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Original Article:

Butorphanol for Post-Operative Analgesia - A Comparative Clinical Study with Ketorolac

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Abstract:
Introduction: Butorphanol, an opioid derivative has been shown to have, in addition to its analgesic properties, several other advantageous effects like antistressor, sedative and anti-shivering action. The efficacy and safety profile of ketorolac, yet another widely used post-operative analgesic is well documented. This study aims to compare the two analgesics. **Aims and objectives:** This study was conducted to compare the analgesic efficacy and other effects of butorphanol and ketorolac, administered intramuscularly, in post-operative patients who have undergone lower abdominal and pelvic surgeries. **Materials and methods:** 50 patients undergoing lower abdominal and pelvic surgeries under general or spinal anaesthesia were randomly divided into two Groups (25 each). At a particular level of post-operative pain, the patients Groups I and II were administered intramuscular ketorolac 30mg and butorphanol 2mg respectively. The analgesic effect was studied using Visual Analogue Scale (VAS) and the verbal category scale. Patients were monitored for the sedative action, respiratory status and other vital parameters for 300 minutes and for other adverse reactions over the next twelve hours. **Observations:** Butorphanol provided better analgesia within the first two hours of administration, while ketorolac was more effective at 4-5 hours. Better sedative action without any significant respiratory depressant effect was demonstrated with butorphanol. There were no clinically significant hemodynamic fluctuations or adverse reactions with butorphanol or ketorolac. **Conclusions:** Butorphanol provides better early analgesia as compared to ketorolac with a desirable and safe sedative effect in post-operative patients who have undergone lower abdominal and pelvic surgeries.

Key Words: Acute post operative pain; Butorphanol; Ketorolac; Analgesia

Introduction:

Inj. ketorolac is extensively used for post-operative pain management.[1] The effectiveness and safety profile of inj. ketorolac in patients undergoing abdomino-pelvic or orthopaedic surgery are well documented.[2,3,4] Parenterally administered butorphanol in doses of 2 to 3mg provides analgesia equivalent to 10mg morphine or 80mg pethidine. Intra-operatively, during the maintenance phase of general anaesthesia, butorphanol has been shown to be superior to fentanyl.[5] Apart from the primary aim of providing analgesia, several collateral advantages of butorphanol like antistressor effect, sedation and 'anti-shivering' property have been described.[6,7]

In this randomized study, we compared the analgesic efficacy and other effects of inj. butorphanol (study drug) with inj. ketorolac (control drug) for post-operative pain relief in patients who underwent lower abdominal surgeries.

Aims and Objectives:

To compare the analgesic efficacy and other effects of butorphanol and ketorolac, administered intramuscularly, in post-operative patients who have undergone lower abdominal and pelvic surgeries.

Materials and Methods:
This randomized study was approved by the Institutional Ethical Committee of A. J. Institute of Medical Sciences. Fifty patients coming under American Society of anaesthesiologists (ASA) Class I and II categories undergoing elective lower intra-abdominal open surgical procedures were assigned randomly to one of the two groups – Group I being the control (ketorolac) group and Group II, the study (butorphanol) group. These included psychologically, biochemically and physically healthy patients or patients with systemic disease like hypertension on regular treatment and with the disease well under control. Exclusion criteria were age over 60 years, ASA class III and IV, the mentally challenged, smokers, alcoholics, and those with abnormal renal and liver function tests.

An informed consent was taken on the pre-operative day. All the patients were instructed on and explained the use of the Visual Analogue pain Scale (VAS), and descriptor words of

pain. Documentation of baseline blood pressure, heart rate, respiratory rate, temperature and weight was done. All patients were in fasting status and received either intravenous inj. ranitidine 50mg, 1 hour before surgery or tab. pantoprazole, 40mg, 3 hours pre-operatively. No other pre-medication was used.

The assessment of the pain was carried out using the numeric VAS, and verbal category scale (descriptor words of pain). Pain assessment charting is explained below.

Visual Analogue Scale (VAS): VAS is a 10cms line anchored at the two end points, "no pain" and "pain as bad as it can be". The patient is asked to place a mark on this line indicating the intensity of his pain. The VAS score is determined by measuring the distance in cms from the end signifying "no pain" to the point indicated by the patient on the scale.

