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MORPHINE VS KETOROLAC;
POST-OPERATIVE ANALGESIA IN CARDIOVASCULAR SURGERY

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ABSTRACT... Objective: Evaluate and assess the efficacy of IV ketorolac "as post CABG" surgery analgesic as compared to IV morphine infusion and study the respiratory depressant and sedative effects of IV morphine "as compared to ketorolac" and assessment of efficacy of ketorolac "as a morphine sparing post-operative analgesic". **Study Design:** Comparative or analytic. **Setting:** This study was carried out in Armed Forces Institute of Cardiology (AFIC/NIHD). **Subject:** 150 IHD patients were selected by non-probability convenience sampling technique between ages of 30-50 years undergoing CABG with NYHA class 1. Patients of COPD, Peptic ulcer disease, NSAID allergies, having deranged renal, liver function or coagulation profile, Addicts and alcoholics were excluded. **Interventions:** ASA 1 patients were selected on pre-anaesthetic assessment. In all patients anaesthesia was induced with IV midazolam 0.2mg/kg propofol 2mg/kg and morphine 0.5mg/kg body wt and maintained with propofol infusion 50µg/kg/min. Patients were divided into three groups of 50 patients each i.e morphine group, morphine and ketorolac group and ketorolac group. **Main Outcome Measures:** Analgesia, sedation and respiratory depression was studied in three groups. **Results:** Quality of pain relief was best in the morphine group. The onset of pain relief was similar in all three groups. A high sedation score was seen frequently in morphine group. A few cases of mild sedation were noted in the morphine + ketorolac group .Patients were fully awake in the ketorolac group. A high incidence of respiratory depression was also noted in the morphine group. There was no incidence of respiratory depression in morphine+ketorolac group and ketorolac group. **Conclusion:** This study has demonstrated that ketorolac can provide acceptable analgesia in many patients with severe pain. Ketorolac has no apparent advantage over morphine in terms of pain relief and ketorolac gives ideal results when it is combined with opioid analgesics.

Key Words: CABG*, Post operative analgesia*, Morphine*, Ketorolac*

INTRODUCTION

In this comparative study, efficacy of intravenous ketorolac as a post CABG (coronary artery bypass grafting) analgesic was compared with intravenous morphine infusion as a sole analgesic and in combination. Respiratory depressant and sedative effects of IV morphine infusion were also compared with IV ketorolac. After the study, we concluded that ketorolac can provide acceptable analgesia in many patients of CABG surgery with severe pain. It has no apparent advantage in terms of pain relief over morphine but the incidence of side effects was low. We recommend that IV

ketorolac gives ideal results when it is combined with IV low dose morphine infusion to achieve balanced analgesia in patients with median sternotomy incisions as in CABG surgery.

HYPOTHESIS

Hypothesis of this study was that IV ketorolac gives ideal results when it is combined with IV low dose morphine infusion to achieve balanced analgesia in post CABG surgery patients and with no undesirable side effects of morphine.

MATERIAL AND METHOD

This study was carried out in Armed Forces Institute of Cardiology (AFIC/NIHD). 150 IHD patients were selected by non-probability convenience sampling technique between ages of 30-50 years undergoing CABG with NYHA class I. Patients of COPD, peptic ulcer disease, NSAID allergics, having deranged renal, liver function or coagulation profile, addicts and alcoholics were excluded.

PRE-ANAESTHETIC VISIT

* Patients were examined and assessed according to ASA status.

* ASA I was selected.

* The patients were briefed about the study method before obtaining written consent.

INDUCTION AND MAINTENANCE PROTOCOL

In all patients anaesthesia was induced with IV midazolam[6] 0.2mg/kg propofol[7] 2mg/kg and morphine[6] 0.5mg/kg body wt and maintained with propofol infusion 50µg/kg/min.

GROUPING

Patients were divided into three groups of 50 patients each.

Group 1 (morphine group)

Morphine was given in a dose of 0.05mg/kg/hr[8] and was started post-operatively after weaning from ventilatory support

Group 2 (morphine + ketorolac group)

In this group morphine infusion was started at a rate of 0.025mg/kg/hr[8] post-operatively after extubation. Analgesia was augmented by recommended IV boluses of ketorolac 15 mg followed by 10mg IV 05 hourly after extubation.

Group 3 (ketorolac)

In that group post-operative analgesia was provided by ketorolac only. It was given as a bolus dose of 15mg IV followed by intermittent boluses of 10mg IV every 05 hours[7].

VARIABLES

PAIN

The presence or absence of pain was assessed by a neutral observer every 02 hourly after extubation for 18 hours. The severity of was represented by a *numerical rating scale* in which 0 meant no pain and 10 meant severe unimaginable pain. Patients in each group complaining of pain score more than 4 were taken as a failure of analgesia. These patients were supplemented with morphine boluses of 0.1mg/kg IV and were not studied further.

