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Randomized, Comparative Study of Efficacy of Morphine, Butorphanol and Fentanyl Along With Local Anesthetic Epidurally, For Post-Operative Pain Management

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Abstract: *Pain following surgery is a protective but an unwanted effect which is to be relieved for the better outcome of surgery. The present study was conducted to (1)Compare the safety and efficacy of opioid analgesics, Morphine, Butorphanol and Fentanyl along with local Anaethetic Bupivacaine, when given epidurally, for post-operative pain management in lower abdominal surgeries.(2)Compare occurrence of side effects of the epidurally given opioids. The study was a Randomized, double- blind, placebo controlled single dose, comparative study comprising three test groups and one control (Placebo) group. 100 Female patients who were fit for epidural anesthesia and scheduled for lower abdominal surgeries at Gynecology operation theatre, Government General Hospital were randomly allocated to 4 study groups with 25 each. Onset of Analgesia, Duration of Analgesia, Onset of Sedation ,Duration of Sedation, Levels of Sedation, Vital data, Side effects were recorded, compared and analyzed statistically. This study showed that post-operative pain was effectively reduced in all study groups except control group. Morphine or Butorphanol along with Bupivacaine can be safely given epidurally to obtain effective post-operative analgesia after lower abdominal surgeries. While epidural Fentanyl and Bupivacaine combination can also be safely and effectively but repeated administrations may be required.*

Keywords: *Epidural analgesia , Bupivacaine , Butorphanol , Fentanyl , Morphine, Sedation .*

I. Introduction

Pain following surgery is a protective but an unwanted effect which is to be relieved for the better out come of the surgery and Anaethesia.The quest for pain relief, following surgery continues from beginning of the history of surgery. Pain is defined by International Association for the study of pain (IASP), as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage (or) described in terms of such damage".

Pain is a subjective phenomenon and it is difficult to measure the feelings of aversion, illness, threat and fear with which it is associated. But pain is also the consequence of altered neuronal activity within the nociceptive system, consisting of peripheral afferents, spinal cord, brain stem, thalamus and cortex. Therefore enhanced neuronal activity in the nociceptive system can be taken as a measure of Pain.

Routes of analgesic drug administration are Oral, Trans-Epithelial, (Transdermal and transmucosal administration) Parenteral ,Intramuscular ,Rectal , Intravenous , Patient Controlled Analgesia (PCA) , Intra-Thecal- Epidural , Combined Spinal Epidural (CSE) , Multimodal Therapies - Epidural analgesia is more popular for post-operative pain management[1]. It was first popularized by Dawkin in 1960. It consists of interruption of pain pathways at the point of communication between first and second order neurons. Epidural analgesia regardless of analgesic agent provided better post-operative analgesia compared with parenteral analgesia[2].The commonly used agents for epidural analgesia include(1)Local Anaethetics ex :- Bupivacaine, Ropivacaine(2)Opioids – Morphine, Fentanyl, Sufentanil, Butorphanol, Hydromorphone, Meperidine. Recent developments in Epidural Analgesia:Single-Dose Extended-Release Epidural Morphine (single-dose EREM) Single-dose EREM (DepoDur TM) was recently approved by the US Food and Drug Administration (FDA) for use in the treatment of pain after major surgery[3]

1.1. Opioid analgesics: Opiods have been the mainstay of pain treatment for thousands of years and remain so today as the discovery and localization of opioid receptors has opened new horizons in pain management. These alkaloids re broadly divided into two classes depending on chemical structures: (1)Phenanthrenes ex; morphine (10% Opium) codeine (0.5% Opium), thebaine (0.2%).(2)Benzylisoquinolines ex; papaverine (1.0% Opium), noscapine (6%).

1.2 Pharmacokinetics of Epidural Opioids : Opioids placed in epidural space may undergo uptake into epidural fat, systemic absorption, or diffusion across the dura into the cerebrospinal fluid . Epidural

administration of opioids produces considerable CSF concentrations of drug. Penetration of the dura is considerably influenced by lipid solubility, but molecular weight may also be important. Drugs administered epidurally can be distributed in several ways. They may diffuse through the spinal meninges into the cerebrospinal fluid (CSF), from which they can reach their site of action, the dorsal horn of the spinal cord directly. Fentanyl and Butorphanol are approximately 800 and 140 times respectively, as lipid soluble as morphine. After epidural administration, CSF concentrations of fentanyl peak in about 20 minutes, Butorphanol in about 40- 60minutes.

1.3. Mechanism of action: At the molecular level, opioid receptors are G - protein coupled receptors and inhibits adenylate cyclase so reducing intra cellular cAMP content.

