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Comparison of the Effectiveness of Unimodal Opioid Analgesia with Multimodal Analgesia in the Management of Postoperative Pain in Patients Undergoing Surgery under Spinal Anesthesia-Double Blind Study

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Abstract

Objective: To evaluate the efficacy and safety of opioid analgesic alone or in combination with a Non-steroidal Anti-inflammatory Drug (NSAID) in management of post-operative pain after regression of spinal anesthesia.

Methods: In this double-blind study, 120 patients who underwent infra-umbilical surgeries under spinal anesthesia were chosen for the study and were randomly allocated into 4 groups of 30 each. Each group received Tramadol 100 mg or Pentazocine 30 mg or Tramadol 100 mg+Piroxicam 20 mg or Pentazocine 30 mg+Piroxicam 20 mg intramuscularly, 30 minutes after the end of the surgery. The primary efficacy end points were the total duration of post-operative analgesia and the intensity of pain relief in different groups, as assessed by VAS. Level of sedation and incidence of side effects were observed as secondary outcomes.

Results: The mean VAS scores of the patients in Pentazocine group was lower, hence better pain relief, than Tramadol group at all time periods. The mean VAS score of the patients in Pentazocine+Piroxicam was lower than Tramadol+Piroxicam group.

In the inter-group comparison of VAS, between all 4 groups, it was observed that VAS, pain score was least for Pentazocine+Piroxicam group and highest for Tramadol group. In this comparison, it was observed that the Ramsay sedation score was highest for Pentazocine group and least for Tramadol group.

In multimodal group, Pentazocine+Piroxicam had longer duration of action compared to Tramadol+Piroxicam group, $p<0.0001$. As far as the adverse effects were concerned, the addition of Piroxicam to Tramadol and Pentazocine reduced the incidence of side effects compared to individual agents

Conclusion: Combining an Opioid and an NSAID, like Tramadol or Pentazocine with Piroxicam, provides better post-operative pain relief than giving an opioid alone.

Keywords: Multimodal analgesia; Tramadol; Pentazocine; Piroxicam; Post-operative pain relief

Introduction

Spinal anesthesia is the most common method of anesthesia used in our day-to-day practice; it is efficient, easy and economical and provides intense anesthesia and analgesia in the intra operative period. It is ideal for infra-umbilical surgeries lasting for 1 to 2 hours. The duration of analgesia lasts for a period of 2 to 3 hours and at the end of which, patient experiences severe pain and requires a rescue analgesic at the earliest. Various modalities and adjuvants have been added intrathecally to increase the duration of spinal anesthesia and hence post-operative analgesia but it comes with the disadvantage of continual motor block also. This increases the time for ambulation, leading to increased duration of hospital stay and hence increase costs. Infra umbilical surgeries like Inguinal hernias, Varicose veins and elective caesarean sections which routinely last for around 45 minutes to 1 hour will benefit from a good post-operative pain relief in place after the regression of spinal anesthetic block. Cesarean delivery patients have even more compelling reasons to treat postoperative pain, as they present with unique challenges; such as, a higher risk for thromboembolic events, which may also be precipitated by immobility from inadequate pain control or excessive sedation associated with the use of opioids [1].

Various rescue analgesics have been used to treat post-operative pain relief; NSAIDs are the main stay of this treatment. NSAIDs inhibit the synthesis of prostaglandins both in the spinal cord and at the periphery, thus diminishing the hyperalgesic state after surgical trauma. NSAIDs are useful as the sole analgesic after minor surgical procedures and may have a significant opioid-sparing effect after major surgery [2].

NSAIDs have many adverse effects like nausea and present a significant GI bleeding risk, along with a risk of a variety of renal complications, and myocardial infarction and other serious cardiovascular complications [3]. In addition, NSAIDs also has ceiling effects, and no therapeutic advantage is gained after increasing dosage

beyond those recommended [4]. The recent guidelines issued by numerous professional medical societies, recommend NSAIDs at the lowest effective dose and shortest possible period, in view of the associated gastrointestinal, renal, and cardiovascular toxicity.

