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AN OBSERVATIONAL STUDY ON EFFECTIVENESS OF MONOTHERAPY AND COMBINATION THERAPY OF ANALGESICS AND NSAIDS IN POST-OPERATIVE PAIN

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ABSTRACT

The study focuses on the effectiveness of monotherapy and combination therapy of analgesics and NSAIDs (non-steroidal anti-inflammatory drugs) in managing post-operative pain. Multimodal analgesia is an effective approach for managing postoperative pain, with various combinations including acetaminophen, NSAIDs, opioids like tramadol, and intravenous medications like aceclofenac and diclofenac. These strategies result in enhanced pain management, reduced opioid use, increased patient satisfaction, faster recovery, fewer adverse effects, and lower healthcare expenses. Data was collected using the WONG-BAKER FACIAL GRIMACE scale, and descriptive statistical analysis and chi-square tests were performed. Results showed that most patients had the highest administration of twice-daily dosing (91%), followed by a shorter administration of once-daily dosing (9%). The majority of patients had a hospital stay duration of 1-3 days (76%), followed by 4-6 days (69%), 7-9 days (2%), and 10–12 days (1%). The usage pattern and effectiveness were predominantly high in the combination therapy of paracetamol and aceclofenac/diclofenac (39.33%), followed by paracetamol (22.66%), paracetamol and tramadol (21.33%), aceclofenac/diclofenac (9.33%), and tramadol (7.33%). In conclusion, the combination therapy of analgesics and NSAIDs has high rates of efficacy in managing post-operative pain compared to monotherapy of analgesics or NSAIDs. This

combination provides a well-tolerated and effective means of analgesia for moderate-to-severe pain and can be used as an alternative or adjunct to opioid use post-surgery. Balanced analgesia with a combination of NSAIDS and analgesics forms the preferred method postoperatively in major surgical procedures.

KEYWORDS: NSAIDs, Safety, Efficacy, Post-operative pain, Multimodal analgesia, Balanced Analgesia.

OBJECTIVES

- To assess the usage pattern of effectiveness of analgesics and NSAIDs in post-operative pain.
- To evaluate the efficacy of monotherapy and combination therapy of analgesics and NSAIDs in management of post-operative pain.

INTRODUCTION

Pain is characterized as an unpleasant, emotional, and sensory encounter resulting from actual or potential harm to the tissues. Pain serves as an indication of a tissue injury or pathological condition. Initially, acute postoperative pain may be categorized as neuropathic, inflammatory, or nociceptive in nature. Furthermore, it may manifest as chronic postoperative pain (CPOP), which exhibits distinct characteristics depending on the specific type of surgery.[1,2] Despite its impact on a significant number of patients annually, chronic postoperative pain is consistently disregarded following surgical procedures, resulting in adverse implications for patient well-being and the economy. It is of utmost importance to effectively alleviate postoperative pain, as doing so not only facilitates early discharge from the hospital but also reduces the likelihood of chronic pain syndromes.[3] The discernment of post-operative pain, recognized as a significant matter of public health, has experienced a multitude of advancements. Analgesics are administered throughout the preoperative, intra-operative, and postoperative stages of surgery with the purpose of impeding the transition of pain from an acute state to a chronic one.[4]

Biological reactions, psychological states, and social circumstances all contribute to the diverse ways in which people experience pain. Several factors are responsible for acute postoperative pain. Surgical procedures result in tissue damage, which triggers a range of responses in the pain matrix. These responses include sensitization of the peripheral and central pain pathways, as well as emotional reactions like fear, anxiety, and frustration.[5,6] An

interdisciplinary approach is imperative for effectively addressing the pain experienced by older patients, given that their pain is often intricate and diverse. To optimize the results of pain management for all individuals, particularly the elderly population, it is essential to implement a comprehensive approach that encompasses the recognition, assessment, record-keeping, and regular reassessment of pain.[7] In the subsequent investigation, the evaluation of pain is conducted through the utilization of the Wong-Baker facial grimace scale, a method that employs simplistic portrayals or facial gestures for the quantification of pain.

