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Pain Management of Patients under General Anaesthesia Nalbuphine Alone or Nalbuphine with Ketorolac

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ABSTRACT

Objective: To compare the efficacy of Nalbuphine alone versus Nalbuphine with Ketorolac for the management of pain in for open cholecystectomy under general anaesthesia.

Study Design: Comparative prospective study.

Place and Duration of Study: Anaesthesia department of CMH, Okara Cantt Pakistan, June 2019- March 2020.

Methodology: Patients were divided into two Groups by the lottery method, Group-A, Nalbuphine (.12milligram/kilogram) and Group-B (Nalbuphine .06millig/kilogram+ Ketorolac 15milligram).They were all given standard anesthetic drugs and analgesics in above mentioned dose at the start of surgery. Patients were assessed regarding postoperative pain intensity using the Numerical Pain Rating Scale at 5minute, 30 minutes and 1 hour after shifting to recovery. Rescue analgesia for moderate to severe pain at 30 minutes was documented. Nausea, vomiting and sedation were also noted in both groups.

Results: Sedation in Group A was 8(10.7%) as compared in Group-B 4(5.3%).The frequency of nausea and vomiting in Group A and Group-B was 6(8.0%), 4(5.3%), and 5(6.7%), 2(2.7%) respectively. Rescue analgesia being lower in Group-A compared to Group-B which was statistically significant, for moderate to severe pain at 30 minutes after shifting. Group-A 10(13.3%) of cases while Group-B 55(73.3%) of cases producing p-value 0.001.A statistically significant difference regarding pain score between both groups, *p*-value <0.001.

Conclusion: Intravenous Nalbuphine (0.12 mg/kg) was more effective in reducing pain intensity and postoperative analgesic requirements after surgery as compared to Nalbuphine (.6mg/kg)+ Ketorolac (15mg) in combination.

Keywords: Ketorolac, Nalbuphine, Non steroidal anti inflammatory drugs (NSAIDs), Pain score.

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INTRODUCTION

Pain is a complex and important protective phenomenon. Adequate intra and postoperative pain relief is of utmost importance, as it reduces patient's distress and ensures a rapid, uncomplicated recovery after general anaesthesia.[1]

Although opioids are widely used in pain management, their side effects, especially respiratory depression, bradycardia, nausea and vomiting have restricted their use. Non-steroidal anti-inflammatory drugs (NSAIDs) have widely been used with very good results in pain reduction and postoperative analgesia requirements.[2]

The semi-synthetic opioid analgesic, Nalbuphine belongs to the phenanthrene family. Although Nalbuphine possesses opioid antagonist activity, there is evidence that in nondependent patients it will not antagonize an opioid analgesic administered just before, concurrently, or just after an injection.[3] When used concomitantly with Nalbuphine the administered opioid analgesic, general anesthetics, tranquilizers, phenothiazines, hypnotics, sedatives and other CNS depressants may exhibit an additive effect. In such scenario of combined therapy contemplation ,dose of one or both agents should be reduced.[4]

Nalbuphine is commonly used drug for per-operative pain management and is associated with certain side effects such as emesis, sedation, central nervous system depression, and pruritus due to its effect on μ2 receptors.[4]

NSAIDs act on prostaglandin synthesis for pain reduction but have certain adverse effects such as bleeding problems in both gastrointestinal tracts and from the surgical site and potential renal dysfunction that have caused some concerns in their widespread application.[5] Ketorolac is a non-steroidal anti-inflammatory drug that has high analgesic potency

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comparable to opioids, for various surgical procedures intra and postoperatively.[5]

Ketorolac is used for treating moderate to severe pain relief or when combined with opoids helps to reduce the opioid dosage. This combination results is the reduction of opioid side effects such as nausea, sedation, central nervous system depression, and urinary retention.[6]

Rationale of this study was to assess the efficacy of Nalbuphine (0.12mg/kg) alone verses Nalbuphine (0.06mg/kg)+Ketorolac (15mg) for the pain management and optimal intraoperative pain control in adults undergoing surgery under general anaesthesia and to determine postoperative re use analgesics.