Opioids, which have a dual mode of action on opioid and monoaminergic receptors, comprise another group of analgesic drugs that are efficacious against both nociceptive and neuropathic pain. Among the opioids, Tramadol has fewer side effects, such as constipation, respiratory depression, and sedation, compared with the typical strong opioids. Tramadol is now considered to be a first-line analgesic for many musculoskeletal indications [5]. Opioids used as a mode of pain relief, require continuous monitoring and lead to nausea, vomiting, constipation and pruritus. Hence, opioids can impede recovery and early rehabilitation; a problem that is of increasing concern with the rapid rise in the number of ambulatory surgeries.

Pain has a multifactorial origin; hence it may be difficult to achieve effective pain control with a single drug [6]. Currently, the American Society of Anesthesiologists Task Force on Acute Pain Management advocates the use of multimodal analgesia [7]. The complex humoral and neuronal response that occurs with surgery requires a balanced approach for perioperative pain management [8].

As such, one approach for multimodal analgesia is the use of regional anesthesia and analgesia to inhibit the neural conduction from the surgical site to the spinal cord and decrease spinal cord sensitization. Spinal cord sensitization that has been well described and demonstrated in animal studies is challenging to demonstrate in humans [9].

Hence, a combination of both an NSAID and an opioid using the synergestic analgesic effects can be used to combat post-operative pain. Moreover, when used in combination the dose requirement of individual drugs also proportionately comes down and so does the side effects.

Combination therapy of analgesics from different groups is advantageous in targeting both peripheral and central pain pathways and hence, helps in production of analgesia at lower and more tolerable doses of the constituent drugs. Combination therapies can have a positive influence on the ability of individual components to minimize pain, with better tolerability and reduced recovery time [10,11]. This combination therapies, now termed as Multimodal Analgesia is the call of the day with ever increasing numbers of ambulatory or day care surgeries. It may be a combination of two or more modalities of analgesia like-Opioids, NSAIDs and COX 2 selective inhibitors, NMDA antagonists, Alpha-2 Adrenergic agonists, GABA mimetic drugs, Glucocorticoids, Cholinergic drugs, regional nerve blocks and last but not the least Local anaesthetic infiltrations at wound site [12,13].

NSAIDs offer an opioid-sparing strategy in which the opioid activity can be potentiated by NSAIDs. This activity is due to an increased conversion of arachidonic acid to 12-lipoxygenase products, which in turn augments the effects of opioids on K+ channels [14]. Tramadol is an atypical, centrally acting analgesic, as a result of its combined effect as opioid agonist and serotonin and noradrenaline reuptake inhibitor [15,16].

Pentazocine is a synthetically prepared, Benzomorphan class of opioid. It is a strong analgesic with weak narcotic antagonist activity. It is advocated for the relief of moderate to severe pain. Pentazocine has a low abuse potential and is not controlled by narcotic regulations. Therapeutic trials comparing pentazocine with other strong analgesics have shown it to possess a strong analgesic effect when given intramuscularly and a lesser analgesic effect when administered orally at a dose of 50 mg. Pentazocine produces side-effects similar to those associated with the morphine-like analgesics, and as with these analgesics the effects are exaggerated in ambulatory patients [17].

Piroxicam is a Non-Steroidal Analgesic and anti-inflammatory Drug. It is similar in potency to indomethacin and superior in action than aspirin and ibuprofen. It has an extended half-life of about 40 hours and is suitable for once daily administration. It has been used effectively for both acute and chronic pain. The most frequently reported side effects are only gastro-intestinal and even these have occurred less frequently than with aspirin or indomethacin [18].

Various studies were conducted to compare the efficacy of NSAIDs and opioids. Cepeda et al. compared the efficacy of Ketorolac *vs.* Morphine. They found that Ketorolac was more effective than morphine. These results contrast with clinical experience and consensus recommendations that opioids are more effective than NSAIDs for moderate-to-severe acute pain [19,20].

