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Comparison of keorolac with morphine for intraoperative analgesia in patients undergoing total abdominal hysterectomy

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Comparison of Ketorolac with Morphine for Intra-operative Analgesia in Patients undergoing total Abdominal Hysterectomy

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Abstract

Objective: To compare ketorolac 0.35 mg.kg^{-1} with morphine 0.1 mg.kg^{-1} for hemodynamic stability, efficacy of analgesia and incidence of side effects in patients undergoing elective total abdominal hysterectomy.

Methods: Fifty ASA I and II patients, were enrolled in a prospective, randomized and double blind study. They were divided in two equal groups. Group K received Inj. Ketorolac 0.35 mg.kg^{-1} while group M received Inj. Morphine 0.1 mg.kg^{-1} 5 minutes before induction of anaesthesia. Hemodynamic responses to laryngoscopy, endotracheal intubation, and surgical incision were noted.

Results: Data was entered and analysis was done using SPSS version 10.0. Student-t test and comparison of proportions were done where required. ANOVA was done and a p - value of <0.05 was considered statistically significant. There was a significant rise in heart rate, systolic, diastolic and mean arterial pressure in ketorolac group (K) as compared to baseline values at points of endotracheal intubation and surgical incision. Patients in Morphine group (M) showed a significant increase in heart rate only. There was no statistically significant difference between the two groups for supplemental analgesia requirement Intraoperatively and postoperatively. Complications seen with group K were increased surgical wound bleeding in 2 patients (8%), nausea and vomiting in 4 patients (16%) while in group M there was nausea and vomiting in 5 patients (20%), and respiratory depression in 1 patient (4%).

Conclusion: Although hemodynamic stability at points of painful stimulation was lower in patients given ketorolac as compared to morphine, Ketorolac has a place in the intraoperative pain relief in Pakistan and other developing countries where availability of powerful narcotics is erratic (JPMA 53:467;2003).

Introduction

Direct laryngoscopy and endotracheal intubation during anaesthesia and cutting, stretching and tissue manipulation during surgery is the most painful time for a patient undergoing surgery. The elicited pain during a surgical procedure is associated with significant hemodynamic changes including rise in blood pressure, heart rate, sweating, pupillary dilatation etc. These hemodynamic changes are not desirable and may produce deleterious effects in patients with hypertension, ischemic heart disease and cerebro-vascular disease and impose a great challenge for anaesthesiologist to maintain physiologic homeostasis during these periods of stress. Opioids are considered to be the corner stone in the management of intraoperative and postoperative pain, morphine being the "gold standard". Use of Opioids to provide intraoperative analgesia is associated with some untoward effects i.e., somnolence, respiratory depression and nausea and vomiting, which are well known causes of delay in discharge from the post anaesthesia care unit (PACU) and unplanned hospital admission or delay in discharge to home[1].

In Pakistan, availability of opioid analgesics is erratic and there has always been a search to find acceptable alternatives. Ketorolac a pyrrolo - pyrrole derivative NSAID has been regarded as an effective agent for the treatment of moderate to severe pain and has been proposed to provide same level of analgesia as compared to morphine when given in equi-analgesic dose[1,2].

The objective of our study was to compare ketorolac with morphine for its analgesic efficacy, hemodynamic stability and side effects during the intraoperative period in patients undergoing total abdominal hysterectomy.

Methods

After taking approval from the hospital human subjects protection committee, fifty ASA I and II patients within the age range of 16 - 60 years undergoing elective total abdominal hysterectomy were enrolled in this prospective, randomized and double blind study after obtaining a written informed consent. This was a prospective, randomized and double blind study. Blindness was ensured by preparation and administration of the study drugs by another anaesthetist, not connected with the study. Patients with history of allergy to NSAIDs or morphine, history of acid-peptic disease, any anticipated difficult intubation, morbidly obese patients, asthmatics and ASA level III or above were excluded. Patients were divided into two groups, K (ketorolac) and M (morphine) of 25 patients in each group. All patients were given tablet midazolam 7.5 mg orally, one hour before surgery as pre-medication. On their arrival in

