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Original Research Article

Use of Patient Controlled Analgesia Using I.V. Tramadol and I.V. Nalbuphine for Postoperative Pain Management after Major Abdominal Surgery - A Comparative Study

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ABSTRACT

Background & Objective: Postoperative pain relief is a major concern for reducing postoperative morbidity. Patient controlled analgesia is a better technique for pain relief and for avoidance of drug overdosing and abuse. Patient-controlled analgesia (PCA) is commonly assumed to imply on-demand, intermittent, IV administration of opioids under patient control (with or without a continuous background infusion). Tramadol and nalbuphine are two potent analgesic drugs with different mechanism of action in the central nervous system. Tramadol is a weak opioid agonist and is used in mild to moderate pain relief. Nalbuphine is a newer opioid drug with antagonism at μ receptor and agonism at κ receptor. The aim of this study was to compare the analgesic efficacy and side effects of these two drugs in PCA for postoperative pain relief.

Method: 80 patients ASA I and II, 40 patients in each group undergoing major abdominal surgery under general anaesthesia were allocated in these randomized, controlled, double blind study. They received either 10 mg tramadol or 2mg nalbuphine through PCA pump at complaint of pain. Pain assessment was done with visual analogue scale (VAS). Pain and sedation assessment was done at 30min, 3hrs, 6hrs, 15hrs, 18hrs, 21hrs, and 24hrs in postoperative period. Adverse effects and time of its occurrence, hemodynamic parameters, and respiratory rate were assessed for 24hrs. Vital parameters were monitored hourly for 24 hours.

Result: VAS score decreased with time in both groups. Mean VAS score at starting of PCA was 5±0.75 in Tramadol group and 4.775±0.69 in Nalbuphine group. The difference was not statistically significant. ($p>0.05$).After 30 mins mean VAS score was 3.8±0.79 in Tramadol group and 2.95±0.64 in Nalbuphine group. Both groups VAS score decreased with time but more in Nalbuphine group. The difference was statistically significant ($p<0.05$). Sedation score decreased throughout the study period. But mean sedation score was significantly more in nalbuphine group. Nausea was observed in 15% and 4% respectively in Tramadol group and Nalbuphine group. Vomiting was observed in 6% and 0% patients respectively in Tramadol group and Nalbuphine group. No other side effects were seen. The comparison of side effects between the two groups was statistically significant.($p<0.05$).

Conclusion: I.V. Nalbuphine bolus administered through PCA is better for postoperative pain management after major abdominal surgery.

Key words: Abdominal surgery, analgesia, post‑operative pain.

INTRODUCTION

Postoperative pain is undertreated for a number of reasons. These include lack of knowledge regarding effective dose ranges, duration of action of opioids, unfounded fear of respiratory depression and addiction in hospitalized patients experiencing pain. The untreated post operative pain may result in altered physiological and psychological changes that increase morbidity and mortality in patients. Through the use of currently available knowledge, drugs, technique well known to anaesthesiologists, effective analgesia for most patients with postoperative pain are possible. Our study was done to find out the efficacy of patient controlled analgesia technique by using PCA pump.

Patient-controlled analgesia (PCA) is commonly assumed to imply on-demand, intermittent, IV administration of opioids under patient control (with or without a continuous background infusion) (GRASS J.A.2005). This technique is based on the use of a sophisticated microprocessor-controlled infusion pump that delivers a pre-programmed dose of opioid when the patient pushes a demand button. The broader concept of PCA is not restricted to a single route or mode of administration. Nor should PCA imply the mandatory presence of a sophisticated and expensive infusion device. Any analgesic given by any route of delivery (i.e., oral, subcutaneous, epidural, peripheral nerve catheter, or transdermal) can be considered PCA if administered on immediate patient demand in sufficient quantities.

Compared to periodic administration, PCA generally results in less total opioid use with more satisfactory pain control. More commonly used drugs morphine & fentanyl are not available in our institute easily. So we use tramadol and nalbuphine in PCA for postoperative pain relief.