Therefore, we designed a randomised controlled double blinded study, first to compare the analgesic efficacy of an NSAID and an opioid in a head-to-head trial by determining the proportion of subjects who obtained adequate postoperative pain relief 30 min after analgesic administration, and second to determine whether the opioid-sparing effect of NSAIDs decreases the risk of opioid side effects, by comparing opioid requirements and side effects in patients who received Tramadol or Pentazocine plus Piroxicam or Tramadol or Pentazocine alone .

Materials and Methods

This prospective, randomised, double blind control study was conducted after the Ethical Committee clearance of Bangalore Medical College and Research Institute, in Victoria and Vani Vilas Hospital, over a period of 12 months from June 2014 to June 2015. 120 patients, of ASA I and II, aged 18-65 yrs, undergoing uni-lateral inguinal hernia, Varicose Veins and elective Caesarean sections under spinal anesthesia were chosen for the study. Patients with any contra indications for spinal anesthesia were excluded from the study. So were patients with peptic ulcer disease or opioid drug abuse. Using a sealed envelope method, (double blind and random) patients were randomly allocated into 4 groups of 30 each Patients demographic data, history and clinical examination findings were recorded. No premedication was given in any of the groups.

Spinal anesthesia in the L2-L3 or L3-L4 interspace was provided by 2 cc of 0.5% Bupivacaine Heavy. A single anesthesiologist was responsible for administration of the. The duration and level of motor block and sensory block was noted. Intraoperative monitoring of vital signs- heart rate, blood pressure, SpO_2 was done. 30 minutes after the end of the surgery, all patients received intramuscular (i.m.) injections of 2 ml each, in either buttock.

Group T patients received Tramadol 100 mg, 2 ml im in one buttock and 2 ml normal saline in the other buttock, Group P patients received Pentazocine 30 mg 2 ml im in one buttock and 2 ml normal saline in the other buttock. Group Tp patients received Tramadol 100 mg, 2 ml in one buttock and Piroxicam 20 mg 2 ml in the other buttock. Group Pp patients received Pentazocine 30 mg 2 ml in one buttock and Piroxicam 20 mg 2 ml in the other buttock.

Normal saline i.m. was given for uniformity of the drug administration in all 4 groups, to avoid any kind of bias, since it is a double blind study. The intramuscular injections were given 30 minutes after the end of the surgery. Level of sensory block at the time of study drug administration was noted. All patients had a sensory level of T8 to T10. The average duration of the surgeries chosen for the study was around one hour.

The syringes containing the drugs were prepared by an anaesthesiologist, identified with a progressive number. Drug administration 30 min after the end of surgery was done by an anaesthesiologist unaware of the content of the syringe and he was responsible for the monitoring of the patients in the following 6 hrs.

Control of postoperative pain was assessed using a Visual Analog Scale (VAS) and sedation assessed by Ramsay Sedation Score (RSS) in the immediate postoperative period, at 30 mins, 1st, 2nd, 4th and 6th hour in the postoperative period. Analgesic duration of action was determined from the interval between drug administration and patient's request for rescue analgesia (VAS>4). All patients were trained to use VAS. Injection Diclofenac 75 mg i.m. was the rescue analgesic given.

Patients were also closely observed for the occurrence of any side effects of the drug administered. Any incidence of Nausea or vomiting was treated with Injection Ondansetron, 4 mg, i.v.

Statistical analysis

Sample size: For power of study as 80%, and confidence limit 95%, to detect a 30% difference in duration of analgesia, minimum sample size required was 25 in each group. Total sample size was taken as 120.

Data obtained were entered into a predesigned sheet and analyzed with the Statistical Package for Social Sciences version 20. Means ± standard deviation (SD) were calculated for the quantitative variables, and the difference between two independent groups was compared using unpaired Student's t-test. The level of significance was set at $P \leq 0.05$.