1.4. Morphine sulphate: Morphine sulphate is one of the principal phenanthrene alkaloid.As the laboratory synthesis of morphine is difficult, the drug is still obtained from opium or extracted from poppy straw. Opium is obtained from the unripe seed capsules of the plant papaver somniferum. The milky juice is dried and powdered to make powdered opium. Pharmacokinetics: Opioid agents produce analgesia by binding to specific receptors located in the brain and spinal cord regions involved in the transmission and modulation of pain. Most opioids are highly selective for mu Opioid receptors. Doses: Epidural analgesia: 1-5 mg injected into epidural space provides analgesia for prolonged periods. 5 mg of epidural morphine can provide analgesia for up to 26 hours.

1.5. Butorphanol: Butorphanol is a nitrogen-substituted 3, 14-dihydroxymorphinan. This synthetic member of the benzomorphan series is structurally similar to other drugs having the various degrees of opioid agonist and antagonist properties at room temperature. Butorphanol exists as white water soluble crystals. The dose is expressed as tartrate salt. One milligram of the salt is equivalent to 0.68 mg of the free base. A Mixed Agonist Antagonist Analgesic : Butorphanol is a potent analgesic with both opioid agonist and antagonist effect. Butorphanol and its major metabolites are agonist at kappa-opioid receptors and mixed agonist-antagonists at mu opioid receptors. The analgesic potential of Butorphanol on a weight basis are 7 times that of Morphine ,20 times that of Pentazocine. ,40 times that of Pethidine .Drug abuse and Dependence: Although Butorphanol has low physical dependence liability, exercise care in administering to emotionally unstable patients and those prone to drug misuse and dependence. [4]

1.6. Fentanyl Citrate : Fentanyl Citrate is a potent synthetic opioid analgesic, synthesized first in 1960. Fentanyl acts primarily as mu opioid receptor agonist. Like other opiates, this produces supraspinal analgesia. It also acts on K (Kappa) and δ (delta) receptors producing spinal analgesia. It also antagonizes 5HT levels in the brain, thereby potentiating the analgesic activity as the opioids. It is formulated as a clear solution with pH adjusted to 4.0 – 7.5 with sodium hydroxide. Fentanyl citrate is also absorbed transdermally and this is an important route for certain indications (chronic pain Fentanyl and Morphine are highly selective for mu opioid receptors.[5]

1.7. Bupivacaine: Bupivacaine is one of the homologous series of mepivacaine and this was first synthesized by Ekenstam and his colleagues in 1957 in Sweden, and used clinically by L.J. Telivuo (1923-1970) in 1963. Since then it has been used widely in Scandinavia. It has been used for all types of nerve blocks, lumbar, caudal epidurals, and Para-cervical block] The local anaesthetics block nerve conduction by decreasing the entry of Na+ ions during upstroke of action potential. The clinical impression that Bupivacaine possess an unusual cardiotoxic characteristic, which has been demonstrated in the cat, dog and sheep. These laboratory animal studies indicate that potential to produce rapid and severe cardiac depression and ventricular arrhythias. [6]

II. Aims And Objectives

The present study was conducted to (1)Compare the safety and efficacy of opioid analgesics, Morphine, Butorphanol and Fentanyl along with local Anaethetic Bupivacaine, when given epidurally, for post-operative pain management in lower abdominal surgeries.(2)Compare the occurrence of side effects of the epidurally given opioids.

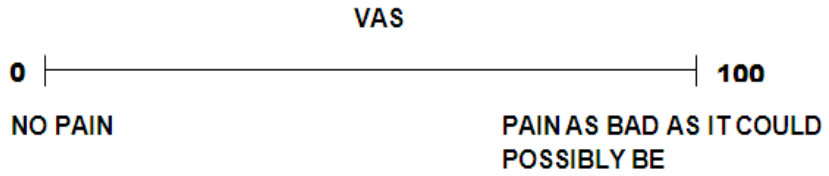
III. Materials And Methods

After obtaining permission from Institution Ethics Committee 100 female patients aged between 20-50 years, who were fit for epidural anesthesia and scheduled for lower abdominal surgeries at Gynecology operation theatre (G.O.T.) Government General Hospital, were selected for this study. They were randomly allocated to 4 study groups with 25 patients in each study group. The patients with any surgical and medical illness conditions were excluded from the study.