Pain perception mainly through Mu and Kappa type opioid receptors Mu (μ) receptors are found primarily in the brainstem and medial thalamus. Mu receptors are responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility, and physical dependence. Subtypes include Mu1 and Mu2; with Mu1 related to analgesia, euphoria, and serenity, while Mu2 is related to respiratory depression, pruritus, prolactin release, dependence, anorexia, and sedation. These are also called OP3 or MOR (morphine opioid receptors). Kappa (κ) receptors are found in the limbic and other diencephalic areas, brain stem, and spinal cord, and are responsible for spinal and analgesia, sedation, dyspnea, dependence, dysphoria, and respiratory depression. These are also known as OP2 or KOR (kappa opioid receptors).Tramadol and nalbuphine act on different types of opioid receptors.

Tramadol is a centrally-acting analgesic with opioid and non-opioid analgesic mechanisms. Tramadol binds to the μ receptor approximately 6000-fold less than morphine and has a weaker affinity for the κ- and σ-receptors. Tramadol and its O-desmethyl metabolite (M1) are selective, but weak OP3-receptor agonists. The opioid-like activity of tramadol derives from low affinity binding of the parent compound to μ-opioid receptors and higher affinity binding of its main metabolite. The analgesic properties of tramadol can also be attributed to norepinephrine and serotonin reuptake blockade in the CNS, which inhibits pain transmission in the spinal cord. Unlike nonsteroidal anti-inflammatory drugs, tramadol has no serious adverse gastrointestinal effects, and renal toxicity. Efficacy of tramadol is not associated with the usual serious opioid side effects which can often be dose-limiting. Respiratory depression with tramadol is less pronounced, when compared to equianalgesic doses of morphine. However, respiratory depression can occur, in particular with overdose. Another opioid side effect, which is reduced with tramadol use, is constipation. Tramadol doesn't elicit histamine release. Tramadol is considered as

hemodynamically stable drug. Only transient increase in blood pressure and systemic vascular resistance is observed immediately after IV injection. Numerous clinical trials have proven its efficacy and safety over a broad range of painful conditions, both acute and chronic; however, in severe pain morphine may be superior to tramadol.

Nalbuphine is an agonist at κ receptors and weak agonist and antagonist at μ receptor. It is without significant effects on delta receptor. Nalbuphine has the potential to maintain or even enhance mu-opioid based analgesia while simultaneously mitigating the common mu-opioid side effects.

Nalbuphine elicits analgesia through a complex interaction of supraspinal κ3 and spinal κ1 mechanisms. Nalbuphine acts primarily at the level of the first synapse in the nociceptive system in producing analgesia.Comparative trials have shown that both nalbuphine and morphine are equally effective on pain relief. At usual therapeutic doses it has a respiratory depressant action equivalent to that of morphine. But ceiling effect to both respiratory depressant and the analgesic action starts at single dose of 20-30mg. The respiratory depression may be reversed by naloxone. Other opioid effects-Include miosis and sedation, less commonly nausea, vomiting constipation and psychotomimetic effects. It has minimal haemodynamic effects. Abuse potential is much less when compared to morphine.

Aims and objectives of our study was

- To compare analgesic efficacy of I.V. Tramadol and I.V. Nalbuphine in patient controlled analgesia , in terms of:
  - Pain score and sedation
  - PCA use
  - Overall patient satisfaction
  - Adverse effects
  - Changes in hemodynamic parameters

Patients and Method:

Formula-Z^2pq/L^2

Confidence limit-95%

Z=1.96

p value- 20%

Two sided

p=anticipated proportion

Allowable error of p (L)-5%

According to this formula sample size was 64, but for convenience in statistical analysis we took 80 patients, 40 patients in each group. Similar sample sizes were taken in previous studies also.

It was a prospective, randomized, double blind study with sample size of 80 patients. 40 patients were allocated in each group. Group T: was received I/V Tramadol (10 mg bolus dose in concentration of 5mg/ml, lockout interval 10 min)

Group N: was received I/V Nalbuphine (2mg bolus dose in concentration of 1.5 mg/ml lock out interval 10 min). Patients of age group 20-60yrs ASA grade I, II, undergoing major abdominal surgery were included.