The occurrence of persistent pain after surgery has remained unchanged over time, and there is a lack of current understanding regarding an efficacious preventative treatment.[7] The evolution of postoperative pain often adheres to a consistent pattern, wherein the most severe discomfort is initially experienced and subsequently improves as the healing process advances. Pharmacological interventions, occasionally employed in the form of multimodal analgesic (MMA) regimens, are utilized in the treatment of acute postoperative pain. Multimodal pain management approaches involve the combination of two or more medications in order to optimize the desired analgesic effect.[8]

The current comprehension of the pain predictors, which may be physiological, genetic, or psychosocial and are exclusively linked to the acute postoperative phase, has resulted in the emergence of several novel treatments to prevent acute postoperative pain.[9] Prolonged postoperative pain is most frequently induced by nerve and tissue damage during surgical procedures.[10] Various systematic reviews were conducted, and approximately 66 trials (n=3,149) were able to identify the primary pharmacological and non-pharmacological therapies for managing acute postoperative pain.[11]

Following surgical procedures, a ground-breaking method for the alleviation of discomfort has been introduced. In order to effectively address both post-surgical acute pain and pain resulting from trauma, the employment of multimodal analgesia is recommended. This therapeutic strategy involves the utilization of pain-relieving medications from various analgesic categories and incorporates pain-alleviating techniques that target distinct pain mechanisms. As a result of this strategy's synergistic effects, which improve pain relief at lower doses of painkillers, the likelihood of adverse drug reactions is reduced. In order to generate a more potent pain-relieving effect while reducing the side effects linked to increasing the dosage of a single drug, balanced multimodal analgesia uses numerous medicines that work through different pathways. With the aim of reducing postoperative pain,

multimodal analgesia, commonly referred to as balanced analgesia, has grown in popularity. Both opioid and non-opioid analgesics will be given in this method. Non-opioid analgesics are increasingly utilized as adjuncts prior to, during, and subsequent to surgical procedures with the aim of expediting the recuperation process in patients undergoing ambulatory surgery. In accordance with preliminary investigations focusing on expediting the healing process, multimodal analgesic approaches have been found to enhance early recovery and yield other clinically significant outcomes following ambulatory surgery. Multimodal analgesia denotes a breakthrough in the provision of treatment for postoperative patients, as it mitigates the intensity of pain and thwarts the emergence of chronic painful symptoms. The recommended multimodal analgesic regimen for controlling post-operative pain hinges upon several patient-specific factors, such as age, concurrent medical conditions, ongoing medications, any prior history of substance abuse, the nature of the surgical procedure, and the hospital environment.[5, 12]

In recent times, there has been a noticeable trend towards the combination of NSAIDs and paracetamol (acetaminophen) for the effective management of acute post-operative pain. The simultaneous use of analgesics from different therapeutic classes may result in additional analgesic effects while minimizing the occurrence of adverse effects compared to the use of a single therapeutic agent. These medications have demonstrated effectiveness and widespread availability, and there have been relatively few studies that provide a comparative analysis between two drugs.[14]

Incorporation of paracetamol with NSAIDs yields an enhancement in their therapeutic efficacy while simultaneously reducing their dose-dependent undesirable outcomes. In contrast to the separate administration of the two medications, the combination of aceclofenac, which exerts a peripheral impact, and paracetamol, which tends to exert a central effect, demonstrates a superior analgesic efficacy.[13,14]

Numerous studies have indicated that the utilization of non-opioid analgesics following surgery as a supplementary measure diminishes the reliance of patients on opioids. The utilization of non-opioid analgesics decreases drowsiness, impaired pulmonary function, and constipation after surgery by reducing the necessity for opioid analgesics. It is noteworthy that the highest rates of chronic postoperative pain occur subsequent to breast, cardiac, thoracotomy, and amputation procedures. The facilitation of effective management of postoperative pain is imperative for the well-being and rehabilitation of the surgical patient

and constitutes a fundamental element of programs aimed at expediting recovery following surgery. It promotes early mobilization, the intake of fluids and nourishment, and the restoration of normal activities.[15,16]

Over the course of the previous three decades, there has been a consistent level of severe discomfort experienced by patients within the initial 24 hours following surgical procedures, with approximately 20% of patients affected. In Western societies, the occurrence of moderate-to-severe pain ranges from 14% to 55%, with the highest incidence observed on the day of surgery. The occurrence of moderate to severe pain exhibits variability across different regions.[16]

