EFFICACY OF EPIDURAL MORPHINE VERSUS MORPHINE WITH TWO DIFFERENT DOSES OF KETAMINE IN POST-OPERATIVE ANALGESIA IN ABDOMINAL HYSTERECTOMY: A DOUBLE BLIND STUDY.

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Abstract

INTRODUCTION: Post operative pain management has always been a challenge to the clinician. If this is not treated adequately, many complication unrelated to surgery may precipitate unnecessarily. The ideal analgesic should have minimal side effects and provide adequate pain relief, not only at rest but also with movements; thereby enabling early ambulation.

METHODS: We had conducted an open prospective case controlled double blind randomized study, on 150 ASA I & II patients, segregated into three equal groups, undergoing total abdominal hysterectomy from January 2008 to June 2009. All consecutive patients between 30 to 60 years of age were included in this study. At the end of surgery the patients were randomized, using sealed envelopes, to receive either morphine alone, or morphine with two different doses of ketamine, through the epidural catheter for post operative analgesia. The assessment of pain as well as the side effects and the number of rescue analgesics and antiemetics administered were noted. All the parametric data were analyzed by using ANOVA and non-parametric data by Friedman Chi-square test, and p-value <0.05 was taken as significant.

OBSERVATION: All the three groups were observed and analysed for analgesic efficacy of the drugs by measuring PEFR, VAS and pain description scores up to 48 hours in the post operative period, simultaneously side effects like nausea vomiting, pruritus, hallucination, sedation and respiratory depression and the number of rescue analgesics and antiemetics were also analysed.

CONCLUSION: Adequate pain relief and early mobilization in the post operative period following gynaecological abdominal surgery improves the physiological parameters and quality of life. We conclude that the synergistic effect of combining morphine 30mcg kg\(^{-1}\) with ketamine 0.25mg kg\(^{-1}\) epidurally provided good analgesia and early mobilization with significantly lesser side effects.

INTRODUCTION

Pain remains the most frequent cause of suffering and disability that impairs the quality of life of millions of people throughout the world especially in the post operative period. If this pain is treated inadequately after any abdominal surgery, it may lead to development of complications, which may not be related to the surgery itself. The quality of effective analgesics is not only to ease patient’s suffering and induce sense of well being in the post operative period, but also to improve the ability for early ambulation, and thereby reducing post operative complications.\(^1\) \(^4\) Epidural opioids can provide potent analgesia in acute pain management, but it precipitates side-effects like respiratory depression even in required analgesics dose. In an effort to maximize analgesia and to minimize the side effects of opioids, epidural ketamine, a NMDA receptor antagonists, may be co-administered with opioids due to its synergistic effect.\(^5\) We had taken these two drugs, morphine and ketamine, in different combinations, to evaluate its efficacy as analgesic during mobilization and physiotherapy, in lower abdominal surgery as well as its side-effects.

MATERIAL & METHODS

This is an open prospective case controlled double blind randomized study. The study cohort included 150 ASA I &II patients who ranged in age from 30 to 60 years. All the consecutive patients, undergoing total abdominal hysterectomy from January 2008 to June 2009 admitted in Subharti Medical College, Meerut in the above age group
were included in our study. This study was started only after obtaining approval from institutional ethical committee and written informed consent from the patients after full explanations of the procedure. The exclusion criteria were patients with systemic diseases like hypertension, chronic obstructive and restrictive pulmonary diseases, diabetes mellitus, coronary artery diseases and hypersensitivity to opioids and local anaesthetics.

Baseline heart rate, BP, peak exploratory flow rate (PEFR) were recorded pre operatively. Pre medication with oral diazepam 0.2mg kg\(^{-1}\) body weight was given on previous night and two hours before the surgery. All patients were preloaded with 500ml of colloid 30 minutes before the procedure. The anaesthesia was given by CSEA (combined spinal epidural anaesthesia) through a single space, needle through needle technique, by Combitec anaesthetic needles GMP, which comprises a Tuohy’s needle 16Gx75mm size and a pencil point spinal needle 26GX108mm, and a T\(_5\) level of sensory block was achieved for the surgical procedure. The motor blockade was assessed according to the Bromage scale and surgery was allowed only after sensory block up to T\(_5\) and motor block score 3 of Bromage scale were achieved.