Descriptor / verbal category scale: Verbal category scale consists of a series of words subjectively describing pain intensity and unpleasant experiences. The patient is asked to select one adjective that best describes his / her pain or feeling. As per the description, the patient is classified into mild, moderate or severe pain categories which are numbered 1, 2 or 3 respectively. 'Mild' includes terms such as tolerable, bearable, just noticeable, mild, weak, and very weak. 'Moderate' encompasses expressions such as unpleasant, uncomfortable, distressing, moderate, and getting intense. Terms such as intolerable, agonizing, miserable, strong, very intense and excruciating comprise the 'severe' category. All these terms are explained and elicited in a language familiar to the patient.

The surgery was performed under general or spinal anaesthesia in all patients. Patients taken up under general anaesthesia received a standard dose of inj. fentanyl, 1 to 2 micrograms per kg intravenously and patients in the spinal anaesthesia group received 0.5% of 2.5 to 3ml of heavy bupivacaine. The time and dose of any additionally administered analgesic like fentanyl, tramadol or diclofenac were documented. In the post anaesthesia care unit, each patient was assigned randomly to one of the two predetermined groups. Patients in Group 1 (n=25) received Inj. ketorolac 30mg and whereas those in Group II (n=25) received Inj. butorphanol 2mg. All injections were given intramuscularly in the gluteal region.

The initial time at which the patient developed VAS pain score of 2 or 3 after the surgical procedure was noted, the control or study drug administered and monitoring commenced. Pain assessment was done at intervals of 30, 60, 120, 180, 240 and 300 minutes following administration of the analgesic (ketorolac or butorphanol). Vital parameters like blood pressure, heart rate, and respiratory rate were noted at similar intervals. Apart from pain intensity, the sedation effect was assessed using a 4 point scale, noting made at the same times as pain assessment (awake=0, mild drowsiness=1, moderate drowsiness=2 and asleep=3). Patients were observed specifically for clinical respiratory depression (low respiratory rate and narcosis) with arterial blood gas analysis contemplated in clinically indicated cases. Other side effects such as headache, nausea, vomiting, weakness, giddiness, sweating, dyspepsia, pruritus and untoward pain at the injection site were documented up to 12 hours after analgesic administration.

Criteria for withdrawal of further monitoring: Patients demonstrating VAS score of 7 or more at any time up to the 300 minute recording, complaining of severe pain according to the verbal category scale, or directly demanding additional analgesia were administered intravenous inj. tramadol 50mg and withdrawn from further observation from that point of time. Any patient suffering from severe or refractory side effects within the 300 minute period was also proposed to be withdrawn from further observation in the study.

Statistical analysis: Data obtained is presented as mean ± standard deviation. Patient demographics like age and weight were compared using Student's t test. Systolic and diastolic blood pressures, heart rate, respiratory rate and time lag for VAS score of 2/3 were also compared using Student's t test. The VAS score, descriptor score, sedation and inter-group fluctuations of vitals were compared using Mann-Whitney U test. A '*p*' value less than 0.05 was considered as the minimum level for statistical significance. All parameters documented except minor side effects like nausea, vomiting etc were subjected to comparative statistical analysis.

Observations and Results:

Preoperative vitals: All preoperative vitals were statistically comparable in the two groups. The systolic blood pressure of Group I averaged 126.64±10.48 versus Group II which showed 125.76±10.74 (*p>.05*). Diastolic blood pressure of Group I was 73.12±10.08 versus 68.48±9.95 in Group II (*p>.05*). The mean heart rate (beats per minute) in Group I was 76±8 and that in Group II was 81±7 (*p>.05*). Similarly respiratory rate was 14±1.7 in Group I versus 13±1.9 in Group II (*p>.05*).

Time lag to develop a VAS score of 2/3 after the procedure varied significantly. In Group I it was 57.80 ±41.005 minutes versus 38.60±27.595 in Group II (*p<.05*).

