opioid receptors. 5. Activation of mu-opioid receptors in the central nervous system. 6. Inhibition of the reuptake of serotonin and norepinephrine. 7. Modulation of ascending pain	1. Acetaminophen is orally ingested or administered. 2. Absorption primarily occurs in the gastrointestinal tract. 3. Distribution of acetaminophen throughout the body, including the central nervous system. 4. Metabolism primarily occurs in the liver: 4.1. Conversion to its primary metabolite, N-acetyl-p-benzoquinone imine (NAPQI), mainly by cytochrome P450 enzymes, 4.2. Conjugation with glutathione to form inactive metabolites. 5. Elimination primarily occurs through renal excretion of metabolites. 6. Central action:	1. Diclofenac is administered orally, topically, or by injection. 2. Absorption primarily occurs in the gastrointestinal tract. 3. Distribution throughout the body, reaching target tissues including inflamed areas. 4. Diclofenac inhibits cyclooxygenase (COX) enzymes: 4.1. COX-1 inhibition leads to decreased production of prostaglandins 4.2. COX-2 inhibition reduces the conversion of arachidonic acid to prostaglandins. 5. Decreased prostaglandin synthesis leads to: 5.1. Reduction in inflammation by suppressing inflammatory mediators. 5.2. Analgesic effect by decreasing sensitization of pain receptors. 5.3. Antipyretic effect by reducing prostaglandin-

pathways in the brain and spinal cord. 8. Altered perception of and response to pain.	7.1. Weak inhibition of prostaglandin synthesis in the central nervous system, primarily in the hypothalamus. 7. Peripheral action: 7.1. Limited inhibition of prostaglandin synthesis at peripheral sites (inhibited primarily by its metabolites). 7.2. Weak anti-inflammatory effect, primarily through the central inhibition of prostaglandin synthesis.	mediated fever response. 6. Diclofenac may also inhibit leukotriene synthesis and neutrophil migration, contributing to its anti-inflammatory effects. 7. Diclofenac's effect on platelet aggregation is reversible. 8. Metabolism primarily occurs in the liver: 8.1. Conversion to several metabolites, including 4'-hydroxydiclofenac, 5-hydroxydiclofenac, and 3'-hydroxydiclofenac. 9. These metabolites are primarily eliminated through renal excretion

MATERIALS & METHODS

This is a prospective cross-sectional observational study conducted among the participants visiting tertiary care teaching hospital located in the southern rural part of India. The study duration was 4 months and data were collected from November 2023 to February 2024. A convenience sampling technique was followed to select the participants and enrolled for the study. At last, the study was completed with 35 participants of different categories. The participants of all age groups, both the genders, undergone surgery and administered tramadol with another analgesic as post-operative medication, with or without comorbidities were included in the study. The data was collected using pre-designed proforma and data was analysed accordingly.

RESULTS

The study illustrates that most participants were males (77.3%) and few were females (22.7%). All participants live in rural areas (100%). Participants were separated into categories based on age >60 years (31.4%), 51-60 years (20%), 41-50 years (22.8), 31-40 years (14.2%), 18-30 years (11.6%). The number of participants with (51.4%) and without comorbidities (48.6%) are almost equal. The associated conditions include, diabetes mellitus (17.1%), systemic hypertension (20%), thyroid disorder (5.71%), pulmonary system related disorders (2.86%), cardiovascular diseases (5.71%), and others (0%). 14.3% participants had more than 2 associated conditions.

The results show that, 37.1% of patients had to undergo surgery due to perforation condition, 20% due to abscess formation, 11.4% due to hernia, 14.3% due to foot ulcer, 8.6% due to inflammation conditions and 8.6% due to others including fistula, goitre etc.,