3.1. Study Drugs & Dosage: The following test drugs were given to the patients as per the allocation: include 1ml Normal saline (0.9%) + 9 ml (0.125%) Bupivacaine as control group , 1 ml Morphine sulphate (3mg) preservative free + 9 ml (0.125%) Bupivacaine as Morphine group , 1 ml Butorphanol tartrate (2 mg) + 9 ml (0.125%) Bupivacaine as Bupivacaine group and 1 ml Fentanyl citrate (50 μg) + 9 ml (0.125%) Bupivacaine as Fentanyl group. The other drugs given to all the patients in common were 0.5% Bupivacaine 2-3 ml – for spinal Anaesthesia. and Inj. Midazolam (2-3mg) –Intravenously as pre-Anaethetic medication

3.2. Method of Epidural Analgesia: Under strict aseptic conditions, epidural catheterization was done at L_2 – L_3 or L_3-L_4 intervertebral space and epidural catheter was secured in position. Through this epidural catheter, either the test drug (or) control drug, along with Bupivacaine was injected later. To complete the surgery, spinal Anaethesia with 2-3 ml of 0.5% Bupivacaine was given separately, at one space below epidural catheter level.

3.3. Pain Assessment: The pain intensity at each time point of the entire study was assessed by Visual Analogue Scale (VAS). VAS is a 100 mm base line, with one end marked as NO PAIN and the other end marked as PAIN AS BAD AS IT COULD POSSIBLY BE. The patient is asked to put a dot on the base line as per the intensity of pain the patient feels. Then the length of the line from the NO PAIN end, which is taken as Zero is measured up to the dot on the line placed by the patient. The end marked as PAIN AS BAD AS IT COULD POSSIBLY BE is taken as 100 mm.



3.3.1The time points of Pain Assessment: Pre-operatively – half an hour before starting the surgery.Post-operatively – (1)When the patient complains of pain, after recovery from Anaethesia i.e. before giving the epidural injection of study drug.(2)When the patient says the starting of relief of pain i.e. after giving the epidural injection of study drug.(3)Every 4 hours while the patient is awake.(4)When the patient complains of starting of pain again i.e. after giving the epidural injection of study drug. Analgesic Efficacy:The analgesic efficacy of the drug is assessed by the pain relief achieved by it, in the following way :

Pain Intensity Difference (PID) = Pain relief.;PID / Pain relief at a time point = IPI – PI.

IPI – Initial Pain Intensity.;PI – Pain Intensity at that time point.

The time point, when epidural injection of the study drug given, is taken as Zero hour.The Pain recorded at Zero hour by Visual Analogue Scale is taken as Initial Pain Intensity (IPI).The time period, from the Zero hour up to the time point, when the patient says starting of relief of pain is taken as Onset of Analgesia of the given drug.The time period, from the Zero hour up to the time point, when the patient complains of starting of pain again i.e. after giving epidural injection of study drug, is taken as Duration of Analgesia of given drug.

3.4. Sedation level Assessment: By SEDATION SCORE by E. WILSON et. al. 1990 as:

I – Awake and Alert.II – Awake and Drowsy.III - Eyes closed but Arousable to verbal commands.

IV – Eyes closed but Arousable to Mild physical stimulation.V – Eyes closed and Unarousable

After the completion of the study in all the patients, unblinding was done. As per the study drugs given to the patients, the CRFs of all the patients were separated in to 4 groups. Finally all the four groups results were analyzed statistically, using students't' test.

IV. Results

"Table – 1." Distribution of Age

Age (years)	Control Group (n=25)	Morphine Group (n=25)	Butorphanol Group (n=25)	Fentanyl Group (n=25)	Total (n=100)
20-30	14 (56%)	12 (48%)	16 (64%)	15 (60%)	57 (57%)
31-40	5 (20%)	8 (32%)	4 (16%)	1 4%)	18 (18%)
41-50	6 (24%)	5 (20%)	5 (20%)	9 (36%)	25 (25%)

The total Number of patients in the study was 100 and 25 patients were in Morphine group, 25 patients were in Butorphanol group, 25 patients were in Fentanyl group and 25 patients were in Control (Normal saline) group.In the total study, the number of patients- 57 (57%), in 20-30 yrs age group was the highest and the

number of patients- 18 (18%), in 31-40 yrs age group was the lowest and- 25 (25%) patients were in 41-50 yrs age group. In all the study groups, more number of Patients were in 20-30 yrs age group (Table-I).