Type of anaesthesia: 17 patients in Group I received spinal anaesthesia compared to19 in Group II. Rest of the patients in both the groups (32 percent versus 24%) received general anaesthesia. There was no statistical differences between the groups (*p*>.05). While Inj. fentanyl was used whenever indicated intra-operatively, no long acting analgesic like diclofenac was administered to any patient in either Group.

Sedation score: (Table I) Mean sedation scores at 0 minute were comparable in the two groups (*p>.05*). Recordings between 30th and 180th minute showed significantly higher sedation values in Group II versus Group I with the highest statistical significance being of comparative readings taken at 60, 120 and 180 minutes (*p*<.005).

Table 1: Distribution of descriptor ratings of pain

	Group I				Group II			
Time(min)	n	Mild	Moderate	Severe	n	Mild	Moderate	Severe
30	25	12	13	0	25	7	17	1
60	25	20	4	1	24	16	7	1
120	24	17	6	1	23	16	7	0
180	23	19	4	0	23	14	8	1
240	23	18	5	0	22	8	10	2
300	23	14	7	2	22	7	8	5
(*p>.05)*								

VAS scores: Comparison of VAS scores between the two groups (Figure 1) revealed a significantly lower score at 60 and 120 minutes (*p<.05*) in the butorphanol treated Group II as compared to the ketorolac treated Group I. The scores showed no significant difference when earlier or later readings were compared.

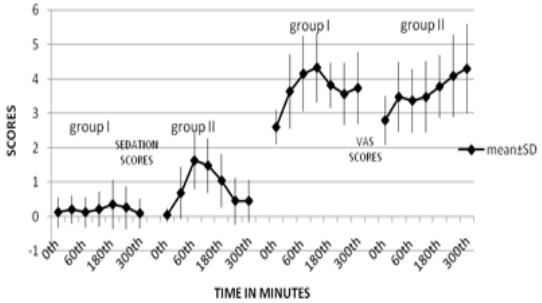

Figure 1: Intergroup comparison of sedation and VAS scores (mean±SD).

Descriptor pain rating: The distribution of descriptor ratings of pain is shown in Table I, 'n' indicating the number of patients observed in each group at various intervals. Patients were excluded from study when they termed the pain as 'severe'. 4 patients of Group I complained severe pain versus 10 patients of Group II during the 300 minutes period of observation. The number of patients in each group, in each pain severity category, at the predetermined time schedule was compared and no statistically significant difference was found between the two groups ($p>.05$).

Comparison of vitals: The systolic and diastolic blood pressures, mean heart rates and respiratory rates in two groups following injection of the respective analgesics was comparable (*p>.05),*(Figure 2, Figure 3). The only statistically significant difference observed was as regards the respiratory rates at 30,60 and 90 minutes, which were lower in Group II ($p<.005$), but this difference was observed even at the onset (0 minute) when the analgesic was administered. There was no instance of clinical respiratory depression in any patient.

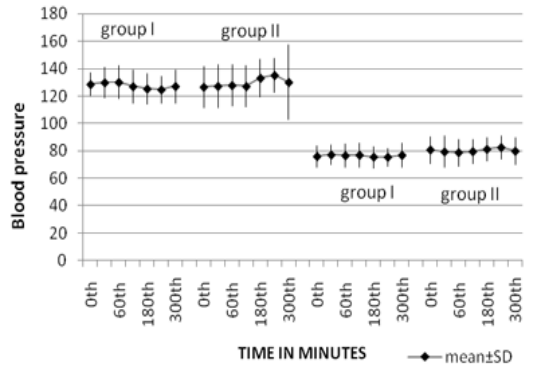

Figure 2: Intergroup comparison of systolic a

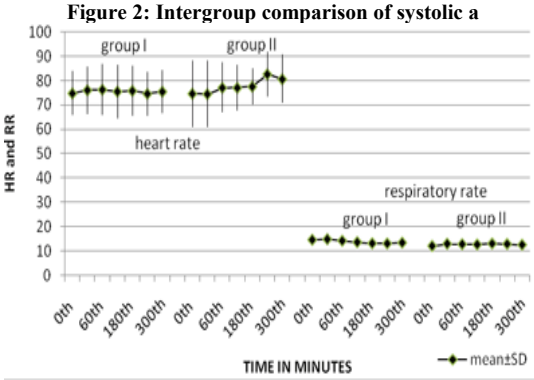

Figure 3: Inter group comparison of heart rates and respiratory rates(mean±SD)