Criteria for Exclusion were Patient refusal, inability to use PCA, liver or kidney disease, history of substance abuse, history of Peptic ulcer disease, History of convulsions, Patient on anti-epileptic medication, Bleeding disorders, Allergy to the drug used, pregnancy and psychiatric disorders involving the use of MAO inhibitors or SSRI.

METHODOLOGY

After approval from the institutional ethical committee, informed and written consent was obtained from all the patients & use of PCA for postoperative pain relief was explained as well as the use of Visual analogue scale (VAS) graded from 0cm (no pain) to 10 cm (maximum pain). All the patients were assessed pre-operatively that includes complete history, clinical examination and recording of vital parameters along with routine and special investigations, if required. All the patients were kept nil orally overnight.

Upon arrival in operation theatre, the patients were lie supine on the operating table, a peripheral vein was cannulated and slow infusion of Ringer lactate was

commenced. Multipara monitor with noninvasive sphygmomanometer, ECG monitor, pulse oximeter were attached and baseline HR, ECG, Systolic & diastolic blood pressure, RR, Temp were monitored.

All patients were premedicated with i.v. glycopyrrolate 0.004 mg/kg, i.v. Midazolam 0.05 mg/kg and pentazocine 0.5mg/kg prior to induction. No local anaesthesia, antiemetics or NSAIDs was used 24 hours before or during surgery.

All patients were randomly allocated to one of the two groups (Group T and Group N) of 40 patients each, applying block randomization.

General anaesthesia was induced using a combination of thiopental and muscle relaxant (Atracurium) and maintained with Isoflurane in a mixture of 60% nitrous oxide in 40% oxygen. All patients were received study drug (either nalbuphine 200 mcg/kg or tramadol 1mg/kg) before the closure of surgery. At the end of surgery, muscle relaxation was reversed with neostigmine 2.5 mg i.v. and glycopyrrolate 0.4 mg i.v and patients were extubated and returned to the recovery unit where they remained for the duration of study.

In postoperative period, they were further reminded how to use PCA. Analgesic solution was connected to PCA & different groups were given their respective drugs:

Group T: was received i.v. Tramadol (10 mg bolus dose in concentration of 5mg/ml, lockout interval 10 min)

Group N: was received i.v. Nalbuphine (2 mg bolus dose lock out interval 10 min)

VAS at rest was assessed every 3 hours for 24 hours observation period. Sedation score was assessed using sedation scale for the same period. For rescue analgesia i.v. paracetamol infusion 1g was given.

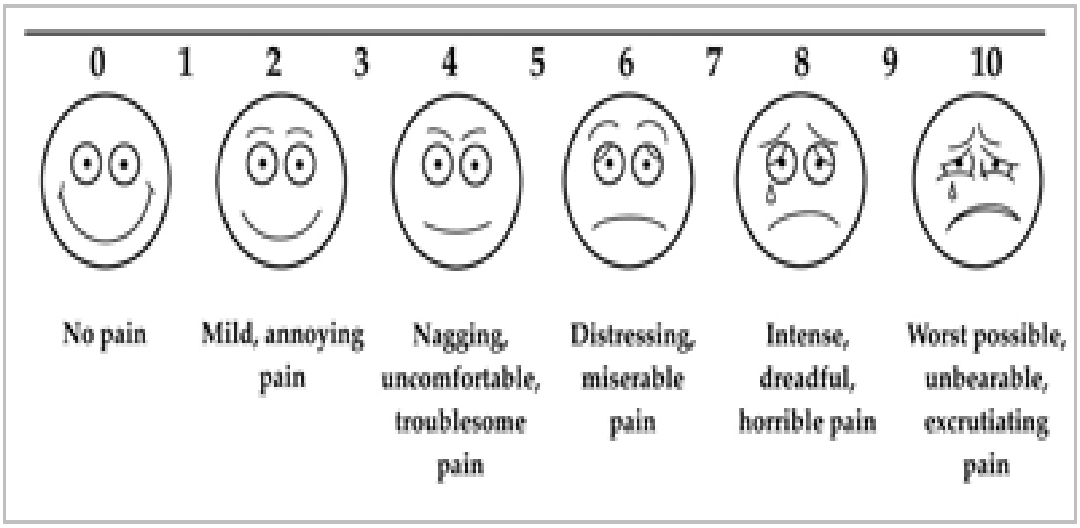
Adverse reactions were promptly and adequately treated. For nausea and vomiting (i.v. Metoclopramide 0.25mg/kg), pruritus (i.v. Promethazine 0.5-1mg/kg), seizures (diazepam 0.5-1mg/kg as needed) and respiratory depression (respiratory rate below 10/min) treated with incremental doses of naloxone (0.5-1µg/kg) as required.