"Table –2." Comparison of Onset & Duration of Analgesia

Groups	Onset of Analgesia (minutes)	Duration of Analgesia (minutes)
Control Group (n=25)	17.96 ± 3.32	127.6 ± 22.32
Morphine Group (n=25)	9.6 ± 0.95	1373.2 ± 114.79**
Butorphanol Group (n=25)	4.64 ± 0.63*	589 ± 100.1*
Fentanyl Group (n=25)	2.72 ± 0.89**	309.6 ± 48.58*

Values are --- Mean ± Standard deviation. * = $p < 0.05$ vs. Control — Significant;
** = $p < 0.001$ vs. Control — Highly Significant

The mean Onset of Analgesia was low- 2.72 ± 0.89 minutes in Fentanyl group with highly significant difference ($p < 0.001$) from that of- 17.96 ± 3.32 minutes in Control group. While the mean Onset of Analgesia was- l4.64 ± 0.63 minutes in Butorphanol group with a significant difference ($p < 0.05$) from that of- 17.96 ± 3.32 minutes in Control group.But there was no significant difference seen in means of Onset of Analgesia in between Morphine group- 9.6 ± 0.95 minutes and Control group- 17.96 ± 3.32 minutes.The mean Duration of Analgesia was high- 1373.2 ± 114.79 minutes in Morphine group with a highly significant difference ($p < 0.001$) from that of -127.6 ± 22.32 minutes in Control group. While the mean Duration of Analgesia was- 589 ± 100.1 minutes in Butorphanol group with a significant difference ($p < 0.05$) from that of- 127.6 ± 22.32 minutes in Control group. And the mean Duration of Analgesia was- 309.6 ± 48.58 minutes in Fentanyl group with a significant difference ($p < 0.05$) from that of- 127.6 ± 22.32 minutes in Control group("Table-2").

"Table –3." Comparison of Onset & Duration of Sedation

Groups	Onset of Sedation (minutes)	Duration of Sedation (minutes)
Control Group (n=25)	30 ± 0	95 ± 7.07
Morphine Group (n=25)	13.63 ± 3.23*	295.45 ± 55.42**
Butorphanol Group (n=25)	9 ± 2.1*	168 ± 28.59*
Fentanyl Group (n=25)	9.28 ± 1.88*	129.28 ± 29.92

Values are --- Mean ± Standard deviation. * = $p < 0.05$ vs. Control — Significant.
** = $p < 0.001$ vs. Control — Highly Significant.

The mean Onset of Sedation was low- 9 ± 2.1 minutes in Butorphanol group with a significant difference ($p < 0.05$) from that of 30 minutes in Control group. While the mean Onset of Sedation was- 9.28 ± 1.88 minutes in Fentanyl group with a significant difference ($p < 0.05$) from that of 30 minutes in Control group. There was a significant difference ($p < 0.05$) seen in the means of Onset of Sedation in between Morphine group- 13.63 ± 3.23 minutes and Control group- 30 minutes. The mean Duration of Sedation was high- 295.45 ± 55.42 minutes in Morphine group with highly significant difference ($p < 0.001$) from that of- 95 ± 7.07 minutes in Control group.While the mean Duration of Sedation was- 168 ± 25.59 minutes in Butorphanol group with a significant difference ($p < 0.05$) from that of- 95 ± 7.07 minutes in Control group. But there was no significant difference, seen in the means of Duration of Sedation in between Fentanyl group- 129.28 ± 29.92 minutes and Control group- 95 ± 7.07 minutes("Table-3").

"Table – 4." Levels of Sedation

Level of Sedation (Grades)	Control Group (n=25)	Morphine Group (n=25)	Butorphanol Group (n=25)	Fentanyl Group (n=25)	Total (n=100)
I	23 (92%)	14 (56%)	15 (60%)	18 (72%)	70 (70%)
II	2 (8%)	5 (20%)	8 (32%)	6 (24%)	21 (21%)
III	0 (4%)	6 (4%)	2 (4%)	1 (4%)	9 (9%)
IV	0	0	0	0	0
V	0	0	0	0	0

In the total study, the number of the patients in grade I level of Sedation (Awake & Alert)- 70 (70%) was the highest and the number of the patients in grade III level of Sedation (Eyes closed but Arousable to verbal commands)- 9 (9%) was the lowest. The number of patients in grade ll level of Sedation (Awake & Drowsy) was- 21 (21%). No one in any study group reached grade IV or grade V levels of Sedation. seen in ("Table-4").