SEDATION

Sedation was assessed by Ramsay's Ordinal Scaling system[9] every 02 hourly for 18 hours after extubation during which period no sedation was given at all. This sedation score has 5 grades that are;

- Conscious, awake and oriented.
- Drowsy, disoriented and irritable.
- Asleep but respond to verbal command.
- Asleep and respond slowly to loud voice.
- No response.

Patients having sedation score 4 and 5 were considered sedated as a side effect of IV morphine infusion.

BLOOD OXYGEN SATURATION

Respiratory depression as a side effect of morphine was assessed by monitoring blood SaO_2 by a pulse oximeter. Blood saturation less than 90% was taken as a case of respiratory depression. This was again recorded every 02 hourly for 18 hours post-operatively but monitored continuously.

RESULTS

Quality of pain relief was best in the group 1 where only 7 patients were given rescue analgesia. In the group 3, 14 patients had to be given rescue analgesia. Six patients had moderate pain in group 2 and were given supplemental IV bolus of morphine in a dose of 0.1mg/kg. The onset of pain relief was similar in all three groups.

The over all observer assessment made at each patient completed the study, favored morphine and combination of low dose morphine infusion with ketorolac over ketorolac.

NATURE AND INCIDENCE OF SIDE EFFECTS SEDATION

Sedation score was recorded as an ordinal data, where sedation scores 4 or 5 were taken as deeply sedated. Patients having sedation score 1,2 or 3 were considered as mildly sedated or awake.

The score was recorded in all 3 groups at o2 hour interval for 18 hours after extubation. A chi-square test was applied on this data. The sedation and sedation scores in all groups are summarized in table.

Following observations were made at the end of study. A high sedation score was seen frequently in morphine group. A few cases of mild sedation were noted in the group 2. Patients were fully awake in the group 3.

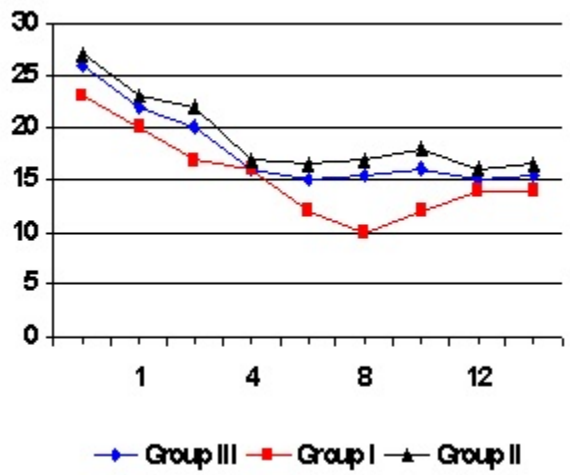
The over all observer assessment made at each patient of 03 groups revealed a high incidence of sedation in the morphine group.

RESPIRATORY DEPRESSION

Blood oxygen saturation was recorded as an ordinal data and interpreted as low when SaO_2 was <90% with out supplemental oxygen by mask. SaO_2>90% was taken as normal.

The blood oxygen saturation was monitored through out and recorded at 2hour interval for 18 hours. A chi-square test was applied on this data. The ventilatory response curves of all the three groups were recorded (Fig. 1).

Fig-1. Ventilatory response curve



VENTILATORY RESPONSE CURVE

A high incidence of respiratory depression was noted in the morphine group. There was no incidence of respiratory depression in group 2 and 3.

Respiratory rate was generally lower in group 1 patients, but rates below 10/min with SaO2<90% were recorded in 10 patients in only group 1, while they were asleep. Wakening the patients up relieved this (Table III).

Table I MEAN PAIN SCORE (0-4)			
Time (hours) after extubation	**Group I (n = 50)**	**Group II (n = 50)**	**Group III (n = 50)**
0	3.0±0.65	3.0±0.67	3.0±0.66
2	0.81±0.47	0.80±0.45	0.94±0.34
4	0.83±0.52	0.76±0.25	0.9±0.27
6	0.8±0.34	0.79±0.36	0.92±0.36
8	0.9±0.39	0.91±0.78	0.95±0.40
10	0.83±0.5	0.78±0.67	0.96±0.6
12	0.75±0.3	0.86±0.56	0.99±0.55
14	0.65±0.35	0.78±0.46	0.85±0.56
16	0.86±0.5	0.78±0.89	0.98±0.66
18	0.76±0.7	0.75±0.24	0.99±0.43