Additional analgesia: Up to 240 minutes (Table 2), 2 patients in Group I and 3 in Group II needed additional doses of intravenous Inj. Tramadol for relief of 'severe' pain as per descriptor rating. Beyond this period, in the last hour of study, 7 in Group II needed Inj. Tramadol as compared to 2 in Group I. The differences observed before and after this cut off period were however not statistically significant ($p>.05$ in both comparisons).

Table 2: Number of patients requiring additional analgesic doses of IV tramadol, inter group comparison.

	n	Group I	n	Group II
Up to 240 mins	25	2	25	3
After 240 mins	25	2	25	7

(*p>.05)*

Other adverse reactions: Nausea and vomiting were observed in 11 (44%) patients of the ketorolac group and 15 (66%) patients of the butorphanol group. Among the select patients who developed this reaction, 33% of patients in the Control group and 36% in the Study group had been administered Inj. tramadol. Other side effects were negligible in both the groups.

Discussion:

In our randomized study, we were able to demonstrate the comparative analgesic efficacy and safety profile of the study drug butorphanol vis-à-vis a control drug ketorolac, both administered intramuscularly.

Mathews KA et al[8] compared inj. ketorolac with inj. butorphanol in controlling post- operative pain following shoulder arthrotomies in dogs. While the pain assessment parameters in animal studies are in no way comparable to the VAS and verbal descriptive scores of our study on humans, their study showed a lower efficacy of butorphanol in relieving pain as compared to ketorolac.

Atkinson BD et al[9] in a double blind study comparing the analgesic properties and outcomes of intravenous inj. butorphanol with inj. fentanyl during labor, reported that butorphanol elicited better VAS scores than fentanyl. In this study, pain was scored independently by the nurse and patient with the VAS. The assessment of pain in our study was by self reports of pain. These self reports are important components in evaluating treatment effectiveness.[10] Clinical researchers have demonstrated that valid self reports of pain are useful in treating patients suffering from acute or chronic pains.[10]

All our patients had VAS scores of either 2 or 3 at the time of administering the analgesic injection. The time lag for developing this score varied significantly between the two study groups. This may be related to the type of anaesthesia and the duration of the surgical procedure. Short procedures under spinal anaesthesia afford a longer time lag as compared to longer procedures under the same anaesthesia or any procedure under general anaesthesia. 0.5% heavy bupivacaine, the drug used for spinal anaesthesia has an average duration of action of 2.5 hours after central neuraxial blockade. However this time-lag factor should not affect the outcome of study since the analgesia was administered and recording of parameters commenced only at a specific point (VAS pain scores 2 or 3), when the anaesthetic effect would have worn out.

The peak plasma concentration of the drugs after intramuscular injection is achieved at 45 to 60 minutes with ketorolac and 60 to 90 minutes with butorphanol.[11] This factor might have resulted in a relatively better score in both the groups in the early postoperative period compared to the later. Between the two drugs however, specifically at 60 minutes and 120 minutes, a statistically significant difference between the VAS scores may suggest that butorphanol provides a better initial pain relief as compared to ketorolac.

Up to three hours after the VAS 2/3 point, majority of patients in both groups reported mild pain symptoms. In the later part of the study (240 and 300 minutes), a much larger percentage of butorphanol treated patients complained of moderate or severe pain and received additional inj. tramadol. Though statistical significance of this difference was not documented, the findings point towards an earlier wearing out of the analgesic action of butorphanol as compared to ketorolac. The observation is in accordance with the documented plasma half lives of ketorolac (5 hours) versus butorphanol (3 hours).[12]

Like other opioids, butorphanol is known to cause sedation in doses of 1 to 2mg.[13] Our study confirmed this attribute of butorphanol. The statistically significant higher sedation scores observed in the butorphanol treated group corresponded to the possible peak plasma concentrations of the drug (60 to 180 minutes). At no occasion did the severity of sedation evoke concern on the possibility of the patient going into respiratory

depression.[12] 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 study drug. The minimal though statistically significant drop in respiratory rates in the study group within the first two hours could be attributed to the greater sedative effect of butorphanol as compared to ketorolac.

