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A COMPARATIVE STUDY OF EPIDURAL BUTORPHANOL AND EPIDURAL MORPHINE FOR THE RELIEF OF POSTOPERATIVE PAIN

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ABSTRACT: Epidural administration of various analgesics gained increasing popularity following the discovery of opioid receptors in the spinal cord capable of producing potential analgesia. The analgesic effect seems to be more when epidural anesthesia is continued in the post-operative period as epidural analgesia. It is now clear that epidural administration of opioids relieves patient of extended pain post-operatively. Ours was a comparative study of epidural butorphanol and epidural morphine for the relief of postoperative pain. **METHODS:** Sixty adult patients in ASA class I and II, weighing 45 to 60kgs of either sex, belonging to 21-60 years of age, posted for elective lower abdominal & lower limb surgeries in orthopaedics, gynaecological, urological, plastic and general surgeries under epidural anaesthesia were selected for the study. The study was undertaken to evaluate the efficacy and safety of epidural butorphanol 2 mg diluted to 10 ml of normal saline in comparison with epidural morphine 2.5 mg diluted to 10 ml of normal saline given for relief of postoperative pain. In the post-operative period the following parameters were studied, 1. Onset of analgesia, 2. Duration of analgesia, 3. Quality of analgesia, 4. Side effects like nausea, vomiting, hypotension, respiratory depression, and pruritus allergic reaction were looked for. **RESULTS:** Mean onset of analgesia was 14.66±4.34 (S. D) minutes in group-A, and in group-B was 34.76±5.73 (S. D) minutes. The Statistical analysis by Student's unpaired t-test showed that time of onset of analgesia in group-A was significantly less when compared to group-B. (t = 15.29 with df-54, P<0.0001) (Table 3). Duration of analgesia was longer in group-A, ranged from 4-8 hours with a mean±SD of 5.20±0.71 hours. Duration of analgesia in group-B ranged from 10-24 hours with a mean±SD of 16.05±3.14 hours. This was clinically and statistically significant (p<0.0001) (Table 4). The quality of analgesia was comparable in both groups and the difference is statistically insignificant. (P>0.05). When compared to group-B, haemodynamic stability was well maintained in group-A. **RESULT:** Side effects with pure opioid like morphine can be avoided by using a mixed narcotic agonist/antagonist like butorphanol, epidurally, which also provides analgesia.

KEYWORDS: Butorphanol, Morphine, Post-Operative analgesia, Epidural.

INTRODUCTION: Proper management of postoperative pain remains one of the most important and most pressing issues of society in general, the scientific community and the health care professionals in particular.

Modern approach to the scientific study of pain and its control began in the 19th century. During the first 50 years of 20th century neuroanatomic, neurophysiologic and psychologic research on pain continued at progressively greater pace. The foundation of the International Association for the Study of Pain (IASP) in 1974 and publication of its Journal PAIN since 1975 must be considered among the most important developments in the field of pain research and therapy Bonica John J.¹

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Despite advances in the knowledge, skill and sophisticated technology that characteristics most aspects of modern surgical treatment, many patients continue to experience considerable discomfort during postoperative period.

Post-operative analgesia not only improves quality of life of the patient but also results in fast recovery and hence reduces the medical costs.

In 1806, Serturmer isolated morphine from crude opium and it was frequently used for preoperative medication and postoperative analgesia¹ Opiate receptors were identified in the CNS in 1973 by Pert and Synder, and in 1977 large populations of these receptors were localized in the dorsal horn of the spinal cord. Butorphanol tartrate; synthesized by Monkovic et al., in 1975 at Bristol Laboratories of Canada.

It has got both agonistic and antagonistic properties. (Stoelting Robert K² in 1979). Ameer B, Slater F J.³ Reviewed chemistry, pharmacology, uses, side effects, pharmacokinetics and dosage of Butorphanol tartrate.

With the discovery of endogenous opioids and opiate receptors a new era in pain relief has commenced. Produce analgesia by interacting with opiate receptors in CNS. Opioid analgesics.

Morphine remains the most widely used analgesic and the gold standard opioid, since its isolation from opium almost 200 years ago. Morphine epidurally widely used. Morphine is less lipophilic, slower onset and associated with respiratory depression, itching and urinary retention.