Monitoring and Evaluation:

At postoperative period 0-24hr

1. **ANALGESIC EFFECTS**
   - VAS at rest every 3hrly

VISUAL ANALOGUE SCALE



- Number of doses & total dose required

Overall patient satisfaction

Degree of overall satisfaction of patient:

Overall satisfaction of patients were assessed using following grade

- Grade0= poor
- Grade1= adequate
- Grade2= good
- Grade3= excellent

2. **SEDATION**

Sedation scale:

0=alert

1=mildly drowsy/easy to arouse

2=somnolent/difficult to arouse

3=asleep

3. HEMODYNAMIC CHANGES

4. ADVERSE EFFECTS

Nausea/vomiting, Pruritus, Dizziness, Requirement of rescue agents, Treatment failure, insufficient analgesia, Hypotension, Allergic reaction, Bronchospasm, Unconsciousness, Respiratory depression

Method of Statistical Analysis

The following methods of statistical analysis have been used in this study. The Excel and Graphpad instat 3 software packages were used for data entry and analysis. The results were averaged (mean +standard deviation) for each parameter for continuous data and numbers and percentage for categorical data presented in Table and figure. The observed parameters were tabulated & statistically analyzed using graph pad instat software with *relevant* test.VAS, Sedation score and Hemodynamic parameters were analysed with the Student t-test. Fisher exact was applied for adverse effects. Chi square test was applied for distribution of sedation. In all the above tests a "p" value of less than 0.05 was accepted as indicating statistical significance.

GROUPING ACCORDING TO PATIENT DISTRIBUTION

Patients were divided into two groups of 40 patients each. According to previous studies nalbuphine and tramadol in 1:5 was equianalgesic so we used nalbuphine and tramadol in a ratio of 1:5. Group T received Tramadol 1mg/kg i.v. and Group N received nalbuphine 0.2 mg/kg before the closure of surgery. In postoperative period, either 10 mg tramadol bolus or 2 mg nalbuphine bolus delivered through PCA pump at the complaints of pain.

DEMOGRAPHIC PROFILE

Age, sex and type of surgery affect the analgesic efficacy of tramadol and nalbuphine. Analgesic requirement is more after major abdominal surgery than orthopaedic surgery. In children, nalbuphine metabolism is faster. We choose 20-60 yrs age group patients. Patients in the two groups were of the age group of 20-60 years of either sex. Maximum numbers of patients (26 in group T; 20 in group N) were in the age group of 20-40 years. In Group T 22 patients were male and 18 were female and Group N 20 patients were male and 20 were female. The difference was not statistically significant ($p>0.05$). Mean weight of the patients in group T was 55.125±4.45 kgs and in group N was 55.10±4.534 kgs. Mean height of the patients in group T was 156.38±3.807 cm and in group N was 156.33±4.932 cm. There were no statistically significant differences ($p>0.05$).