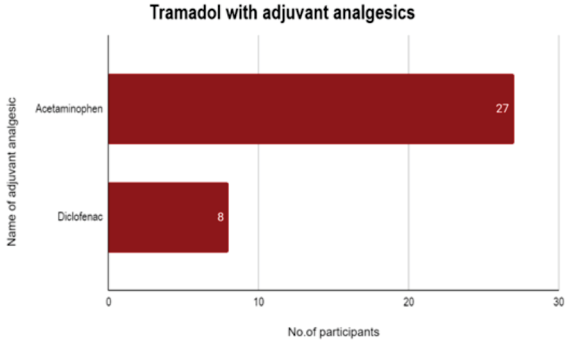
Most number of patients had undergone surgery in gastrointestinal tract (62.9%) including laparotomy (14.3%), omental patch repair (14.3%), hernioplasty (5.7%). appendectomy (14.3%), and peritoneal lavage (8.6%). Other procedures include incision & drainage (5.7%), fistulectomy (8.6%), wound debridement (5.7%), excision and biopsy (2.8%), amputation (8.6%) and thyroidectomy (5.7%).

The findings suggests that almost all the participants were administered with tramadol 100mg at frequency of two times per day in intramuscular route of administration (85.7%) and minor participants were administered with dose of 50mg at frequency of two times per day in intramuscular route of administration (14.3%). The adjuvant analgesics used include acetaminophen (77.1%) and diclofenac (22.9%).

Table 2- Dose, Route And Frequency Of Administration Of Adjuvant Analgesic

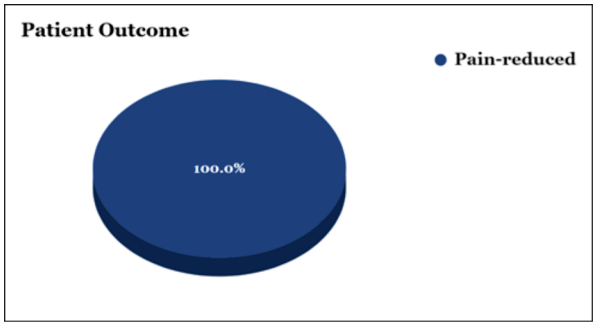
Parameter	Acetaminophen		Parameter	Diclofenac	
Dose (n=27)	1gm	54.1%	Dose (n=8)	50mg	14.4 %
	500mg	22.8%		100mg	8.6%
Route of adminis-tration (n=27)	Intramuscular	14.8%	Route of adminis-tration (n=8)	Intra-muscular	22.9 %
	Intravenous	62.9%		Intra-venous	0
	Per oral	22.3%		Per oral	0
Frequency (n=27)	Twice a day (BD)	60%	Frequency (n=8)	Twice a day (BD)	22.9 %
	Thrice a day (TDS)	17.1%		Thrice a day (TDS)	0

The data signifies that 25.7% of participants have been administered with combination of analgesic, either acetaminophen or diclofenac for less than 3 days, 65.7% for 3 to 6days and 8.6% for greater than 6 days. Among which 57.1% of patients experienced side effects and 42.9% patients did not experience any side effects. The side effects include drowsiness (30.5%), gastric irritation (8.9%), constipation (23.2%), decreased appetite (5.3%), dizziness (3.6%), nausea and vomiting (16%) and fatigue (12.5%).



Graph 1- Tramadol With Adjuvant Analgesic

The results imply that, 31.5% of participants had been in-hospitalized for ≤3 days, 57.1% for 4 to 7 days and 11.4% for >7days. Every trial participant experienced less post-operative pain after receiving tramadol and an adjuvant analgesic.



Graph 2- Patient Outcome In Post-operative Pain Management

DISCUSSION

Post-operative pain is the discomfort patients experience after a surgical procedure, varying in severity based on factors like surgery type, extent, individual pain thresholds, and pain management strategies. It is caused by tissue damage, manipulation, and inflammatory responses during the healing process. The intensity and duration can range from mild to severe, persistent pain. Effective pain management is crucial for patient comfort, recovery, and preventing complications.

In this study the opioid analgesic is administered only in intramuscular (IM) route than intravenous (IV) as IV tramadol should be diluted appropriately, administered slowly over period of time required close monitoring of patients, and higher incidence of adverse reactions making IM route comparatively safer. Tramadol is typically administered as an IM injection into a large muscle mass, such as the gluteus maximus or vastus lateralis. IM injections can occasionally cause pain, irritation, or localized reactions at the injection site.