But orphanol tartarate is a synthetically derived agonist-antagonist opioid analgesic analgesic potency is 4–8 times that of morphine. And relatively lipophilic, with lesser side effects than morphine.

Del Pizzo A⁴ had done a double-blind study on the effect of butorphanol compared with morphine in balanced anesthesia.

Hence this clinical study of comparative evaluation of epidural butorphanol with epidural morphine is undertaken to evaluate the onset, quality and duration of pain relief and side effects with epidural butorphanol and epidural morphine.

METHODOLOGY: Sixty adult patients of ASA class I and II, weighing 45 to 60 kg of either sex, belonging to 21-60 years of age, posted for elective lower abdominal and lower limb surgeries in orthopedics, gynecological, urological, plastic and general surgeries were selected for the study.

EXCLUSION CRITERIA:

1. Patients with cardio-respiratory disorders.
2. Patients with renal and / or hepatic disorders.
3. Contraindications for epidural anaesthesia.
4. Patients physically dependent on narcotics.
5. Patients with history of drug allergy.
6. Head injury cases.
7. Patients in whom epidural anaesthesia was not adequate and supplemented with other types of anaesthesia.

Fig. 1

Fig. 2

Fig. 3

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Ethical Committee clearance from our college was taken for this study.

Patients were randomly divided into two groups of 30 each.

Group "A"- Butorphanol group and

Group "B"- Morphine group.

A detailed pre-anesthetic evaluation was done. Patients were explained about epidural technique with catheter in situ and also educated about usage of linear visual analogue scale [VAS].

All patients were premedicated with Tablet Alprazolam 0.5mg given night prior to the surgery. On table, basal vital parameters (pulse rate, Non-invasive blood pressure, Pulse oximetry, ECG) were recorded. Patient was placed in sitting or lateral position. Under aseptic precautions, epidural space was identified by Loss of resistance technique using 18 Gauge Touhy needle at L2-L3 or L3-L4 interspace. Epidural catheter was introduced cephalad so that 2-3 cms was in epidural space.

Intravascular and intrathecal placement of the catheter was ruled out using 3ml of 2% lignocaine with adrenaline 1: 2,00,000. Epidural anaesthesia was activated using 16-18 ml bolus dose of 0.5% Bupivacaine. Subsequent top up doses were given according to requirement. Intra-operatively pulse rate, Non-invasive blood pressure, SPO2 and respiratory rate were recorded at 3 minutes interval for the first half an hour then five minutes interval for the next half an hour, thereafter every 15 minutes till the end of the surgery.

In the post-operative period, when the patient first complained of pain, intensity of pain was assessed using VAS scale. When the VAS score was >5, study drug was given through epidural catheter as:

Group A – received butorphanol 2mg diluted to 10ml in normal saline and.

Group B – received morphine sulphate 2.5mg diluted to 10 ml in normal saline.

The following parameters were recorded:

1. Onset of analgesia.
2. Duration of analgesia.
3. Quality of analgesia.
4. Cardio-respiratory effects: Pulse rate, Blood pressure & Respiratory rate.
5. Side effects like drowsiness, pruritus, nausea, vomiting, urinary retention, respiratory depression and hypotension.

The intensity of pain and pain relief was at every 5 minutes for the first hour and thereafter at 1 hour interval for 8 hours and then at 4 hours interval for 24 hours post-operative period.

Onset of analgesia is time interval from drug administration till VAS score came down to 5. Readings of >5 was considered as unsatisfactory analgesia and rescue analgesia was given. Duration of analgesia is time interval between the start of analgesia (That is when VAS score is at 5), till patient complaints of pain (That is when VAS score is >5) when rescue analgesia was given.

At the time at which rescue analgesia was given, the patient was asked to give a global assessment of the overall effectiveness of the analgesic treatment. Quality of analgesia was assessed depending on this as noted below and compared in both the groups.

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PAIN SCORE	PAIN RELIEF	VAS SCORE
0	NO PAIN RELIEF	10
1	POOR PAIN RELIEF	7-9
2	FAIR PAIN RELIEF	5-7
3	GOOD PAIN RELIEF	2-5
4	EXCELLENT PAIN RELIEF	0-2

TABLE 1

HEMODYNAMIC PARAMETERS: Pulse rate, Blood pressure and Respiratory rate were observed after giving study drugs at 0, 5, 10, 15, 30, 60 and 120 minutes post-operatively.