Several areas of research have been identified as lacking in knowledge, including the most effective techniques and timing for educating patients after surgery, the use of non-pharmacological methods, the combination of different analgesic techniques, the tracking of patient responses to treatment, the methods for administering neuraxial, topical, and regional analgesia, and the models for organizing care delivery. Despite the availability of advanced clinical settings, a wide range of analgesics, and various anesthesia procedures, there is still a deficiency in the treatment of postoperative pain.[17]

The primary reason for seeking medical attention and being admitted to hospitals is the experience of pain, which is a matter of concern for public health on a global scale. This issue is associated with medical ramifications, diminished patient satisfaction, and an increased likelihood of developing chronic pain if not effectively alleviated or adequately managed. A multitude of studies have provided evidence that if left untreated, post-operative pain can persist and become chronic. Chronic post-surgical pain (CPSP) is a significant challenge that warrants attention. Depending on the specific surgical procedure, an incidence rate as high as 50% has been observed. In addition to biological factors such as pre-existing pain, intense acute post-operative pain, anesthesia methods, and surgical techniques, there is a probable link between CPSP and psychosocial aspects, including melancholy, psychological vulnerability, stress, and a delayed return to work.[18]

Globally, the repercussions of pain exert a substantial influence on the social structure, economic prosperity, and operational capacity of society. Furthermore, the effect of pain on both healthcare utilization and engagement in the workforce is noteworthy. Consequently, it is imperative to accord utmost importance to effectively tackling suitable pain control.[19]

MATERIALS AND METHODS

Methodology

Study site

The study was conducted at the Department of Surgery and Orthopedics at MVJ Medical College and Research Hospital, Bengaluru a 950-bed hospital.

Ethical clearance

Ethical clearance was obtained from the Institutional Ethics Committee of MVJ Medical College and Research Hospital **(MVJMC&RH/IEC-75/2023).**

Study duration

The total duration of the study was 6 months, from March 2023 to August 2023.

Study design

The study was a prospective observational study carried out among post-operative patients admitted to MVJ Medical College and Research Hospital.

Study population: 150

Sample Size Calculation

The sample size was calculated using the formula: $\mathbf{Z^2\text{-}x\ P\ (1\text{-}P)\ /\ d^2}$

Z^2 = standard normal variate (at 5% type 1 error ($p<0.05$) it is 1.96

Where, P = the expected proportion in population based on previous studies which was found to be 0.120

d = absolute error on precision, which is 0.052

Sample Size = $(1.962)^2$x 0.120(1-0.120)/ $(0.052)^2$ = 150

Study criteria

Inclusion criteria

All post-operative patients above 18 years of age group receiving various analgesics and NSAIDs were admitted to surgery and orthopedics ward irrespective of their gender and diagnosis.

Exclusion criteria

- Patients with a history of chronic analgesic use.
- Patients did not consent for the study.

Study materials

The study material used was case record form (CRF) and Wong Baker Facial Grimace Scale.

Statistical Analysis

Usage pattern of analgesics and NSAIDs was first calculated. Continuous data were presented as Mean ± Standard deviation. Categorical data were presented as frequencies with percentages and were analyzed by chi-square test. Comparison of various variables like age, sex, monotherapy, and combination therapy, was done using chi- square analysis.

For comparison of effectiveness of monotherapy and combination therapy of analgesics and NSAIDs, Chi-square test was performed.

All analyses were performed using Statistical Analysis System (SAS) version 9.4. P value below or equal to 0.05 was considered to indicate statistical significance.

RESULTS

Among 150 post-operative patients whose usage habits were evaluated, the majority administered twice daily (BD) at the highest rate (91%), and one daily (OD) at a lesser rate (9%). Of the 150 patients examined, the majority (76%), followed by those with stays of approximately 4-6 days (69%), those with stays of approximately 7-9 days (2%), and those with stays of approximately 10–12 days (1%) had the longest hospital stays. When the length of hospital stays in monotherapy of analgesics or NSAIDs was reviewed for the 150 post-operative patients who were enrolled, the majority of patients had stays of approximately 1-3 days (70.5%), followed by stays of 4-6 days (26.3%), and fewer stays of approximately 7-9 days (1%), & 10-12 days (1%) The length of hospital stays in combination therapy of analgesics and NSAIDs for 150 post-operative patients were reviewed; the majority of patients had stays of approximately 4-6 days (59%), followed by stays of approximately 1-3 days (36%), and fewer stays of approximately 7-9 days (3%), & 10-12 days (2%). The statistical analysis indicates that there were no differences between the groups, with a p-value of 0.000589 and a significant result at $p < 0.05$. A WONG-BAKER FACIAL GRIMACE SCALE was used to record the pain scores of 150 post-operative patients. This scale is used to classify post-operative patients based on the type of pain they experience throughout, such as no pain, mild pain, moderate pain, severe pain, and worst possible pain. It is used to compare the pain scores on the day of admission as well as on discharge. The greatest percentage of patients(24%) reported having severe pain, which was followed by patients who reported having the worst possible pain(23%), patients who reported having moderate