METHODOLOGY

The comparative prospective study was conducted after Hospital Ethical Committee approval (IERC/Anaes/ 2020/02), at the Anaesthesia department of Combined Military Hospital Okara Cantt Pakistan, from June 2019 to March 2020 for 10 months. Sample size of 150 cases (75 patients in each Group A and B) was calculated, using WHO sample size calculator. Keeping 85% statistical power at a 5% level of significance,[2] taking the expected proportions of patients undergoing open cholecystectomy requiring rescue analgesics to be 25% in the Group A and 8.3% in the Group B. It was non probability consecutive sampling.

Inclusion Criteria: All elective cases, ages between 20 and 40 years, planned for open cholecy-stectomy under general anaesthesia, with ASA class I and II were inlcuded.

Exclusion Criteria: Patients already taking analgesics, emergency cases, ASA Grade ≥ 3, or with any sort of respiratory, cardiovascular, or neurological disorder were excluded from the study.

All of the patients were drawn from the elective list of our hospital who underwent open cholecystectomy. They were visited day before surgery and entire procedure was explained to the patient, informed written consent was obtained. Complete history regarding systemic diseases, bleeding disorders, drug intake, drug allergies or sensitivity and previous anesthetic experience was taken. Complete general physical examination including airway evaluation, cardiac and chest auscultation was conducted. Laboratory evaluation, complete blood count (CBC); ECG; X ray chest; liver function tests; renal function tests; Hepatitis screening. All patients fasted for an appropriate period of 6 hours for food and 4 hours for water). Upon arrival at the operating theatre, IV access was established by 18 G cannula insertion.

Patients were allocated into respective Groups using the lottery method, Nalbuphine 0.12mg/kg (Group A); and Nalbuphine 0.06mg/kg+ Ketorolac 15mg (Group B), they were all administered standard anesthetics, propofol (1.5–2.0 mg/kg) for induction, Atracurium (0.5mg/kg) was used for endotracheal intubation. General anesthesia was maintained with low-flow oxygen (0.5–1.0 L/min) plus 2% sevoflurane. Atracurium 0.1 mg/kg was used for maintenance of general anesthesia. The standard class II general anesthesia monitoring was applied (three-lead electrocardiograph , pulse oximetry anh heart rate and NIBP (non invasive blood pressure.). Neuromuscular blockade was reversed with neopyrolate and the patients were extubated.

Nalbuphine (0.12 mg/kg) or Nalbuphine (0.06mg /kg)+Ketorolac (15mg) was administered to patients at the start of operation. Patients were assessed for postoperative pain intensity using the Numerical Pain Rating Scale, Figure-1 at 5 mins, 30 mins and 1 hour after shifting to recovery room, by an on-duty doctor who was unaware of the drugs regimen used. According to pain scale 0-3 denotes mild, 4-6 moderate and 7-10 is severe pain.

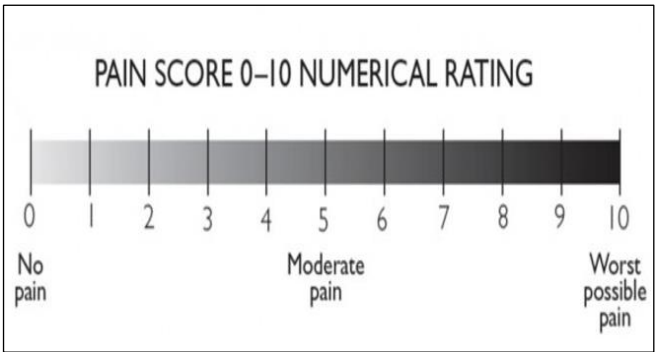

Figure-1: Numerical Pain Rating Scale

They also assessed patients for Postoperative seda-tion, using Richmond Agitation sedation scale (RASS) Figure-2. Patients with pain scores ≥4 were given paracetamol (10 mg/kg), which was then documented. Other side effects like nausea, vomiting and sedation were recorded. If the pain didn't settled after parace-tamol, Reuse of analgesia Nalbuphine (0.12 mg/kg) for pain scores ≥4 are given at 30 mins and was also noted. After 1 hour of observing patient in recovery and repeat assessment by a senior

Anesthetist of duty team, patients were shifted to their respective wards.