Statistical Analysis: Continuous data was analyzed by student's t-test and categorical data by Chi-square test. Any possible significance has been determined considering it statistically significant if it's $P < 5\%$ level of significance.

In 1978, Popio et al,⁵ compared the haemodynamic and respiratory effects of Morphine and Butorphanol. A total of 20 patients were studied at the time of diagnostic cardiac catheterization. Patients were given equipotent doses of either morphine sulphate (0.125 mg/Kg) or butorphanol tartrate (0.025 mg/Kg). Butorphanol decreased pH, pO_2 , and systemic artery pressure and increased pCO_2 , cardiac index and pulmonary artery pressure. Morphine caused similar changes in pH, pO_2 , systemic artery pressure and pCO_2 , but much smaller changes in cardiac index and no change in pulmonary artery pressure

RESULTS: In this Study, the demographic data between the two study groups were comparable.

Fig. 4

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Mean onset of analgesia was 14.66 ± 4.34 (S. D) minutes and in group-B was 34.76 ± 5.73 (S. D) minutes. The Statistical analysis by Student's unpaired t-test showed that time of onset of analgesia in group-A was significantly less when compared to group-B. ($t = 15.29$ with $df=54$, $P < 0.0001$) (Table 3). Duration of analgesia was longer in group-A, ranged from 4-8 hours with a mean $\pm$ SD of 5.20 ± 0.71 hours. Duration of analgesia in group-B ranged from 10-24 hours with a mean $\pm$ SD of 16.05 ± 3.14 hours. This was clinically and statistically significant ($p < 0.0001$) (Table 4). The quality of analgesia was comparable in both groups and the difference is statistically insignificant. ($P > 0.05$) (Table 5).

In 1976, M Tavakolli, G Corssen,⁶ F S Caruso, in a double-blind study compared the parenteral analgesic activity of Butorphanol and Morphine. It was done on 127 patients having moderate to severe pain following major operations. Postoperatively single IM doses of either butorphanol tartrate 0.73 mg (0.5mg base), 1.46 mg (1 mg base), or 2.92mg (2 mg base) or morphine sulfate 5 mg or 10 mg were administered. The mean values for blood pressure, pulse rate, and respiratory rate recorded during the 2 hour period following medication showed no statistically significant changes within or between any of the 5 treatment groups. Butorphanol tartrate was 7 times as potent as morphine sulphate. In providing relief from pain, the low dose of butorphanol and morphine were approximately equivalent, and that either the mid or the high dose of butorphanol was approximately equivalent to the high dose of morphine sulphate. Authors concluded that butorphanol tartrate is a safe, potent and effective analgesic agent with probably low potential for drug dependence.⁷

When compared to group-B, haemodynamic stability was well maintained in group-A.

Fig. 5

SIDE EFFECTS: In 1980, Bromage et al⁷, after a study of epidural morphine, were of the opinion that -
a) In contrast to I. V. narcotic administration central depressant effects of epidural narcotic were less pronounced.

In 1981, Pratibha. S⁸ assessed epidural morphine 3 mg in 50 patients. All patients had complete pain relief for 12-24 hours on an average 19 hours, 7 patients had vomiting. There was no respiratory depression and majority of patients were catheterized, so they could not make out exact incidence of urinary retention.

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In 1984, Narinder Rawal et al,⁹ in their experimental and clinical study of respiratory depression after epidural morphine, concluded that between smaller (2-4 mg) and larger (10 mg) doses of epidural morphine, there was a dose dependent depression of central respiratory control.

Although the ventilatory depression associated with 4mg epidural morphine is mild, there is a danger of severe respiratory depression in the presence of additional risk factors such as advanced age, impaired respiratory function, concomitant use of parenteral sedatives and/or opiates, residual anaesthesia, supine position etc.. Intravenous infusion of naloxone prevented the respiratory changes after epidural morphine. Surveillance of patients for 12-24 hours after injection of epidural morphine is well advocated.

The incidence of nausea, vomiting, pruritus and hypotension was more in group B. ($P < 0.05$). Incidence of sedation was more in group-A ($P < 0.05$). There was no respiratory depression in both the groups.