pain(21%), patients who reported having mild pain(18%), and finally, patients who reported having neither pain nor an acceptable range of pain (14%). demonstrates that the greatest number of patients (26%), those who presented with no pain, those who presented with mild pain (24%), those who presented with moderate pain (21%), those who presented with the worst possible pain (15%), and those who presented with severe pain (14%), were the next most common patient presentations.

Table 1: Evaluation of effectiveness of combination therapy of analgesics and NSAIDS by determining the p-value.

WONG BAKER SCALE CLASSIFICATION	FREQUENCY OF REPORTED CASES (DOA)	FREQUENCY OF REPORTED CASES (DOD)	P-VALUE
NO PAIN	20(30.00) [3.33]	40(30.00) [3.33]	
MILD PAIN	26(31.00) [0.81]	36(31.00) [0.81]	
MODERATE PAIN	31(31.05) [0.01]	32(31.50) [0.01]	
SEVERE PAIN	37(28.50) [2.54]	20(28.50) [2.54]	
WORST POSSIBLE PAIN	36(29.00) [1.69]	22(29.00) [1.69]	**0.002166**

The p- value for the effectiveness of combination of analgesics and NSAIDs based on wong baker facial grimace scale is *P*- 0.002166. The result is significant at $P < 0.05$ showing that there is no differences between the groups statistically.

Table 2: Determination of p-value for effectiveness of combination therapy of PCT+ACCECLOFENAC/DICLOFENAC.

THERAPY	PAIN CLASSIFICATION	SCORE AT DOA	SCORE AT DOD	P- VALUE
PARACETAMOL+ ACECLOFENAC/ DICLOFENAC	NO PAIN	2	20	
	MILD PAIN	14	12	
	MODERATE PAIN	15	11	
	SEVERE PAIN	13	7	**0.000862**
	WORST- POSSIBLE PAIN	15	9	

The chi square statistic for Determination of p-value for effectiveness of combination therapy of PCT+ACCECLOFENAC/DICLOFENAC is 18.7965 for which the value is *P*- 0.000862. The result is significant at $P < 0.05$ shows that there is no differences between the groups statistically.

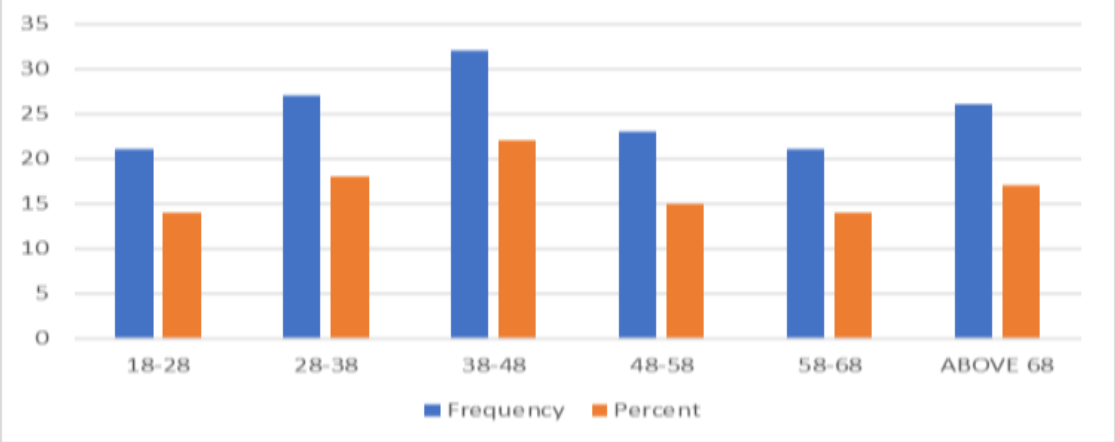

Fig 01: Distribution of Age.