Fluctuating cardiovascular responses like tachycardia are noted with inadequate analgesia. An effective analgesic prevents this response. The sedative property of an analgesic like butorphanol could also dampen this effect. Direct cardiovascular effects reported with butorphanol include increased cardiac workload, a stable or increased blood pressure with a stable heart rate.[14] Phillip BK et al[5] observed a fall in heart rate and low diastolic pressures with intravenous administration of butorphanol. It is fortuitous that we did not encounter any serious or clinically significant fluctuations in haemodynamic parameters within each group nor did we observe a difference in values between the two groups. Had such effects been noted, it would have been difficult to assign the relative contributions of such drug actions and the pain itself to the observations.

A higher incidence of nausea and vomiting was observed in our study group patients as compared to the controls. Inj. tramadol itself induces vomiting and its role in the aetiology of this adverse effect cannot be excluded. However, in patients who developed post-operative nausea and vomiting, the extent of use of inj. tramadol was similar when the two Groups were compared. This observation suggested a higher 'nauseogenic' and emetic effect for butorphanol as compared to ketorolac. Opioids stimulate the chemoreceptor trigger zone in the area postrema of the medulla possibly through delta receptors, leading to nausea and vomiting.[14] Early post-operative nausea and vomiting (PONV) is a known entity caused by various factors including pain itself.[15] Surgical causes of nausea and vomiting, type and duration of surgery and other unidentified factors might have contributed to this adverse effect.

The possibility of interactions with other analgesic drugs used intra-operatively and during the period before the commencement of assessment of study parameters was seriously considered. Long acting analgesics like diclofenac might play a significant role in influencing early post-operative pain either due to their stand alone actions or due to their additive actions with the study or control drug. However, patients in either Group, who needed additional intra-operative analgesia, received only short acting analgesics like inj. fentanyl.

Advantages and limitations of our study: Our study design had an inherent advantage in that no patient initially included after going by the exclusion criteria needed to be totally withdrawn from the study. The data provided up to the point of discontinuing monitoring either due to severe pain (high VAS or descriptor verbal score) or refractory side effects could be usefully documented and statistically analysed. However, there were some pitfalls too. We used both the drugs in fixed doses; and differences in body weight, volume of distribution, and individual metabolism could have resulted in varying plasma levels of the drugs in different patients. We did not measure the plasma levels of the analgesic drugs during the study. Patient factors like psychological makeup and variations in pain threshold might have had a bearing on our observations. The tissue trauma related to the extent of surgery too may have had a contributory effect, surgeries like appendectomy not truly comparable with more major pelvic surgeries. Finally, the small numbers of patients in each group might have limited the true clinical significance of our comparisons.

Summary and Conclusions:

We compared intramuscular inj. butorphanol to inj. ketorolac for post-operative pain relief in patients who underwent lower abdominal and pelvic surgeries. We were armed with the knowledge that butorphanol is an opioid analgesic and may therefore provide adequate pain relief. Apart from analgesia, butorphanol has other actions like sedation and anti-shivering properties that may prove beneficial in the post-operative period. At the same time, being an opioid, its respiratory depressant property may pose a major problem. The study attempted to evaluate the comparative efficacy and adverse reactions between the two drugs in the post-operative period.

We observed that butorphanol (2mg) produces better analgesia in the initial 2 hours after injection compared to ketorolac (30mg) while ketorolac provided more effective analgesia in the later period of 4 to 5 hours following injection. Butorphanol produces better sedation without any significant respiratory depressant effects. Like ketorolac, butorphanol has little effect on cardiovascular hemodynamics. A relatively higher incidence of nausea and vomiting following its administration can be treated effectively. Intramuscular butorphanol can be used effectively and safely for post-operative pain relief in doses of 2mg for minor to moderate lower abdominal and pelvic surgeries. However the usage of the drug in similar dosage for major surgeries needs further evaluation.

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