VAS SCORE

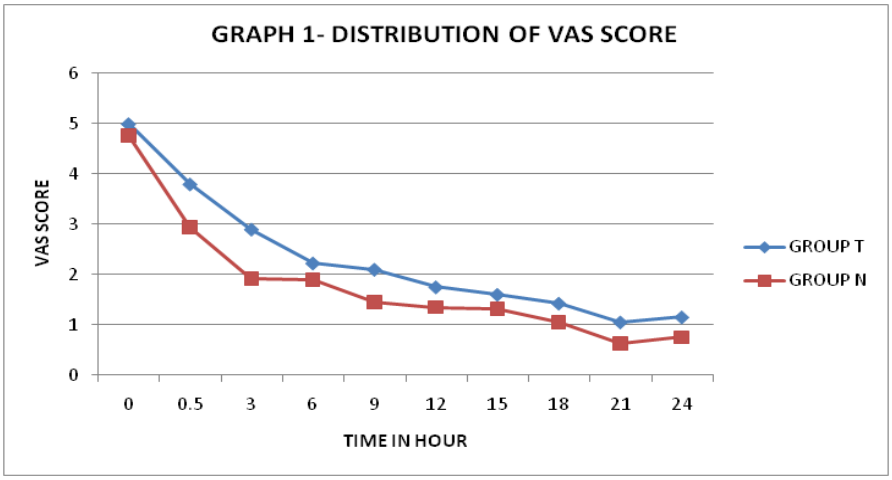
Table-1, Graph-1shows distribution of VAS score. Mean VAS score at the start of PCA was 5±0.75 in group T and 4.775±0.69 in group N. The difference was not statistically significant. ($p>0.05$). VAS score decreased with time in both the groups. After 30 mins, mean VAS score was 3.8±0.79 in group T and 2.95±0.64 in group N. The difference was highly significant. ($p<0.05$).All patients were respondents as VAS score decreased after medication within 30 min. VAS score at 3,6,9,12,15,18,21,24 hrs was 2.9±07, 2.225±0.65, 2.1±0.63, 1.75±0.43, 1.60±0.49, 1.425±0.63, 1.05±0.71, 1.15±0.66 in tramadol group versus 1.925±0.52, 1.9±0.81, 1.45±0.50, 1.35±0.48, 1.325±0.47, 1.05±0.59, 0.625±0.49, 0.75±0.588 in nalbuphine group. In both groups VAS score decreased with time, but the drop in VAS score was more in group N. The difference was statistically significant. ($p<0.05$). There was no case of failure of analgesia in either group as evident by the fact that no patients requested the rescue analgesic paracetamol infusion at any point of the study.

Pain relief was significant in Nalbuphine group throughout the study period. VAS score was 1.15±0.66 in

tramadol group and 0.75±0.588 in nalbuphine group after 24 hrs. Patients in nalbuphine group complained of no pain or very low pain at the end of study.

Table 1: Distribution of Vas Score

	Group T			Group N			
Time (hr)	Mean	SD	SE	Mean	SD	SE	p-Value
0	5	0.75	0.1188	4.775	0.69	0.1103	0.1690
0.5	3.8	0.79	0.125	2.95	0.64	0.10	0.0001ext s
3	2.900	0.67	0.1062	1.925	0.52	0.0831	0.0001ext s
6	2.225	0.659	0.104	1.9	0.81	0.128	0.0527S
9	2.1	0.632	0.1	1.45	0.503	0.0796	0.001ext s
12	1.750	0.438	0.069	1.35	0.483	0.0763	0.0002 ext s
15	1.60	0.4961	0,0784	1.325	0.4743	0.075	0.0133
18	1.425	0.636	0.1006	1.05	0.597	0.094	0.0081
21	1.05	0.7143	0.1129	0.625	0.4903	0.07752	0.0021S
24	1.15	0.66	0.1047	0.75	0.588	0.093	0.005 S