Results

The results were compared within opioid groups alone (unimodal analgesia) or opioids in combination with NSAIDs (multimodal analgesia) and then all 4 groups were compared with each other for inter group, group variance.

All groups were comparable in the demographic variables, types of surgeries and also average duration of surgery. None of the patients had sensory regression below T 10 at the time of drug administration (Table 1).

	Group T	Group P	Group Tp	Group Pp
Age (yrs)	28 ± 6.3	30 ± 4.8	29 ± 5.7	30 ± 5.2
Height (cms)	158 ± 2.4	160 ± 1.3	157 ± 3.7	159 ± 2.6
Weight (kg)	78 ± 5.0	76 ± 4.9	82 ± 3.5	80 ± 2.8
Inguinal hernia	16	18	15	18
Varicose vein	7	4	7	6
Caesarean section	7	8	8	6
Duration of surgery (mins)	64 ± 6.8	66 ± 4.9	65 ± 5.3	67 ± 5.0

Table 1: The mean VAS scores of the patients in Pentazocine (P) group was lower when compared to Tramadol (T) group at all time periods, $p<0.001$. The mean VAS scores of the patients in Pentazocine+Piroxicam (Pp) was lower when compared to Tramadol+Piroxicam group (Tp) at all time periods, $p<0.001$. In the Inter-group comparison of VAS, between all 4 groups, it was observed that VAS was lowest for Pentazocine +Piroxicam (2.71) group and highest for Tramadol group (5.83), $p<0.001$.

In this (Figures 1-3) comparison, it was also observed that the Ramsay sedation scores were highest for Pentazocine group (2.83) and lowest for Tramadol group (1.61), $p<0.001$.

When the duration of post-operative pain relief was compared, it was observed that, in unimodal group, pentazocine had longer duration of action compared to tramadol.

In multimodal group; Pentazocine+Piroxicam had longer duration of action compared to Tramadol+Piroxicam group, $p<0.0001$.

The mean RSS of the patients in Pentazocine group was higher when compared to Tramadol group at all time periods (Figure 4).

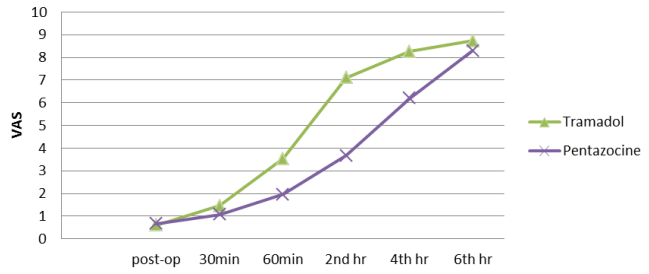

Figure 1: Visual Analog Scale comparision between unimodel analgesia groups.

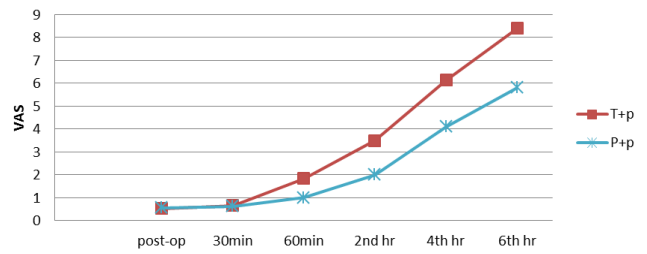

Figure 2: Visual Analog Scale comparision between multimodel analgesia groups.

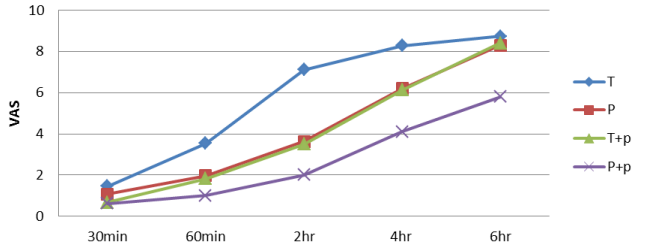

Figure 3: Visual Analog Scale comparision between unimodel and multimodel analgesia groups.