Description	**Group I**	**Group II**	**Group III**
Number	50	50	50
Age year	40.2 ±9.7	42.1 ±8.9	41 ±7.5
Weight (kg)	72 ±10.4	74.5 ±14.2	73 ±9.5
Sex (M/F)	34/16	38/12	35/15
Analgesic	IV morphine	Iv Morphine+ketorolac	IV ketorolac

Table II Statics of Group I (chi$_2$ test)			
	Pain score in group I	**Sedation score in group I**	**Respiratory depression in group I**
Chi-square	25.920	8.000	32.000
Df	1	1	1
Asmyp. Sig.	.000	.005	.000

Table III Frequency of side effects			
Nature of side effects	**Group I (n = 50)**	**Group II (n = 50)**	**Group III (n = 50)**
Respiratory depression (SaO_2<90%)	5	Nil	Nil
Sedation (sedation Score ≥4)	35	13	Nil

Table: IV. Rescue analgesia			
Type of Surgery	**Group I (n = 50)**	**Group II (n = 50)**	**Group III (n = 50)**
CABG	7	6	14

DISCUSSION

Pain is the dominant factor in the production of a variety of complications in the post-operative period and the effective pain relief after surgery is not merely at making the patients more comfortable, but is of vital importance in reducing morbidity. That is the reason that management of post-operative pain is presently a subject of much discussion and study. No single analgesic technique has so far been developed to provide sufficient pain relief, with out side effects.

Morphine and pethidine have been used to relieve the pain but have possible disadvantages of causing nausea, vomiting, sedation and respiratory depression. Our study was aimed at comparing a new drug ketorolac, a NSAID, potentially suitable for pot-operative pain with minimum reported side effects after short-term use, with a drug of established efficacy but with possible side effects. We studied the analgesic effects of these drugs in median sternotomy incisions as in CABG surgery.

The other NSAID usually studied for pot-operative pain include diclofenac, ketoprofen, indomethacin etc. A number of studies were conducted in the treatment of pot-operative pain using ketorolac. They have found it to produce effective analgesia after menisectomy, oral surgery, abdominal and orthopedic surgery[1,2]. Some other studies conducted compared various doses of ketorolac with each other and with morphine[3].

These studies revealed that ketorolac 30 mg and 90 mg was similar and some times better than morphine 10 mg for patients with moderate and severe pain after major abdominal and orthopedic surgery. In one study, ketorolac was compared with papavertum for post-operative analgesia in elderly patients[4]. This study indicated that ketorolac could provide pain relief equivalent to papavertum for many patients. In a similar study, intra-muscular ketorolac was compared with intra-muscular pethidine for analgesia after caesarian section[5]. It concluded that ketorolac 30 mg and pethidine 75 mg has similar short, but variable efficacy after caesarian section. In our study we found that the combination of IV ketorolac 15mg IV stat and then 10mg IV 05 hourly with low dose morphine infusion 0.025mg/kg/hr is far better than ketorolac alone in terms of analgesia and far safer than morphine alone in terms of its side effects for median sternotomy incisions in CABG surgery.

A loading dose of 15 mg followed by intermittent bolus doses of 10mg were chosen in this study because there is evidence of gastric irritation when the dose exceeds 120mg/day. The quality of analgesia in the group 1 and 2 was similar after two hours, although pain scores were low in morphine group. The initial severe surgical pain is incisional in origin due to injury to nerve endings. In injured tissues, maximal concentration of prostaglandin occurs 3-4 hours in response to injury and this correlates with the peak intensity of post-operative pain. Ketorolac decreases the production of peripheral tissue prostaglandin in response to injury, rather than providing afferent block, although there is some evidence suggesting a central role of NSAID in reduction of afferent input. The incidence of side effects was significantly low in the ketorolac group.

This signifies that the drug can be safely given in the immediate post-operative period in adequate doses without involving monitoring techniques and vigilant care. However, care is to be taken in patients with peptic ulcer, renal failure and known allergic to NSAIDs and bleeding tendencies. The cost of ketorolac is relatively high as compared to morphine but keeping in view the lesser incidence of side effects and the requirement of vigilant monitoring with the use of opioids, this is probably worthwhile to bear a little extra cost. Ketorolac has

another obvious advantage over morphine is that; it is easily and freely available in open market. It is not subjected to strict regulation as in case of morphine.

CONCLUSION

This study has demonstrated that ketorolac can provide acceptable analgesia in many patients with severe pain. Ketorolac has no apparent advantage over morphine in terms of pain relief. Ketorolac may have a place in the treatment of post-operative pain in patients in whom the sedative respiratory depressant effects of opioids would be disadvantageous. Ketorolac gives ideal results when it is combined with opioid analgesics. Ketorolac reduces opioid requirement, and if used in combination, improves quality of analgesia. Low incidence of side effects and easy availability of ketorolac makes it a relatively more suitable drug for routine use.

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