Urinary retention could not be assessed because indwelling urinary catheters in urinary bladder were left in place for 24 hours in most of the patients.

DISCUSSION: Postoperative pain is major concern after surgery. The use of epidural opioids had become an increasingly popular technique for the management of acute postoperative pain in recent times. Recent studies would indicate that it is possible to achieve better analgesia with lower doses of opioid medication when these drugs are administered in extradural space as compared to intramuscular or intravenous routes of administration. However, there are disadvantages associated with narcotics as they are not always simple to use and may be associated with some unpleasant adverse effects, like nausea and vomiting (PONV), pruritis, respiratory depression and urinary retention.

Stimulation of spinal opiate receptors (κ , μ) can also produce spinal analgesia but with fewer side effects. Therefore, a drug such as butorphanol, a mixed narcotic agonist/antagonist, first introduced in 1978 acts as a μ (μ) agonist/antagonist and κ agonist, also produces analgesia, associated with fewer side effects and also low abuse potential. (In 1995, Gould Daniel B).

Its high lipid solubility and high affinity for opioid receptors are additional factors that contribute to paucity of side effects with its use.

Here an attempt has been made in this clinical study to assess the efficacy and safety of epidural butorphanol in comparison with epidural morphine in the management of postoperative pain.

In our study, the mean time of onset of analgesia in group-A (butorphanol) was faster compared to group B ($P < 0.0001$). Mok et al., did the study to evaluate the analgesic efficacy and safety of epidural butorphanol 4 mg in comparison to the of epidural morphine 5 mg in patients with post-operative pain.¹ He reported faster onset of pain relief with epidural butorphanol compared to epidural morphine.

Palacios.² et al., compared epidural butorphanol 1, 2 and 4 mg with epidural Morphine 5 mg for postoperative analgesia for the relief of post caesarean section pain.² The mean median pain scores 15, 30, 45 and 60 minutes following each dose of butorphanol were significantly lower than corresponding values in the patients who received morphine. Time of onset of epidural analgesia following butorphanol was more rapid than following morphine.

Onset of analgesia in our study was comparable to above studies.

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In our study, duration of analgesia in group-A (butorphanol) ranged from 4-8 hours with a mean+SD of 5.2+0.71 hours and in group-B (morphine) ranged from 10-24 hours with a mean+SD of 16.05+3.14 hours. ($P < 0.0001$). Abboud et al. compared the epidurally administered butorphanol 1, 2, 4 mg with epidurally administered morphine 4 mg for the relief of post caesarean section pain. Duration of pain relief was significantly longer in the morphine group ranged from 6-24 hours when compared to butorphanol groups ranged from 4-8 hours.

Mok et al.¹⁰ did the study to evaluate the analgesic efficacy and safety of epidural butorphanol 4 mg in comparison to the that of epidural morphine 5 mg in patients with postoperative pain.¹ Duration of pain relief was more in morphine group averaged 15.2 hours when compared to butorphanol group averaged 5.4 hours.

Duration of analgesia in our study was comparable to above studies.

Quality of Analgesia: Quality of analgesia in butorphanol group, 60% of patients graded their pain relief as excellent, but in morphine group 50% of patients graded their pain relief as excellent. This difference was statistically insignificant ($P > 0.05$). In both the groups, majority of patients expressed their analgesia as good to excellent.

Naulty et al.¹¹ studied the epidural butorphanol 1mg, 2mg, 4 mg and 6 mg for post caesarean delivery pain management.³ They noted a statistically significant ($p < 0.01$) prolongation of post-operative analgesia with butorphanol doses greater than 1 mg, with increasing duration seen with increasing dose.

Palocios et al.¹² Compared epidural butorphanol 1, 2 and 4 mg with epidural morphine 5 mg for postoperative analgesia.² The global assessments of the adequacy of epidural analgesia following butorphanol were indistinguishable from those following morphine.