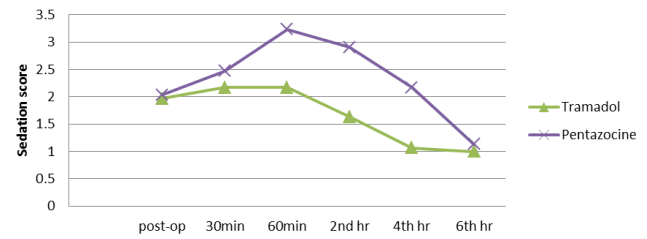

Figure 4: Ramsay sedation score comparision in unimodel analgesia groups.

The mean RSS of the patients in Pentazocine+Piroxicam (Pp) was higher when compared to Tramadol+Piroxicam group (Tp) at all time periods (Figure 5).

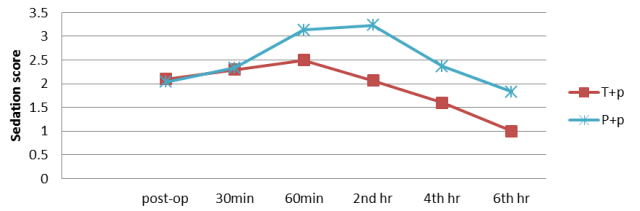

Figure 5: Ramsay sedation score comparision in multimodel analgesia groups.

Inter-group comparison of Ramsay sedation score. In the comparison, it was observed that the sedation scores were highest for Pentazocine group (2.83) and lowest for Tramadol group (1.61) (Figure 6).

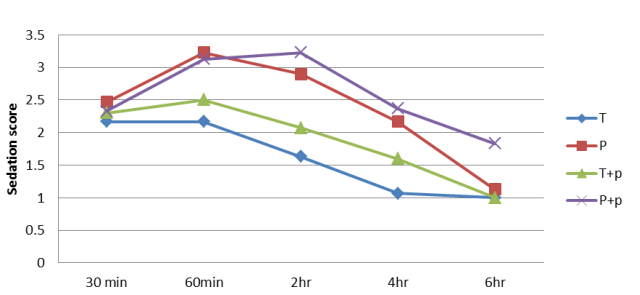

Figure 6: Ramsay sedation score comparision in unimodel and multimodel analgesia groups.

Inter-group comparison of duration of action. In unimodal group, pentazocine had longer duration of action compared to tramadol. In multimodal group, Pentazocine+Piroxicam had longer duration of action compared to Tramadol+Piroxicam group. In the comparison, it was observed that Pentazocine+Piroxicam group (7.31 hours) had the longest duration of action and Tramadol group (2.53 hours) had the lowest duration of action (Table 2 and Figures 7 and 8).

Parameters	Unimodal Analgesia Groups			Multimodal Analgesia Groups		
Groups	Tramadol Group (T) N=30	Pentazocine Group (P) N=30	P-value	Tramadol+Piroxicam group(Tp) N=30	Pentazocine+Piroxicam group (Pp) N=30	P-value
Duration of action (hrs) Mean(SD)	2.53 (0.50)	4.08 (0.37)	<0.0001	5.35 (0.55)	7.31 (0.54)	<0.0001

Table 2: Comparision between Unimodal and Multimodal Analgesia Groups.

As far as the adverse effects were concerned, the addition of Piroxicam to Tramadol and Pentazocine reduced the incidence of side effects compared to individual agents.

The incidence of adverse effects was higher with Pentazocine and Pentazocine+Piroxicam as compared to Tramadol and Tramadol +Piroxicam.

It was also observed that the combination of Pentazocine +Piroxicam had lower incidence of side effects compared to Pentazocine group and the combination of Tramadol+Piroxicam group had lower incidence of adverse effects compared to Tramadol (Table 3).