Data were analyzed using the SPSS version 22. For quantitative variable such as age, mean and standard deviation was calculated. For qualitative variables, like gender, sedation, nausea, vomiting, pain score and reuse analgesia; frequencies and percentages were calculated. Pain score in both Groups at 5, 30 mins and 1hour after shifting to the recovery room and reuse analgesia Nalbuphine (0.12 mg/kg) for moderate to severe pain with pain scores ≥ 4 -10 at 30 mins in both Groups was compared using the chi-square test. The *p* value ≤ 0.05 was taken significant.

RESULTS

Total of 150 patients were assessed ,75 in each Group A (Nablbupine alone) and Group B (Nalbupine + Ketarolac). Mean age in Group A was 30.18±6.7 years and in Group B it was 33.61±4.7 years. Frequency of male and female patients in Group A was 60(80%) and 15(20%) and in Group B it was 33(44%) and 42(56%) respectively. There was more sedation in Group A 8(10.7%) as compared in Group B 4(5.3%).

Table-I: Richmond Agitation Sedation Scale (RASS) (n=150)

Score	Term
+4	Combative
+3	Very Agitated
+2	Agigated
+1	Restless
0	Alert & Calm
-1	Drowsy
-2	Light Sedation
-3	Moderate Sedation
-4	Deep Sedation
-5	Unarousable Sedation

The frequency of nausea and vomiting in Group A was 6(8.0%) and 4(5.3%) and in Group B was 5(6.7%) and 2(2.7%) respectively. There was a significant difference concerning the reuse analgesia Nalbuphine (0.12 mg/kg) , being lower in Group A compared to Group B which was statistically significant, for pain score ≥ 4 at 30 mins after shifting in the recovery room in Group A is n10 (13.3%) of cases while Group B is n 55(73.3%) of cases, producing *p*-value 0.000. Percentage of rescue analgesia is shown in Figure-2.

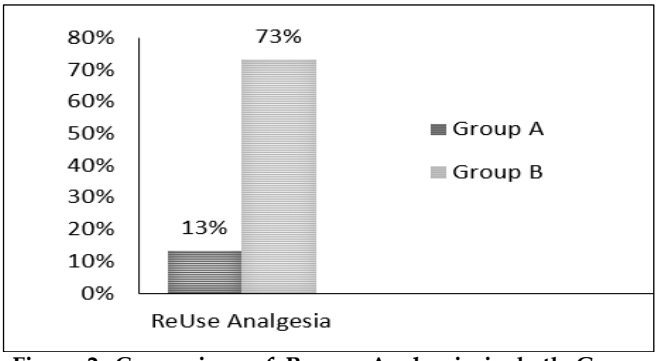

Figure-2: Comparison of Rescue Analgesia in both Groups (n=150)

There was a statistically significant difference concerning pain score between Group A and Group B, pvalue <0.001. Comparison of pain score as no pain, mild, moderate and severe in both Groups at 5 min,30 min and 1 hour after shifting to the recovery room is shown in Table-II.

DISCUSSION

Postoperative pain management in patients undergoing general anaesthesia is an important, but significantly understudied. Numerous options for acute post-surgical pain management are being introduced. The severity of pain ranging from moderate to severe in acute post-operative patients is 15–60%.[7]

Different trials have compared narcotic analgesics, nonsteroidal anti-inflammatory drug (NSAID), and neuro axial drugs and blocks.[8] For acute post-surgical pain management after major surgeries, narcotic analgesics are most commonly used. Among them Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain, it has less respiratory side effects as compared to other opioids.[9] Ketorolac decreases production of prost-aglandin by blocking cyclooxygenase 1 and 2 (COX1 and COX2).[10]

Table-II: Pain Score in both Groups (n=150)

	Group-A (Nalbuphine)			Group-B (Nalbuphine + Ketorolac)		
	Pain 5mins	Pain30mins	Pain1 hour	Pain 5mins	Pain 30mins	Pain 1hour
No pain	30(40%)	30(40%)	30(40%)	5(6.7%)	5(6.7%)	5(6.7%)
Mild pain	35(46.7%)	35(46.7%)	45(65%)	15(20%)	15(20%)	70(93.3%)
Moderate pain	5(6.7%)	10(13.3%)	-	20(26.7%)	55(73.3%)	-
Severe pain	5(6.7%)	-	-	35(46.7%)	-	-

*Data expressed as Mean±(SD); *p-value <0.05*

Many studies assessed different routes and drug regimens for adequate analgesia.[11] In contrast with our study Forrest *et al.* reported that Ketorolac was superior to opioid analgesics for controlling post-tonsillectomy pain. This was due to decrease rates of nausea, vomiting, sedation, and central nervous system depression.[12]

In disagreement with our study, Tarkkila and Saarnivaara compared Ketorolac, ketoprofen, and diclofenac for post operative pain management after elective tonsillectomy. They reported lesser use of opioid and improved pain control.[13] These findings were contrary to our results.