"Table –5." Side effects

Side effects	Control Group (n=25)	Morphine Group (n=25)	Butorphanol Group(n=25)	Fentanyl Group (n=25)	Total (n=100)
Hypotension	0 (4%)	4 (16%)	3 (12%)	2 (4%)	9 (9%)
Nausea & Vomiting	1 (4%)	4 (16%)	2 (4%)	1 (4%)	8 (8%)
Pruritus	0 (4%)	6 (24%)	1 (4%)	1 (4%)	8 (8%)
Respiratory depression	0	0	0	0	0

In the total study, Hypotension was seen in- 9 (9%) patients. The number of patients with Hypotension in Morphine group- 4 (16%) was the highest and the number of patients with Hypotension in Fentanyl group- 2 (8%) was the lowest. The number of patients with Hypotension in Butorphanol group was- 3 (12%) and no one (0%) had Hypotension in Control group.In the total study, Nausea & Vomiting was seen in- 8 (8%) patients. The number of patients with Nausea & Vomiting in Morphine group- 4 (16%) was the highest and the number of patients with Nausea & Vomiting in Control group- 1 (4%) and in Fentanyl group- 1 (4%) were the lowest. The number of patients with Nausea & Vomiting in Butorphanol group- 2 (8%). In the total study, Pruritus was seen in- 8 (8%) patients. The number of patients with Pruritus in Morphine group- 6 (24%) was the highest and the number of patients with Pruritus in Butorphanol group- 1 (4%) and in Fentanyl group- 1 (4%) were the lowest. No one (0%) had Pruritus in Control group.Occurrence of Respiratory depression was not observed in any study group ("Table-5").

V. Discussion

The effective and adequate post-operative pain management is important, not only for humanitarian reasons but because of the deleterious effects of post-operative pain on various organ systems and the negative impact on post-operative recovery. Effective post-operative analgesia decreases morbidity, which allows early ambulation and discharge. Pain relief may involve administration of analgesic drugs by various routes and/or non-pharmacological techniques. Out of all these measures, epidural administration of local Anaethetics, combination of local Anaethetics and opioids or combination of local Anaethetics and other adjuvants are proved to be very effective in providing good post-operative analgesia. The discovery of spinal opioid receptors has paved a new way to extend the duration of analgesia offered by spinal analgesics in the post- operative period with reduced doses of local Anaethetics and avoiding prolonged residual motor paralysis. The addition of small doses of opioids has made this possible, at the same time avoiding their potential side effects which are commonly seen with their use by other routes i.e. IM, IV for post operative pain relief. Thus combination of Local Anaethetics and Opioids enables to give both the drugs in reduced doses with the advantages of very low incidence of side effects and better pain relief than when either is used alone.

So, to compare the efficacy and safety of different types of opioids, given epidurally, a small study comprising 100 female patients scheduled for lower abdominal surgeries was done. The study was a randomized, double blind, controlled, single dose, comparative study.

The mean Onset of Analgesia of the patients in Fentanyl group- 2.72 ± 0.89 minutes was lower than that in Butorphanol group- 4.64 ± 0.64 minutes and Morphine group- 9.6± 0.96 minutes was highly significantly ($p < 0.001$) less than - 17.96 ± 3.32 minutes in Control (Normal saline) group. These results were similar to that of the studies done by Scott DA Beilby .[7]

The mean Duration of Analgesia of the patients in Morphine group- 1373.2 ± 114.79 minutes was highly significant ($p < 0.001$), that in Butorphanol group- 589 ±100.1 minutes and that in Fentanyl group- 309.6± 48.58 minutes were significantly higher ($p < 0.05$) than that in Control group- 127.6 ± 22.32 minutes. These results were correlated well, with the studies by Akerman W E, Juneja MM et al. [8]

VI. Summary And Conclusion

This study was done to compare the efficacy and safety of epidurally given .Morphine sulphate, Butorphanol tartrate, Fentanyl citrate along with (0.125%) Bupivacaine for post-operative pain management in lower abdominal surgeries. 100 female patients who fulfilled Inclusion and Exclusion criteria were randomly selected and by double blind method were given one of the combination study drugs. Onset of Analgesia, Duration of Analgesia, Onset of Sedation Duration of Sedation, Levels of Sedation, Vital data, Side effects like Nausea & Vomiting, Respiratory depression, Pruritus, Hypotension were recorded, compared and analyzed statistically. This study showed that post-operative pain was effectively reduced in all the study groups except the control (Normal saline) group. The analgesic efficacy of Morphine sulphate + Bupivacaine was higher than the other combinations, in addition to this; the Morphine + Bupivacaine combination also produced significant good conscious sedation (Awake & Drowsy) which is supportive to the analgesic effect. All the Three test groups showed a good safety profile with few minor side effects like Nausea & Vomiting, Hypotension & Pruritus.

In conclusion, Morphine or Butorphanol along with Bupivacaine can be safely given epidurally to obtain effective post-operative analgesia after lower abdominal surgeries. While epidural Fentanyl and Bupivacaine combination can also be safely and effectively used for post-operative analgesia in lower abdominal surgeries but repeated administrations may be required

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