their arrival in operating room, patient's heart rate, systolic, diastolic and mean arterial pressure were noted and recorded as the baseline values on attached chart. A 20G intravenous cannula was inserted under local anaesthesia.on the dorsum of the hand for administration of drugs and i.v. fluids. Study drug ketorolac or morphine was prepared in 10 ml syringes and the calculated dose of the study drug was mixed with normal saline to make a total solution of 10 mls. Group K patients were given injection ketorolac in a dose of 0.35 $mg.kg^{-1}$ via I/V cannula while group M patients received injection morphine 0.1 $mg.kg^{-1}$ I/V. Hemodynamic parameters were measured and recorded on the study form every minute till the start of laryngoscopy. Anaesthesia was induced with injection thipentone sodium 5 $mg.kg^{-1}$ five minutes after administration of the study drug. Injection pancuroneum bromide was used to facilitate endotracheal intubation and provide muscle relaxation. Ventilation was assisted manually for three minutes with oxygen mixed with nitrous oxide 50:50% and halothane 0.5% using magill's breathing circuit. Direct laryngoscopy was done after three minutes of assisted ventilation and trachea was intubated with a disposable portex size 7.5 mm ID cuffed endotracheal tube. Anaesthesia was maintained with oxygen 40% mixed with nitrous oxide 60% and halothane 0.5%. Ventilation was controlled and adjusted using a cycled manley ventilator so as to keep the end tidal carbon dioxide between 35 - 40 mm of Hg. Heart rate, systolic, diastolic and mean arterial pressures were recorded every minute for three minutes, and at 5th minute. Adequacy of intraoperative analgesia was monitored clinically by observation of signs of sympathetic stimulation i.e., rise in heart rate and or blood pressure (>20% of baseline value), sweating and lacrimation. An additional top up bolus of initial analgesic dose was given in the presence of any two of the above mentioned signs of increased sympathetic activity. Group K patients were not given ketorolac in excess of a total dos of 30 mg and if required, further analgesia was provided with boluses of injection morphine 0.025 $mg.kg^{-1}$. All patients were continuously monitored for ECG, pulse oxygen saturation, end tidal carbon dioxide. Blood pressure (systolic, diastolic and mean arterial pressure) was measured non-invasively every 5 minutes as per routine. At the end of surgery, halothane was turned off and neuromuscular blockade was reversed. Patients were then extubated and shifted to recovery room. Same monitoring except end tidal carbon dioxide was continued in the recovery room and supplemental oxygen therapy was instituted with a facemask. According to patient's requirement further analgesia provided in the recovery room with 25% of the initial dose of the analgesic drug used in OR. Patients in group K were not allowed to exceed the total dose of 30 mg and if required further analgesia was provided with boluses of injection morphine 0.025 $mg.kg^{-1}$.

Results

Both groups were similar in age, weight and height (Table 1). Baseline hemodynamic variables for heart rate, systolic, diastolic and mean arterial pressures were taken and no statistically significant difference was found between the two groups (Table 2).

After administration of analgesia: There was no significant variation from baseline hemodynamic parameters, but patients in both groups generally showed a slight decrease in heart rate, systolic, diastolic and mean arterial pressure values, this decrease was more in group M patients (Table 3).

After laryngoscopy and endotracheal intubation: In group K, patients showed a significant rise in heart rate and systolic pressure at 1,2 and 3 minutes (Figure 1), systolic pressure at 1 and 2 minutes, rise in diastolic pressure at 1 and 2 minutes and rise in mean arterial pressure 1 minute after laryngoscopy and endotracheal intubation as compared to baseline values (Figure 3). In group M, there was a statistically significant increase in heart rate at 1 and 2 minutes after laryngoscopy and endotracheal intubation but no statistically significant variation in systolic diastolic and mean arterial pressure was seen at this point of observation.

Hemodynamic response to surgical incision: At this point, a significant rise in heart rate at 2nd and 3rd minutes after surgical incision was observed in group K patients (Figure 1). Other variables did not show any significant change at this point.

Supplemental analgesia requirement: Seven (28%) out of 25 patients in each group required additional top up boluses of analgesia. In group K, 4 (57.14%) out of these 7 patients required supplements of narcotics after they had received a total dose of 30 mg of ketorolac (Table 4).

In post anaesthesia care unit (PACU) 12 (48%) out of 25 patients in group K and 10 (40%) out of 25 patients in group M were given additional supplemental top up boluses of analgesia as required. 2 (16.6%) out of 12 patients in group K received morphine top ups when they had already received ketorolac in a total dose of 30 mg (Table 5).

Increased intraoperative bleeding was noticed in 2 (8%) patients in group K, post-operative nausea and vomiting was seen in 7 (28%) patients in group K and 4 (16%) in group M. One patient in group M developed respiratory depression.

Statistics

Data was entered in SPSS version 10.0 and cleaned and verified, before analysis.