According to Carney *et al*. Ketorolac decreased the use of opioids and postoperative morbidity. The incidence of bleeding and kidney injury didn't increased with Ketorolac as compared to morphine.[14]

Shende and Das reported good analgesia and decreased emesis while using Ketorolac.[15]

Moyao-Garcia found that tramadol was significantly better than Nalbuphine for the management of APSP in children after inguinal herniotomy.[16]

Amir H compared the efficacy of Ketorolac and pethidine for postoperative pain relief in the first 24 hours after tonsillectomy. 100 patients between age Group 5-12 years under going tonsillectomy, who received either inj. Ketorolac 0.5 mg/kg or inj. Pethidine 1 mg/kg. M postoperatively on 6 hourly bases. Patients were assessed in the recovery room and ward for pain according to pain scale and also for any side effects. Amount of rescue analgesia required by both Groups was also recorded. They concluded that ketorolac provides similar analgesic effects as pethidine=' in the doses mentioned above with much less incidence of nausea, vomiting and drowsiness in the first 24 hours post adenotonsillectomy.[17]

In our study, we concluded that patients had less pain in Group A mild pain 5(6.7%) as compared to Group B 35(46.7%) one hour postoperatively. Rescue analgesia Nalbuphine (0.12 mg/kg) was given to less number of patients in Group A 10 (13.3%) compared to Group B 55 (73.3%) which was statistically significant. So intravenous Nalbuphine (0.12 mg/kg) in Group A reduces postoperative analgesic requirements more efficiently alone as compared to Nalbuphine (.06mg/kg) + Ketorolac (15mg) together in Group B after extubation from general anaesthesia undergoing open cholecystectomy. When both Nalbuphine (.6mg/kg) + Ketorolac (15mg) used together in combination did not give the best result in terms of pain management and side effects.

Our study found that patients in 'Group A' were significantly more sedated compared to patients in 'Group B' using the Ramsay sedation score at 5 minutes and 30 minutes after shifting to the recovery room. Sedation was 8 (10.7%) in 'Group A' and 4(5.3%) in 'Group B' which was statistically significant. So Nalbuphine (12mg/kg) alone is more sedative and causes less agitation during the early postoperative period which is preferred in the recovery of patients after operations under general anaesthesia.

The incidence of postoperative vomiting was comparable in Group A 4 (5.3%) and Group B 2(2.7%). Although exact mechanism is not known, but Opioid induced vomiting is explained as altered lower esophageal sphincter activity, resulting in sphincter relaxation. Gastric emptying is delayed by opioids via spinal, supraspinal (vagus nerve-mediated) and peripheral mechanisms but not significant with the dose of Nalbuphine (12mg/kg) used in our study.

It is recommended that the use of intravenous Nalbuphine (0.12 mg/kg) is the most effective way as compared to other regimen, for postoperative pain management for patients undergoing general anaesthesia for open cholecystectomy and is safe in terms of side effects and cost effective.

LIMITATION OF STUDY

Limitation to the study was that patients were not followed up for more than 1 hour, This was because all the patients were shifted from Operation theater recovery to ward and discharged after 48 to 72 hours. Follow up of most of the patients coming from rural areas would have been very difficult after they have left the hospital.

CONCLUSION

It was concluded that intravenous Nalbuphine (0.12 mg/kg) is more effective in reducing pain intensity and re use analgesics requirements after open cholecystectomy as compared to Nalbuphine .6mg/kg+ Ketorolac 15mg in combination. It is generally safe because of very low incidence of postoperative complications like respiratory depression.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

FS & BZ:, Conception, study design, drafting the manuscript, approval of the final version to be published.

MA & NA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

QAR & NAB: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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