The above study illustrates that most of the individuals have been administered with acetaminophen than diclofenac. The preference of

acetaminophen may be due to reduced incidence of gastrointestinal side effects, kidney impairment, increased risk of bleeding, interaction with other medications like antihypertensives, anti-platelet agents etc., and due to tolerance and dependence. On comparison diclofenac have higher incidence of gastrointestinal side effects than acetaminophen, like GI bleeding, ulcer, nausea, vomiting, and constipation[1]. Acetaminophen is also less likely to cause renal toxicity. NSAIDs like diclofenac can increase bleeding risk, causing concern for surgery patients or bleeding disorders, while acetaminophen is safer due to its lack of bleeding risk. Acetaminophen is a preferred option for long-term pain management due to its lower risk of tolerance and dependence compared to other NSAIDs. Acetaminophen might also be preferred due to following interactions of diclofenac with other agents,

- **ACE Inhibitors, ARBs & Beta-Blockers:** This interaction occurs due to diclofenac inhibiting prostaglandin synthesis, leading to sodium and water retention.
- **Diuretics:** NSAIDs can decrease diuretic efficacy and increase risk of renal dysfunction.
- **Anti-diabetic Medication:** There is a potential risk of kidney damage when NSAIDs like diclofenac are used concomitantly with any oral hypoglycaemic agents.
- **Aspirin (Acetylsalicylic Acid):** Both aspirin and diclofenac inhibit the cyclooxygenase (COX) enzyme involved in prostaglandin synthesis, but aspirin irreversibly acetylates the enzyme, leading to inhibition of thromboxane A2 production and subsequent platelet aggregation. Diclofenac reversibly inhibits COX, which may interfere with aspirin's antiplatelet effects.
- **Clopidogrel, Ticagrelor and Prasugrel:** Diclofenac may increase the risk of bleeding when used concomitantly with clopidogrel, ticagrelor and prasugrel, a platelet aggregation inhibitor. The combination of diclofenac and these antiplatelet agents may potentiate the risk of bleeding complications.

The evidence portrays occurrence of side effects is vast number of participants. The side effects may be due to concomitant use of NSAIDs with tramadol. The combination of tramadol and NSAIDs can potentially increase the risk of side effects, as they interact and enhance each other's effects, reducing inflammation and pain. The commonly observed side effects due to tramadol include nausea, vomiting, GI ulcers, renal function impairment, cardiovascular events, dizziness, drowsiness, headache, confusion, and respiratory depression. Tramadol can affect multiple organ systems: gastrointestinal, central nervous system (seizure, CNS depression, low-grade coma, anxiety, and over time anoxic brain damage), cardiovascular system (palpitation, mild hypertension to life-threatening complications such as cardiopulmonary arrest), respiratory system, renal system (renal failure with higher doses of tramadol intoxication), musculoskeletal system (rhabdomyolysis), endocrine system (hypoglycaemia), as well as, cause serotonin syndrome[2].

Overall, tramadol represents a valuable option for post-operative pain management, particularly when used as part of a multimodal approach tailored to the individual patient's needs. By adhering to best practices in tramadol prescribing and monitoring, healthcare providers can effectively manage post-operative pain, enhance patient comfort, and promote optimal recovery outcomes following surgery.

CONCLUSION

Post-operative pain management often requires a multimodal approach involving tramadol, acetaminophen, and diclofenac. These medications offer unique benefits and reduce reliance on opioids. By tailoring medication regimens to individual patient needs and closely monitoring for adverse effects, healthcare providers can optimize pain control and enhance patient comfort. Patient education is crucial for safe and effective pain management, with clear instructions on medication use, potential side effects, and adherence to prescribed regimens. Patients should also be counselled on non-pharmacological pain management techniques and encouraged to communicate any concerns or changes in pain intensity to their healthcare providers. In summary, tramadol with acetaminophen had lower incidence of side effects and preferred over tramadol with diclofenac in post operative pain management due to its safety profile.

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