Among the 150 post-operative patients examined, the age groups with the highest percentage of patients were above 68 (17%), 48-58 (15%), 58-68 (14%), and 18-28 (14%).

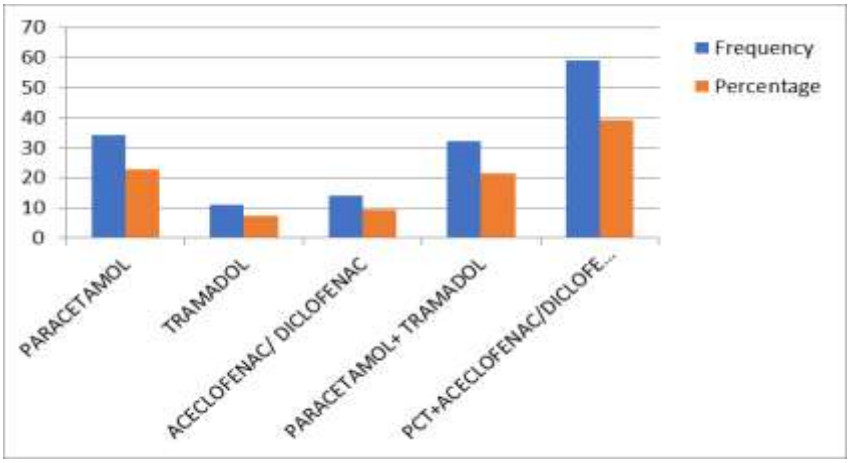

Fig. 02: usage pattern of monotherapy and combination therapy.

The analysis of 150 post-operative patients revealed that the use of combination therapy with paracetamol and aceclofenac/diclofenac was predominant (39.33%). This was followed by the use of paracetamol monotherapy (22.66%), combination therapy with paracetamol and tramadol (21.33%), aceclofenac/diclofenac monotherapy (9.33%), and tramadol monotherapy (7.33%).

DISCUSSION

In this study, an assessment was carried out on the utilization pattern of postoperative patients who were admitted to the surgical and orthopedic units of a tertiary care hospital. Additionally, the age and gender of these patients were carefully examined. Within the scope of our investigation, it was observed that a higher proportion of male patients, accounting for

(58%), had undergone minor and/or major surgical procedures compared to the (42%) of female patients. This observation aligns with the findings of a study conducted in Tamil Nadu, India in 2014 by Sivakumar Periaswamy, which reported that (51.3%) of patients were male and (46.8%) were female.[21] Conversely, other studies have demonstrated dissimilarities with our results. For instance, a study carried out by Kyuong Lin Chae in 2019 found that both male and female individuals within the target population were evenly distributed at (50%).[20]

In our study, an analysis was conducted on 150 patients who underwent post-operative procedures. It was observed that the majority of these patients were categorized within the age range of 38-48, accounting for (22%) of the total population. Remarkably, this finding aligns with a previous investigation conducted by Kyuong Lin Chae in 2019, where a significant proportion of patients fell within the age range of 20-45, representing (30.8%) of the total sample.[20] Nevertheless, certain disparities were noted when comparing our results to other studies, such as the one conducted by Tania Curiso in 2009. In this particular study, a predominant number of patients were found to be over the age of 60 years old.[22]

Out of the 150 patients who underwent surgery, a thorough examination was conducted to analyze the duration of hospital stays for those receiving either analgesics or NSAIDs as monotherapy. The majority of patients, amounting to 70.5%, had a duration of stay ranging from 1 to 3 days. Following this, 26.3% of patients stayed in the hospital for 4 to 6 days, while a smaller percentage, 1% and 1% respectively, had stays lasting 7 to 9 days and 10 to 12 days. Similarly, among the 150 post-operative patients included in the study, the duration of hospital stays for those receiving combination therapy of analgesics and NSAIDs was examined. The majority of patients, comprising 59%, had a stay lasting 4 to 6 days. This was followed by 36% of patients who stayed for 1 to 3 days, and a smaller percentage, 3% and 2% respectively, who had stays of 7 to 9 days and 10 to 12 days. These findings are consistent with study carried out by Weicheng Xu in 2015, which demonstrated a shorter median duration of hospital stay when the drug was administered twice daily.[23]