Discussion

The World Health Organization and International Association for the Study of Pain have recognized pain relief as a human right [21]. Poorly managed postoperative pain can lead to complications and prolonged rehabilitation [22]. Uncontrolled acute pain is associated with the development of chronic pain with reduction in quality of life [23].

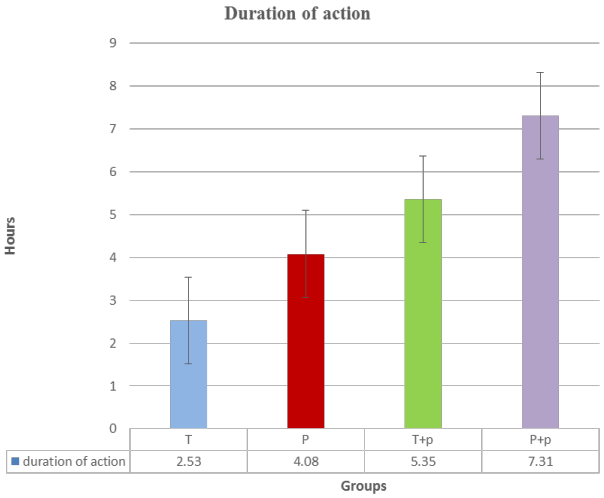

Figure 7: Duration of action.

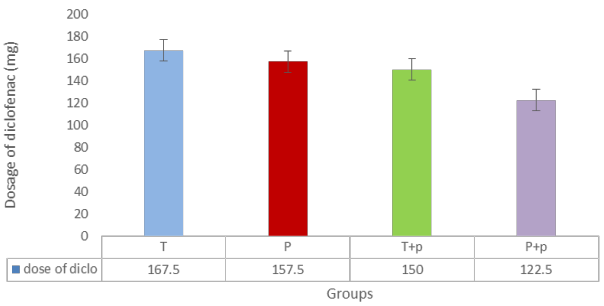

Figure 8: Dosage of rescue analgesic (Inj.Diclofenac i.m.) in different groups.The mean dose of Inj. diclofenac required in the first 24 hours was least in Pentazocine+Piroxicam group and highest in Tramadol group.

Adverse drug effects	$Tramadol_{100}$	$Pentazocine_{30}$	$Tramadol_{100}$ + $Piroxicam_{20}$	$Pentazocine_{30}$ + $Piroxicam_{20}$
Headache	-	-	-	-
Nausea	2(6.6%)	5(16.6%)	3(10%)	3(10%)
Vomiting	2(6.6%)	7(23%)	2(6.6%)	5(16.6%)
Abdominal pain	-	-	-	-
Vertigo	-	1(3.3%)	-	-
Diarrhea	-	-	-	-
Rashes	-	-	-	-
Pruritis	-	-	-	-
Drowsiness	-	-	-	2(6.6%)
Dry mouth	-	-	-	-
Bleeding	-	-	-	-
Anxiety/agitation	-	-	-	1(3.3%)
Psychotic symptoms	-	-	-	-
Respiratory depression	-	-	-	-
Sweating	-	2(6.6%)	-	-

Table 3: Adverse drug effects.

In a study that assessed patients' postoperative pain experience and the status of acute pain management in a random sample, approximately 80% of patients said they experienced acute pain after surgery.

The authors concluded that; despite an increased focus on pain management programs and the development of new standards for pain management, many patients continue to experience intense pain after surgery [24]. To address the under treatment of postoperative pain and the limitations of opioid monotherapy, a strategy known as multimodal pain management was introduced in the early 1990s [25,26].

This approach simultaneously administers two or more analgesic agents with different mechanisms of action. Principles of a multimodal strategy include control of postoperative pain to allow early mobilization, early enteral nutrition and attenuation of the perioperative stress response through the use of regional anesthetic techniques and a combination of analgesic agents (i.e., multimodal analgesia) [27].

To achieve a maximum short-term and long-term benefits from multimodal analgesic therapies, the pain management would be initiated as a preventive in the preoperative period continued in the early postoperative period and extended into the postcharge period for 3-7 days [28,29].