At the end of surgery the patients were randomized, using sealed envelopes. These envelopes were containing slips labeled either X, Y or Z. These labeled drugs were prepared with the help of another consultant and anaesthesia technician, and were made to an equal volume of 10 ml with the help of normal saline, so that the observer as well as patient was blinded to the constitution of the drug. In one group, the drug was in a combination of morphine 30mcg kg\(^{-1}\) with ketamine 0.25mg kg\(^{-1}\) (mor-ket\(_{25}\)). In the second group, there was a combination of morphine 30mcg kg\(^{-1}\) with ketamine 0.5mg kg\(^{-1}\) (mor-ket\(_{50}\)) whereas the third group was comprised of morphine alone in the dose of 30mcgkg\(^{-1}\) (mor). The zero hour HR, BP, RR, PEFR, pain assessment using both VAS scale and pain description score were noted before administering the allotted drug. The drug assigned was administered at the end of surgery through the epidural catheter slowly over a period of 5 minutes after confirming negative aspiration for blood or CSF, and was repeated in ward at 8 hourly intervals by the blinded observer. HR, BP, RR, VAS, PEFR and pain descriptive score were noted at 4 hourly intervals for next 48 hours. The side effects like nausea, vomiting, sedation, respiratory depression, hallucination, pruritus were scored. The rescue analgesic (Inj. Pethidine 0.05 mg kg\(^{-1}\)) was administered IV if the VAS was > 4, and rescue antiemetic (Inj. Ondensetron 4 mg) IV if nausea vomiting score was >2.

All the parametric data were analyzed by paired sample t-test using ANOVA and non-parametric data by chi-square test, and p-value < 0.05 was taken as significant. At the end of the study disclosure of coding were done. In X –group, the drug was combination of morphine 30mcg kg\(^{-1}\) with ketamine 0.25mg kg\(^{-1}\) (mor-ket\(_{25}\)), in Y-group, the combination was morphine 30mcg kg\(^{-1}\) with ketamine 0.5mg kg\(^{-1}\) (mor-ket\(_{50}\)) and in Z-group, the drug was only morphine 30mcgkg\(^{-1}\) (mor).

**OBSERVATION**

We observed that there was an overall significant drop in the PEFR at the end of surgery (0-hour) as compared to its pre-operative values (n=150). The PEFR was almost towards normal value in the combination groups as compared to morphine alone group (Graph-1). In between the combination groups the PEFR was better in mor-ket\(_{50}\) group. The statistical comparison between the mor-ket\(_{25}\) and mor as well as between mor-ket 50 and mor group also shows significant ‘p’ value throughout the study period as illustrated in table-1. The values of VAS were on higher side in morphine alone group through out the post operative period. After 8-hour the VAS in the combination groups were below 3 (Graph-2). Statistical significance were found in between mor-ket\(_{25}\) and mor as well as mor-ket\(_{50}\) and mor group. But there was no significance among the combination groups (Table-2).

**Figure 1**

![Graph-1 Showing Comparison of PEFR in Different Period](image-url)
The score of 4 and above was achieved after 8 hours of surgery in the combination groups. The patients were comfortable and mobile in these combination groups, whereas in the patients of mor group, pain descriptive scores (Graph-3) was below 3 throughout the study period as illustrated in the graph-3. The higher value of pain descriptive score is indicative of better analgesic efficacy with movement. We observed that all the three parameters i.e. PEFR, VAS and pain descriptive score were significantly altered soon after the drug administration, which were constantly observed all throughout 48 hours of post-operative period in all three groups. There were significant changes in between mor-ket25 versus mor and mor-ket50 versus mor, but it was not significant between mor-ket25 and mor-ket50 group (Table-1-3).
The nausea vomiting score was more in mor group followed by mor-ket\textsuperscript{50} and was least in mor-ket\textsuperscript{25} (graph-4). The sedation was minimal in mor group and in mor-ket\textsuperscript{25} but was high in mor-ket\textsuperscript{50}. Though the sedation scores were higher in mor-ket\textsuperscript{50} it was towards the latter half of the study period probably because of cumulative effect (graph-5).

Rescue analgesia was administered more frequently in mor group. In group with mor-ket\textsuperscript{25} the rescue analgesia was needed in 9 patients and in the group of mor-ket\textsuperscript{50} it was needed in 5 patients only, which was administered just during early post operative period (0-4 hour)(graph-6). Rescue antiemetics were administered frequently in mor group followed by mor-ket\textsuperscript{50} and least in mor-ket\textsuperscript{25} (graph-7).
Efficacy of epidural morphine versus morphine with two different doses of ketamine in post-operative analgesia in abdominal hysterectomy: A double blind study.