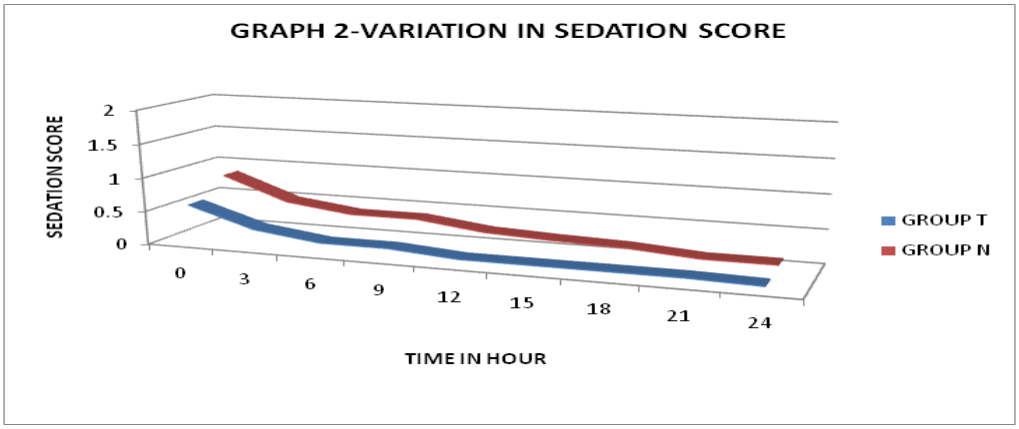


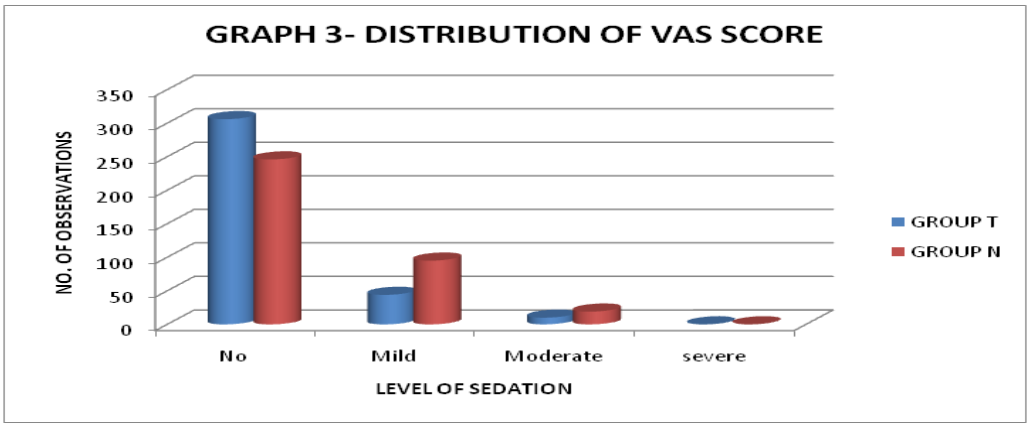
SEDATION SCORE

Table-2, Graph-2 and 3 shows variation and distribution in sedation score. Sedation score decreased throughout the study period. But mean sedation score was significantly greater in nalbuphine group at 3hr, 6hr, 9hr, 12hr, 15hr, 18hr. Sedation score at 0, 3, 6, 9, 12, 15, 18, 21, 24 hrs was 0.575±0.84, 0.275±0.45, 0.15±0.361, 0.15±0.361, 0.075±0.24, 0.075±0.24, 0.075±0.24, 0.075±0.24, 0.05±0.22 versus 0.85±0.92, 0.5±0.506, 0.375±0.545, 0.375±0.587, 0.25±0.43, 0.205±0.4, 0.175±0.38, 0.1±0.3, 0.1±0.3. Sedation score was greater in nalbuphine group at 3hr, 6hr, 9hr, 12hr, 15hr, 18hr, which was statistically significant. ($p<0.05$) Out of a Total of 360 observations in group T, 306 (85%) were awake, 44(12.5) were mild drowsiness and 10(2.7%) were moderate drowsiness. Out of 360 observations in group N, 246 (68.33%) were awake, 95(26.3%) were mild drowsiness and 19(5.2%) were moderate drowsiness. Severe drowsiness or a sleep condition was not seen in any patient.

Table 2: Distribution of Sedation Score

	GROUP T			GROUP N			P value
Time in hr	Mean	SD	SE	Mean	SD	SE	
0	0.575	0.84	0.13	0.85	0.92	0.14	0.16
3	0.275	0.45	0.07	0.5	0.506	0.08	0.03
6	0.15	0.361	0.05	0.375	0.545	0.08	0.031
9	0.15	0.361	0.05	0.375	0.587	0.09	0.04
12	0.075	0.24	0.042	0.25	0.438	0.069	0.034
15	0.075	0.24	0.042	0.205	0.40	0.065	0.038
18	0.075	0.24	0.042	0.175	0.38	0.06	0.018
21	0.075	0.24	0.042	0.100	0.30	0.048	0.69
24	0.05	0.220	0.035	0.100	0.30	0.048	0.3979