PAIN SCORE	QUALITY OF ANALGESIA	GROUP-A No. of cases (%)	GROUP-B No. of cases (%)
0	NO PAIN RELIEF	0	0
1	POOR PAIN RELIEF	0	0
2	FAIR PAIN RELIEF	1 (3.3%)	2 (6.7%)
3	GOOD PAIN RELIEF	11 (36.7%)	13 (43.3%)
4	EXCELLENT PAIN RELIEF	18 (60%)	15 (50%)

Table 2

In group-A, 36.7% of patients had pain score of 3 when compared to group-B 43.3% of patients had pain score of 3. 60% of patients had a pain score 4 in group-A, when compared to group-B 50% of patients had pain score of 4. This difference was statistically insignificant by chi-square test. ($X^2 = 0.60$, $df = 1$, $P > 0.05$).

Cardio-respiratory effects: when compared to morphine group, haemodynamic stability was well maintained with butorphanol group. 2 patients in group-B (morphine) developed hypotension and no patients in both groups had respiratory depression (Respiratory rate < 10 breaths/min).

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VITALS	GROUP-A				GROUP-B			
	BEFORE		AFTER		BEFORE		AFTER	
	RANGE	MEAN + S. D	RANGE	MEAN + S. D	RANGE	MEAN + S. D	RANGE	MEAN + S. D
PULSE RATE (bpm)	64-90	75.70 +7.83	65-88	74.20 +6.61	64-94	78.30 +8.58	60-90	74.20 +8.05
SYSTOLIC B. P (mm of Hg)	110-130	121.33 +5.99	100-130	118.40 +6.50	110-130	121.20 +6.33	86-128	115.00 +9.60
DIASTOLIC B. P (mm of Hg)	70-90	79.86 +5.91	66-88	76.80 +5.90	68-90	81.00 +6.78	54-88	76.60 +8.77
RESPIRATORY RATE (cpm)	12-18	14.63 +2.07	12-17	13.53 +1.56	12-18	14.56 +2.22	11-17	13.10 +1.64

Table 3

In Palocios et al.¹² and in Abboud et al.¹³ studies, also found, no patients had clinical respiratory depression.

Side Effects: In our study, group-A (butorphanol) patients had side effects like, nausea and vomiting were less when compared to group-B (morphine) and this was statistically significant ($P < 0.05$). In other studies also found that, butorphanol group had fewer episodes of nausea and vomiting when compared to morphine group.

Sedation was more in butorphanol group when compared to morphine group and this was statistically significant ($P < 0.05$). Abboud et al.⁴ also found somnolence was the more in patients who received epidural butorphanol than with epidural morphine.⁴

Pruritus in morphine group was more when compared to butorphanol group and this was statistically significant ($P < 0.05$) and it was observed most commonly around the site of catheter placement and peripheries. In Abboud et al.¹² And in Palocios et al.¹⁰ Studies also found, pruritus was more with epidural morphine.

In our study, Urinary retention could not be assessed because indwelling urinary catheter in urinary bladder were left in place for 24 hours in most of the patients.

No patient had respiratory depression in both groups.

Over all frequencies of side effects were more in morphine group when compared to butorphanol group.

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SIDE EFFECTS	GROUP-A No. of cases (%)	GROUP-B No. of cases (%)	X ² value	P value
Nausea	3 (9.9%)	10 (33.3%)	4.31	P< 0.05
Vomiting	2 (6.7%)	8 (26.7%)	4.32	P< 0.05
Pruritus	0	12 (40%)	15	P< 0.05
Sedation	20 (66.7%)	8 (26.7%)	9.64	P< 0.05
Hypotension	0	2 (6.7%)	2.06	P>0.05
Respiratory depression	0	0	0	0

Table 4

From the study it is concluded that epidural butorphanol provides a rapid, excellent but shorter duration of analgesia when compared to epidural morphine. Epidural butorphanol had lesser side effects like nausea, vomiting, pruritus and hypotension. Sedation was main side effect in epidural butorphanol.

In 1995, Gould Daniel B¹⁴ did the study for the general efficacy of postthoractomy pain management using epidural analgesia. Author prefers to administer the kappa opioid butorphanol for postthoractomy pain and also concludes in this study that butorphanol causes neither pruritus nor urinary retention; alone it provides excellent (lumbar) epidural post thoractomy analgesia.

In view of its safety profile, epidural butorphanol can be routinely employed in the treatment of post-operative pain for various surgical procedures. However, a continuous vigilant monitoring by qualified person is mandatory during postoperative period for known complications of epidural opioids.

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