In our analysis of 150 patients who underwent surgery, the predominant usage pattern observed was the combination therapy of Paracetamol and aceclofenac/diclofenac, accounting for 39.33% of cases. This finding aligns with the results of a study conducted by Anil Pareek in 2009, which reported that approximately 50.8% of the study population benefited from the combination therapy of paracetamol and aceclofenac.[24] Our study also

corroborates the findings of a study carried out by Vinoothan Bavireddy in 2017, which showed that 40% of patients who received the combination therapy of paracetamol and acceclofenac experienced benefits.[25]

The evaluation of pain management involving various analgesics and NSAIDs holds significant importance, as it has been demonstrated that improved acute pain management with appropriate analgesics and NSAIDs decreases the risk of chronic pain and overall morbidity, as stated by Tetzlaff JE in 2012 and Johnson QI in 2013.[26,27] In our study, pain scores were recorded for all participants enrolled to assess the effectiveness of both monotherapy and combination therapy. The distribution of pain scores revealed that the majority of patients (26%) reported no pain, according to the Wong Baker FACES scale. This finding is consistent with a study conducted by Sushanta Kumar Das in 2020, where 27% of patients also reported no pain.[27]

The study was limited by its single-center design, preventing generalizability of the findings. Additionally, patients' side effects and adverse events were not closely monitored, which may have compromised the accuracy of the results. Furthermore, patients may have struggled with adherence to prescribed timings, potentially impacting the study's effectiveness. The study also faced restrictions in obtaining patient performance data, prioritizing pain management and strategies following significant and major surgical procedures. Moreover, pain scores after surgery were not monitored, which is a crucial aspect of assessing the study's outcomes.

CONCLUSION

An observational study was carried out to evaluate the usage pattern and effectiveness of combination of analgesics and NSAIDs in post-operative patients admitted to the department of Surgery and orthopedics of MVJ medical college and research hospital, Bengaluru. Surgery was performed more in male patients (58%) and among the age groups of 38-48 years (22%). The usage pattern was pre-dominantly high for combination therapy of Analgesics and NSAIDs (38.67%) compared to other types of therapies. In our study the effectiveness of various therapies was evaluated by using WONG- BAKER FACIAL GRIMACE SCALE by recording and comparing the pain scores on admission as well as on discharge.

Our study concludes that the combination therapy of analgesics and NSAIDs usually have a high rate of efficacy in managing post-operative pain compared to monotherapy of analgesics

or NSAIDs. Even the frequency of usage pattern is highly based on effectiveness which plays a major role in promoting the medication adherence of the patient. The combination of analgesics and NSAIDs provides a well-tolerated and effective means of analgesia for moderate to severe pain, which can be used as an alternative or adjunct to opioid use post-surgery. Balanced analgesia with a combination of NSAIDs and Analgesics forms the preferred method of post-operative in major surgical procedures.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Aweke Z, Seyoum F, Shitemaw T, Doba DN. Comparison of pre-emptive paracetamol, paracetamol-diclofenac & paracetamol-tramadol combination on postoperative pain after elective abdominal surgery under general anaesthesia, Ethiopia: a randomized control trial study, 2018. BMC Anaesthesiology, 2020 Aug 4; 20(1).
2. Urman R, Vadivelu N, Mitra S, Kodumudi V, Kaye A, Schermer E. Preventive analgesia for postoperative pain control: a broader concept. Local and Regional Anaesthesia [Internet], 2014 Apr; 7: 17.
3. Chen Y - Y. K, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic postoperative pain: a narrative review. Anaesthesia, 2021 Jan; 76(S1): 8–17.
4. C Small, H Laycock, Acute postoperative pain management, British Journal of Surgery, January 2020, 107(2): e70–e80.
5. Wardhan R, Chelly J. Recent advances in acute pain management: Understanding the mechanisms of acute pain, the prescription of opioids, and the role of multimodal pain therapy. F1000Res, 2017; 6: 2065.