In our study, control of post-operative pain was better with multimodal analgesia as compared to monotherapy.

Among the Multimodal groups, the combination of Pentazocine +Piroxicam achieved better control of post-operative pain and had longer duration of action as compared to the combination of Tramadol +Piroxicam. Among the Unimodal groups, Pentazocine had a longer duration of action and offers better pain control as compared to Tramadol.

The mean consumption of rescue analgesic (Inj.diclofenac) was lower in the Pentazocine+Piroxicam group compared to other groups. The incidence of adverse effects was higher with Pentazocine alone than Pentazocine+Piroxicam also higher in Tramadol alone than Tramadol+Piroxicam group.

The value of NSAIDs in minor, moderate, or severe postoperative pain is well documented [30,31], but their efficacy is too small to be the sole analgesic in more severe pain states, although they represent an ideal alternative component in the multimodal approach to postoperative pain treatment.

So far, only one such study is available. It demonstrates improved analgesia by fixed-dose combination with piroxicam and opioid after total hip replacement [32]. The combination of systemic NSAID with a central neural block with bupivacaine and/or opioids has been studied in major abdominal [33] and thoracic surgery [34], in which additional treatment with piroxicam 20-40 mg daily did not improve analgesia during rest, cough, or mobilization during an otherwise effective epidural low-dose bupivacaine-opioid regimen After cesarean section the combination of low-dose epidural morphine and intramuscular diclofenac provided analgesia superior to either drug alone [35].

Combination of systemic NSAID with intraarticular bupivacaine may reduce pain and analgesic requirements [36].

Limitations

The possible confounding influence of the spinal analgesia agent (bupivacaine) on the observed analgesic effects of all agents studied was a limitation of our study.

Conclusion

A multimodal approach combining pentazocine or tramadol with an NSAID, such as Piroxicam, offers better control of pain in the postoperative period than when the opioid is given alone.

Though Pentazocine offers better pain control and acts longer, it is associated with higher incidence of adverse effects compared to tramadol. However, the addition of an NSAID to opioid not only decreases the adverse effects but also has an opioid sparing action.