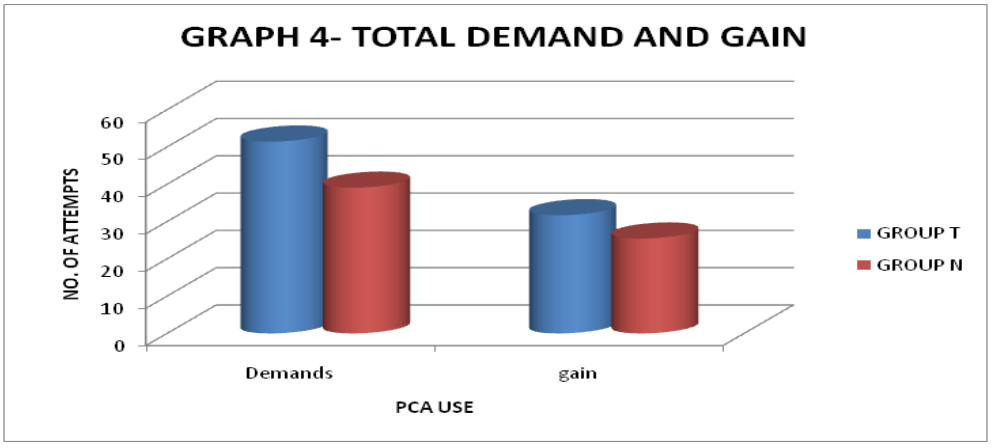


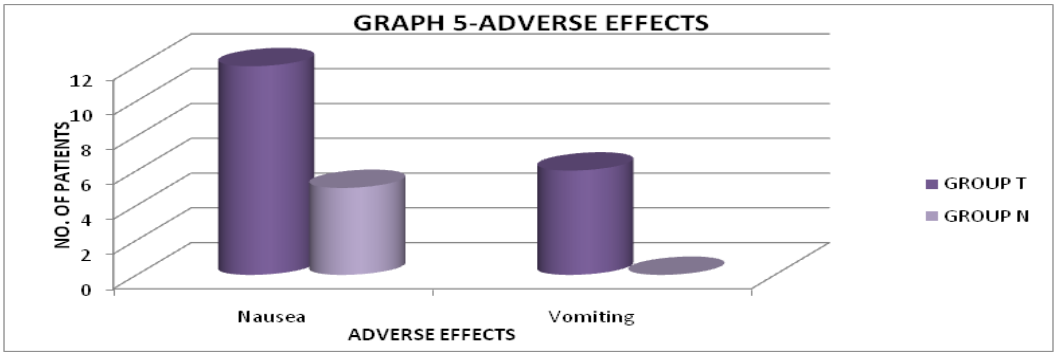
TOTAL DEMANDS AND GAIN IN PCA USE

Graph-4 shows demands and gain in PCA use. Total numbers of demands were 51.436±436 in group T Vs 39.077±3.390 in group N. The difference was statistically significant. ($p<0.05$).Total number of gain were 31.692±3.294 in group T Vs 25.436±2.634 in group N. The difference was statistically significant ($p<0.05$). Both total number of demand and gain were lesser in group N. (Graph-4)

Adverse effects-

Graph -5 shows adverse effect between the groups. No serious side effects were seen. Nausea was observed in 15% and 4% respectively in group T and N. Vomiting was observed in 6% and 0% patients respectively in group T and N. No other side effects were seen. The comparison of side effects between the two groups were statistically significant ($p<0.05$). (Graph-5)





Hemodynamic parameter, RR and SpO_2

HR, SBP, DBP, RR and SpO_2 of patients were comparable in both groups throughout the study period. There was no statistically significant difference ($p>0.05$).

Patient satisfaction-

Table-3 shows patient satisfaction among group members.Overall patient satisfaction among groups.Most of the patients were satisfied with PCA use.30 patients (75%) in group T and 34 patients(85%) claimed excellent the technique of adminstration of drug by using PCA pump

Table 3: Overall Patient Satisfaction

Grade	GROUP T	GROUP N
0	00	00
1	2	1
2	8	5
3	30	34

DISCUSSION

Postoperative pain is a major concern for an anaesthetist. All the medications which are used for analgesia can also be use for drug abuse. Through the use of currently available knowledge, drugs, technique well known to anaesthesiologists, effective analgesia for most patients with postoperative pain are possible. Our study was done to find out the efficacy of patient controlled analgesia technique by using PCA pump using drug tramadol and nalbuphine.