6. Kaye AD, Urman RD, Rappaport Y, Siddaiah H, Cornett EM, Belani K, et al. Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. Journal of Anaesthesiology, Clinical Pharmacology [Internet].
7. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. Journal of Pain Research [Internet], 2017; 10(10): 2287–98.
8. Correll D: Chronic postoperative pain: recent findings in understanding and management. F1000Res, 2017; 6: 1054.
9. Wylde V, Dennis J, Beswick AD, et al.: Systematic review of management of chronic pain after surgery. Br J Surg, 2017; 104: 1293-306.
10. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. Lancet, 2006; 367: 1618-25.
11. Chaparro LE, Wiffen PJ, Moore RA, Gilron I: Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev, 2012; CD008943.
12. Varrassi G, Hanna M, Macheras G, 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: 1165-73.
13. Thybo KH, Hägi-Pedersen D, Dahl JB, Wetterslev J, Nersesjan M, Jakobsen JC, et al. Effect of Combination of Paracetamol (Acetaminophen) and Ibuprofen vs Either Alone on Patient-Controlled Morphine Consumption in the First 24 Hours After Total Hip Arthroplasty. JAMA, 2019 Feb 12; 321(6): 562.
14. Varrassi G, Yeam CT, Rekatsina M, Pergolizzi JV, Zis P, Paladini A: The expanding role of the COX inhibitor/opioid receptor agonist combination in the management of pain. Drugs, 2020; 80: 1443-53.
15. Chou R, Gordon DB, de Leon-Casasola OA, et al.: Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anaesthesia and Pain Medicine, and the American Society of Anaesthesiologists' Committee on Regional Anaesthesia, Executive Committee, and Administrative Council. J Pain, 2016; 17: 131-57.
16. Sommer M, de Rijke JM, van Kleef M, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. Eur J Anaesthesia, 2008; 25(4): 267–274.
17. Gordon DB, de Leon-Casasola OA, Wu CL, et al.: Research gaps in practice guidelines for acute postoperative pain management in adults: findings from a review of the evidence for an American Pain Society Clinical Practice Guideline. J Pain, 2016; 17: 158-66.

18. Ruoff G, Lema M. Strategies in Pain Management. Journal of Pain and Symptom Management, 2003 Feb; 25(2): 21–31.
19. Bisgaard T. Analgesic Treatment after Laparoscopic Cholecystectomy. Anaesthesiology, 2006 Apr; 104(4): 835–46.
20. Chae, K. L., Park, S. Y., Hong, J. I., Yim, W. J., Lee, S. C., & Chung, C. J. (2019). The effect of gender and age on postoperative pain in laparoscopic cholecystectomy: a prospective observational study. Anaesthesia and Pain Medicine, 14(3): 364–369.
21. Periasamy, S., Poovathai, R., & Pondiyadanar, S. (2014). Influences of gender on postoperative morphine consumption. Journal of Clinical and Diagnostic Research.
22. De Menezes Couceiro, T. C., Valênça, M. M., Lima, L. C., De Menezes, T. C., & Raposo, M. C. F. (2009). Prevalence and influence of gender, age, and type of surgery on postoperative pain. Revista Brasileira De Anaesthesiologic, 59(3): 314–320.
23. Xu, W., Daneshmand, S., Bazargani, S., Cai, J., Miranda, G., Schuckman, A., & Djaladat, H. (2015). Postoperative Pain Management after Radical Cystectomy: Comparing Traditional versus Enhanced Recovery Protocol Pathway. The Journal of Urology, 194(5): 1209–1213.
24. Pareek, A., Chandurkar, N., Sharma, V., Desai, M. M., Kini, S., & Bartakke, G. (2009). A randomized, multicentric, comparative evaluation of aceclofenac–paracetamol combination with aceclofenac alone in Indian patients with osteoarthritis flare-up. Expert Opinion on Pharmacotherapy, 10(5): 727–735.
25. Vinoothna Bavireddy et al. Assessment of Drugs in Post-Operative Pain Management. Indo American Journal of Pharmaceutical Research, 2017; 7(07).
26. Tetzlaff JE. A review of mechanisms of Acute Pain and Treatment Strategies in Orthopedic Patients with special emphasis on Pre-emptive Analgesia. Practical pain management, 2012.
27. Johnson Q, Borsheski RR, Reeves-Veits JL. A Review of management of Acute Pain. Science of Medicine, 2013; 110(1): 74-79.