Two patients complained of pruritus that belonged to mor group, which were managed with antihistaminic. One patient had mild hallucination around 40 hours of the study, belonged to mor-ket $^{50}$ and was managed with administration of benzodiazepines. None of the patients developed respiratory depression.

**DISCUSSION**

The primary emphasis of this study was not merely the pain relief at rest, but also to provide adequate analgesia during normal functions, such as coughing, early mobilization and physiotherapy. Epidural opioids when used alone in its usual analgesic dose provide pain relief mainly at rest. It does not provide optimal pain relief during coughing or mobilization, though in higher doses it can be achieved on the cost of its side effects especially nausea, vomiting, excessive sedation and respiratory depression. Epidurally administered opioids produces analgesia without sympathetic or motor blockade which is an added advantage in haemodynamically fragile patient or who need to ambulate in early post operative period. Ketamine, NMDA receptor antagonist, although an anaesthetic agent, has been recommended for post operative analgesia. It provides marked analgesia in sub-anesthetic doses, which is $< 1$mg kg$^{-1}$, without inducing excessive salivation, hallucination, nausea and vomiting and respiratory depression. In different studies, it has also been observed that ketamine when used alone in this mentioned dose, does not provide effective post operative analgesia in abdominal gynaecological operations. However, when used along with morphine- it enhances the analgesic effect of morphine and reduces the dose of intrathecal morphine. A major mechanism of spinal opioids analgesic is inhibition of transmitter release from C-fiber primary afferent terminals. The pre-synaptic action of opioids along with the post-synaptic location of NMDA receptors is the rationale for combination of these two drugs. The ketamine interacts as agonist with opiate receptors, by producing synergistic effect; to achieve the desired level of post operative analgesia, with concomitant reduction of side effects. This was the rationale for choosing morphine and ketamine in this study. We had studied the different combinations of these two drugs in different doses with a view of its analgesic efficacy and side effects monitoring.

The post-operative PEFR did not improve in the morphine group, whereas it returned to base line value in combination groups (graph-1). Since PEFR is a more objective parameter than VAS, which is a more subjective one, its return to pre-operative value would be a reliable indicator of pain relief with mobilization and physiotherapy. Although VAS scores were almost similar in the patient group receiving combination drugs, but it was towards higher side in alone morphine group (vide graph-2). Pain descriptive score, which was the hallmark of pain assessment during mobilization, was lower in the alone morphine group all throughout the 48-hour of post-operative study period. Higher and similar pain description scores were observed in the two combination groups, suggesting optimal analgesia in these groups (graph-3).

Number of rescue analgesics was needed more frequently and in more number of patients in morphine group (n=16), followed by the group comprising of mor- ket$^{25}$ (n=9) and least in the mor-ket $^{50}$ group (n=5). The demand of analgesics in mor- ket$^{25}$ group was more in early post operative period as evident in the graph-6. All the patients who required the rescue analgesics demanded their first dose within first four hours of post operative period. The explanation could be that effect of spinal bupivacaine was waning off and the epidural drug has not achieved a satisfactory therapeutic level.

Incidence of nausea and vomiting was higher in all the three groups, probably because of opioid side effects. It was more in morphine alone and in the group comprising of mor-ket$^{50}$, as compared to the group comprising mor-ket$^{25}$, whereas the corresponding VAS score was toward lower side as compared to the other two group, suggesting an optimal drug dose with effective analgesia (graph-2&4). The requirement of rescue antiemetics was at regular interval in morphine alone group, whereas it was also higher in mor-ket$^{50}$ group, but it was administered after the epidural top ups and more towards the later half of the study period (graph-7). Sedation score was higher in mor-ket$^{50}$ group and it was observed...
during later half of the study, probably due to cumulative drugs toxicity.

CONCLUSION

A combined spinal epidural technique for abdominal hysterectomy proved to be a better mode of anaesthesia as it offers the flexibility of achieving a desired level of sensory and motor block. The synergistic effect of combining ketamine with morphine epidurally had provided good analgesia and facilitated early mobilization. The side effects like nausea, vomiting and sedation were minimal in the group comprising of morphine 30mcg kg\(^{-1}\) with ketamine 0.25mg kg\(^{-1}\). To conclude this clinical study, we found that morphine 30mcg kg\(^{-1}\) with ketamine 0.25mg kg\(^{-1}\) is the ideal combination, as it provides effective analgesia as well as early mobilisation without causing much side effects like nausea, vomiting and sedation.

References

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