References

1. Pan PH (2006) Post cesarean delivery pain management: multimodal approach. Int J Obstet Anesth 15: 185-188.
2. American Society of Anesthesiologists Task Force on Acute Pain Management (2004) Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology 100: 1573-1581.
3. McCarberg B, Tenzer P (2013) Complexities in the pharmacologic management of osteoarthritis pain. Curr Med Res Opin 29: 539-548.
4. Mercadante S (2001) The use of anti-inflammatory drugs in cancer pain. Cancer Treat Rev 27: 51-61.
5. Schug SA (2007) The role of tramadol in current treatment strategies for musculoskeletal pain. Ther Clin Risk Manag 3: 717-723.
6. Vanderah TW (2007) Pathophysiology of pain. Med Clin North Am 91: 1-12.
7. Ashburn MA, Caplan RA, Carr DB (2004) Practice guidelines for acute pain management in the perioperative setting. An updated report by the American Society of Anesthesiologists task force on acute pain management. Anesthesiology 100: 1573-1581.
8. Kehlet H, Dahl JB (2003) Anaesthesia, surgery, and challenges in postoperative recovery. Lancet 362: 1921-1928.
9. Woolf CJ (2007) Central sensitization: uncovering the relation between pain and plasticity. Anesthesiology 106: 864-867.
10. Rawal N, Macquaire V, Catala E, Berti M, Costa R, et al. (2011) Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: a double-blind, double-dummy, randomized, parallel-group trial. J Pain Res 4: 103-110.
11. Raffa RB (2001) Pharmacology of oral combination analgesics: rational therapy for pain. J Clin Pharm Ther 26: 257-264.
12. Buvanendran A, Kroin JS (2009) Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 22: 588-593.
13. Garimella V, Cellini C (2013) Postoperative pain control. Clin Colon Rectal Surg 26: 191-196.
14. Brunton LL, Chabner BA, Knollmann BC (2011) Goodman and Gilman's The Pharmacological Basis of Therapeutics. (12thedn). New York, McGraw Hill.
15. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, et al. (1992) Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 260: 275-285.
16. [Authors not listed] (2005) Australian and New Zealand College of Anaesthetists (ANZCA). Acute Pain Management: Scientific Evidence. (2ndedn). Melbourne, Australian and New Zealand College of Anaesthetists.
17. Brogden RN, Speight TM, Avery GS (1973) Pentazocine: A Review of its Pharmacological Properties, Therapeutic Efficacy and Dependence Liability. Drugs 5: 6-91.
18. Brogden RN, Heel RC, Speight TM, Avery GS (1981) Piroxicam: A Review of its Pharmacological Properties and Therapeutic Efficacy. Drugs 22: 165-187.
19. Cepeda MS, Vargas L, Ortegon G, Sanchez M, Carr DB (1995) Comparative analgesic efficacy of patient-controlled analgesia with ketorolac versus morphine after elective intra-abdominal operations. Anesth Analg 80: 1150-1153.
20. Carr DB, Jacox AK, Chapman CR, Fields HL, Heidrich G, et al. (1992) Acute pain management: Operative or medical procedures and trauma, Clinical Practice Guideline. (950034thedn). Rockville, Agency for Health Care Policy and Research.
21. Brennan F, Carr DB, Cousins M (2007) Pain management: a fundamental human right. Anesth Analg 105: 205-221.
22. Kehlet H, Holte K (2001) Effect of postoperative analgesia on surgical outcome. Br J Anaesth 87: 62-72.
23. Kehlet H, Jensen TS, Woolf CJ (2006) Persistent postsurgical pain: risk factors and prevention. Lancet 367: 1618-1625.
24. Apfelbaum J, Chen C, Mehta S, Gan T (2003) Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 97: 534-540.
25. Kehlet H, Dahl JB (1993) The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 77: 1048-1056.
26. White PF (2008) Multimodal analgesia: its role in preventing postoperative pain. Curr Opin Investig Drugs 9: 76-82.
27. Ulufer Sivrikaya G (2012) Multimodal Analgesia for Postoperative Pain Management, Pain Management-Current Issues and Opinions.
28. Bisgaard T (2006) Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. Anesthesiology 104: 835-846.
29. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, et al. (2007) The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. Anesth Analg 104: 1380-1396.
30. Dahl JB, Kehlet H (1991) Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br J Anaesth 66: 703-712.
31. Mather LE (1992) Do the pharmacodynamics of the nonsteroidal anti-inflammatory drugs suggests a role in the management of postoperative pain? Drugs 44: 1-12.
32. Gore M, Sadosky A, Zlateva G, Clauw D (2010) Initial use of pregabalin, patterns of pain-related pharmacotherapy, and healthcare resource use among older patients with fibromyalgia. Am J Manag Care 16: S144-153.
33. Mogensen T, Vegger P, Jonsson T, Matzke AE, Lund C, et al. (1992) Systemic piroxicam as an adjunct to combined epidural bupivacaine and

morphine for postoperative pain relief--a double-blind study. Anesth Analg 74: 366-370.

34. Bigler D, Meller J, Kam-Jensen M, Berthelsen P, Hjortso NC, et al. (1992) Effect of piroxicam in addition to continuous thoracic epidural bupivacaine and morphine on postoperative pain and lung function after thoracotomy. Acta Anaesthesiol Scand 36: 647-650.

35. Sun HL, Wu CC, Lin MS, Chang CF, Mok MS (1992) Combination of low-dose epidural morphine and intramuscular diclofenac sodium in postcesarean analgesia. Anesth Analg 75: 64-68.

36. Smith I, Shively RA, White PF (1992) Effects of keterolac and bupivacaine on recovery after outpatient arthroscopy. Anesth Analg75: 208-212.