During study we found that Pain relief was significant in Nalbuphine group throughout the study period. VAS score was 1.15±0.66 in tramadol group and 0.75±0.588 in nalbuphine group after 24 hrs. Patients in nalbuphine group complained of no pain or very low pain at the end of study. All patients were respondents as VAS score decreased after medication within 30 min. This was due to fastest onset of action of both drugs. But Tramadol had slower onset of action than nalbuphine because the opioid agonist action in humans was mediated through the o-demethylated metabolite MI and not tramadol itself. Kamath S.S. et al (2013) also in their study observed that VAS score was significantly lower in nalbuphine group till 8 hrs. Alon E.et al (1992) in their study observed that there was no significant difference between tramadol and nalbuphine group. In postoperative period VAS score decreased from 7.14 ±3.45 to 2.03 ± 1.25 in nalbuphine group and 7.81 ±2.85 to 1.57 ± 1.40 in tramadol group. But general well being of the patients on a 4 point scale was significantly better in the nalbuphine group after 45, 60 and 90 minutes. The results were similar to our study. Vandenberg A.A. et al (2006) in their study observed that nalbuphine was better than tramadol for postoperative pain relief in children. Restlessness-pain score was significantly lower in nalbuphine group. The results were similar to our study. Siddiqui K.M. et al (2007) in their study observed that nalbuphine had a better early postoperative recovery with better pain control in comparison with tramadol. In nalbuphine group, 80% of patients had no pain and 19% patients had mild pain, whereas 51% had no pain and 48% had mild pain in tramadol group. The results were similar to our study.

Garcia D.M.et al (2009) and Barsoum M.D. (1995) in their study observed that tramadol was better analgesic than nalbuphine for postoperative pain relief

in children. In children contradictory results may be due to shorter half life and larger volume of distribution (Vd) of nalbuphine in children.

Thus the results of our study are comparable to those of Kamath S.S. et al (2013), Alon E.et al (1992), Siddiqui K.M. et al (2007). In controlled studies, parenteral nalbuphine (NB) was found to be 0.8-0.9 times as potent as parenteral morphine sulphate (MS). Comparison of intravenous patient-controlled analgesia with tramadol (T) vs. Morphine in female patients undergoing reconstructive breast surgery resulted in the potency ratio estimate of 1:11 (MS: T). Better analgesic efficacy of nalbuphine can be explained by comparatively higher potency.

Sedation score was greater in nalbuphine group at 3hr, 6hr, 9hr, 12hr, 15hr, 18 hr, which was statistically significant. As postoperative period is a stressful period this mild to moderate sedative effect of nalbuphine can be beneficial to patient. Also, at no occasion did the severity of sedation evoke concern on the possibility of the patient going into respiratory depression. Such sedation relieves surgery related anxiety, provides the much needed comfort for a post-operative patient and should therefore be considered a beneficial effect of the nalbuphine.

No serious side effects were seen. Nausea was observed in 15% and 4% respectively in group T and N. Vomiting was observed in 6% and 0% patients respectively in group T and N. No other side effects were seen. The comparisons of side effects between the two groups were statistically significant. ($p<0.05$).A higher incidence of nausea and vomiting was observed in tramadol group patients. Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla possibly through delta receptors, leading to nausea and vomiting. Early post operative nausea and vomiting (PONV) is a known entity caused by various factors including pain itself. Surgical causes of nausea and vomiting, type and duration of surgery and other unidentified factors might have contributed to this adverse effect. A significantly lower incidence of nausea and vomiting was observed with nalbuphine. HR, SBP, DBP, RR and SpO_2 of patients were comparable in both groups throughout the study period. There was no statistically significant difference ($p>0.05$).

CONCLUSION

To conclude our study, i.v. nalbuphine administered as bolus dose in PCA is better for postoperative pain management after major abdominal surgery. Nalbuphine provide hemodynamic stability, good sedation and significantly lower incidence of nausea and vomiting.

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