Analysis was done in two ways: Simple descriptive statistics was performed on variables that gave us feedback on various continuous and categorical variables.

Table 3. Haemodynamic variable changes after analgesia.

	Group K (Ketorolac)	Group M (Morphine)	P-value
Heart rate	84.2±14.01	89.56±18.95	NS
Systolic blood pressure (mmHg)	127.4±19.8	122.04±12.92	NS
Diastolic blood pressure (mmHg)	81.6±11.48	76.04±10.36	NS
Mean arterial pressure	96.5±13.33	91.32±10.95	NS

NS = not significant

after surgical incision was observed in group K patients (Figure 1). Other variables did not show any significant change at this point.

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Table 4. Additional analgesia top ups required intraoperative.

Study group	No. of patients	Analgesia required		
		Ketorolac	Ketorolac +Morphine	Morphine
Group K (n = 25)	7	3	4	-
Group M (n= 25)	7	-	-	7

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Statistics

Data was entered in SPSS version 10.0 and cleaned and verified, before analysis.

Analysis was done in two ways: Simple descriptive statistics was performed on variables that gave us feedback on various continuous and categorical variables.

Inferential statistics: One way ANOVA was performed, one sample t-test was done on these variables. Chi square test was also done on non-continuous variables, however due to cell counts less than 5 we could not produce the $\chi 2$ - value. These results were therefore analyzed by comparison of proportions.

Surgical manipulation is the most painful period for a patient undergoing a procedure. Anaesthesia does not abolish the acute pain during a surgical procedure. In the presence of adequate depth of anaesthesia, muscle relaxation and ventilation a rise in blood pressure and heart rate usually indicate inadequate analgesia. In addition of rise in heart rate and blood pressure and other signs of sympathetic stimulation for e.g. sweating, lacrimation, and pupillary dilation are also seen in response to the painful surgical stimulation. These responses are undesirable and the rise in blood pressure and heart rate may be deleterious in patients with hypertension, ischemic heart disease or cerebro-vascular disease. This also makes a challenge for the anaesthetist to attenuate these responses in order to maintain body's physiological homeostasis. Good quality analgesia is required to alleviate pain during surgery and in the post operative period. Opioids have been considered to be the corner stone in the management of acute surgical pain.[1,2] Opioids are associated with some untoward effects as well e.g. somnolence, respiratory depression and nausea and vomiting which may contribute to morbidity and may delay in discharge in the day care center.

The use of perioperative NSAIDs has become popular in operations ranging from minor out patient procedures to major in patient surgery.[3]

Ketorolac is a pyrrolo - pyrrol derivative NSAID and acts by inhibition of prostaglandin synthesis. It has been shown in many studies to have analgesic efficacy comparable with that of morphine in equipotent doses.[3-5] Ketorolac has been shown a valuable morphine sparing effect in patients undergoing upper abdominal surgery with a promising 30% reduction in 24 hours morphine consumption.[6] Ketorolac has been suggested to have a place in the management of pain in patients where sedative effects of opioids would be disastrous.[7] The most common Adverse reactions with ketorolac are increased bleeding time, gastrointestinal ulceration and increased risk of acute renal failure.[8-10] These adverse effects occur mainly due to inhibition of prostaglandin synthesis.[7]

Most of the previous studies have compared the analgesic efficacy of ketorolac with morphine in the post operative period.[1,2,4-7] In our study, taking morphine as the gold standard, we have compared the analgesic efficacy, haemodynamic stability, and side effects of ketorolac 0.35 $mg.kg^{-1}$ with morphine 0.1 $mg.kg^{-1}$ in patients undergoing elective total abdominal hysterectomy. We selected this dose of ketorolac because of its ceiling effect and doses between 0.35 and 0.9 mg may produce similar degree of pain relief and is as effective as morphine 10 to 12 mg.[11] The haemodynamic stability was assessed by the change

Conclusion

We conclude that ketorolac 0.35 $mg.kg^{-1}$ is comparable with morphine 0.1 $mg.kg^{-1}$ for its analgesic efficacy but this dose was not adequate to blunt the hemodynamic response to laryngoscopy and endotracheal intubation and surgical incision. The incidence of nausea and vomiting was higher with ketorolac possibly because of inadequate analgesia. There was also increased surgical bleeding with ketorolac in 8% of patients. Increasing the dose of ketorolac may not improve analgesia due to its ceiling effect but may increase the untoward effects. We therefore recommend a combined use of ketorolac with an opioid for the management of pain of moderate to severe intensity.

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