Journal of Postgraduate Medicine
Volume 49, Issue 2, April-June, 2003
Print ISSN 0022-3859 CD ISSN 0972-2823

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Journal of Postgraduate Medicine is indexed/listed with
A Comparison of Intravenous Ketoprofen Versus Pethidine on Peri-Operative Analgesia and Post-operative Nausea and Vomiting in Paediatric Vitreoretinal Surgery

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Abstract:
AIM: To compare the efficacy of ketoprofen and pethidine for peri-operative analgesia and post-operative nausea and vomiting in children undergoing vitreoretinal surgery and surgery for retinal detachment. MATERIAL AND METHODS: Children aged 7 to 16 years and ASA I status, undergoing vitreo-retinal surgery were randomly allocated to receive either ketoprofen 2mg/kg or pethidine 1mg/kg intravenously for peri-operative analgesia. In all patients, general anaesthesia was induced with thiopentone and intubation was facilitated with vecuronium bromide and maintained with 33% oxygen in nitrous oxide and isoflurane. Intra-operative and post-operative monitoring was done by an observer blinded to the technique. Intra-operative rescue analgesia was used if heart rate and/or blood pressure increased by 25% from pre-incision values. Post-operative pain and episodes of nausea and vomiting were evaluated at recovery (0 hour), 2, 6 and 24 hours intervals. Standard rescue analgesia and anti-emetic agents were administered if required. RESULTS: Eighty-six children were enrolled in the study. Forty-four received ketoprofen while 42 received pethidine. Intra-operative analgesia was comparable in both the groups and no significant difference was found in the requirement of intra-operative rescue analgesia, as well. Postoperatively 6/44 (13.6%) children in ketoprofen group had pain at recovery compared to 17/42 (40.4%) in pethidine group. Pain at 2, 6 and 24 hours, and postoperative analgesic requirement were not significantly different among the two groups. Post-operative nausea, vomiting, and antiemetic requirement were significantly less in the ketoprofen group at all time intervals. CONCLUSION: Ketoprofen is a satisfactory alternative analgesic to pethidine for vitreoretinal surgery and results in a lower incidence of postoperative nausea and vomiting. (J Postgrad Med 2003;49:123-126)

Key Words: Children, post-operative pain, analgesia, pethidine, ketoprofen

Vitreoretinal (VR) and retinal detachment (RD) surgery constitute a significant proportion of ophthalmic surgery. Both procedures take a long time and involve extensive handling. The majority of patients undergoing RD or VR surgery are hospitalised for severe pain and post-operative nausea and vomiting (PONV). In children and young adults, narcotic agents are the mainstay for intra-operative analgesia with general anaesthesia. These agents can exaggerate the PONV associated with RD or VR surgery. In many adults, these procedures are managed under regional blocks, obviating the use of narcotic agents. Although non-steroidal anti-inflammatory drugs (NSAID) have been used extensively and studied in paediatric strabismus surgery, there is no study evaluating the use of NSAID as sole peri-operative analgesic for VR and RD surgery.

Ketoprofen is an NSAID with central and peripherally mediated analgesic activity. It has liposomal membrane stabilising action and anti-bradykinin activity and inhibitory effects on leukotriene synthesis. Ketoprofen acts rapidly, producing analgesia 10 minutes after an intravenous bolus dose. It has been safely and effectively used for acute pain including post-operative pain. Ketoprofen has been shown to have a low incidence of serious reactions.

A study was therefore undertaken to compare the analgesic efficacy of ketoprofen versus that of pethidine and to compare their effects on PONV when used for peri-operative analgesia in VR and RD surgery in children.

Patients and Methods
Children (aged 7-16 yrs) belonging to ASA 1 status scheduled for retinal detachment or vitreoretinal surgery were included in this study. The research project was approved by the Hospital Ethics Committee. The pa-
Patients were enrolled in the study after obtaining informed written consent from the parents or lawful guardians. Patients with history of asthma or bronchospastic disease, allergy to non-steroidal anti-inflammatory drugs (NSAIDs), those with symptoms of peptic ulcer disease or history of chronic NSAID use were excluded from the study. All patients were pre-medicated with oral diazepam 0.2 mg/kg 60-90 minutes before surgery and were explained to express their pain verbally, as many study subjects were visually disabled. Patients were allocated to one of the two groups using a random number table. Group I received ketoprofen 2mg/ kg IV, while group II received pethidine 1mg /kg IV 15 minutes before induction. All the study drugs were prepared in identical syringes, to blind the investigator and observer.

Induction of anaesthesia and maintenance was done by a doctor who was unaware of the nature of analgesic (ketoprofen or pethidine) used in the patient. Anaesthesia was induced with thiopentone 5mg/kg and tracheal intubation was facilitated with vecuronium bromide (100µg/kg). Anaesthesia was maintained with 33% oxygen in nitrous oxide and isoflurane with controlled mechanical ventilation through a closed circuit, to maintain normocapnia and an end-tidal concentration of 0.6-0.8% isoflurane. Intra-operative monitoring consisted of electrocardiography (EKG), non-invasive blood pressure (NIBP) monitoring, pulse oximetry (SpO2), capnography (EtCO2) and determination of inhalational agent concentration. Rescue analgesia (0.25 mg/kg pethidine IV) was used if heart rate and/or NIBP increased by 25% from pre-incision values. At the end of the procedure, residual neuromuscular blockade was reversed with neostigmine (0.05mg/kg) and atropine (0.02mg/kg) and the trachea was extubated when adequate spontaneous ventilation was established. The patients were observed in the recovery room for 6 hours and kept overnight in their wards.

Post-operative pain was assessed using verbal scoring system at recovery (0 hour), and at 2, 6 and 24 hours after recovery. Pain was expressed as:

0 - No pain
1 - Mild pain, which is tolerable requiring no treatment
2 - Moderate pain requiring oral ibuprofen
3 - Severe pain – the worst that could be experienced by the patient requiring intravenous pethidine

For a score of 2, oral ibuprofen 8mg/kg was given and for a score of 3, pethidine 0.5 mg/kg intravenous was administered.

Post-operative nausea and vomiting were recorded at 0 hr (recovery), 2 hr, 6 hr and 24 hr after recovery. Ondansetron 100 µg/kg was given after 2 episodes of vomiting.

For all pain scores, statistical analysis was done using Mann-Whitney test. PONV episodes, analgesic and antiemetic requirements were subjected to statistical analysis using Pearson’s chi-square test ($\chi^2$ test). $p<0.05$ was considered as significant.

### Table 1: Demographic Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (n=44)</th>
<th>Group II (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean±SD, years)*</td>
<td>11.68±2.81</td>
<td>11.62±2.99</td>
</tr>
<tr>
<td>Weight (Mean±SD, kg)*</td>
<td>32.50±9.85</td>
<td>30.98±11.84</td>
</tr>
<tr>
<td>Male:Female*</td>
<td>7:37</td>
<td>10:32</td>
</tr>
<tr>
<td>Time for Surgery (Mean±SD, hr)*</td>
<td>2.08±0.8</td>
<td>2.12±0.9</td>
</tr>
</tbody>
</table>

*indicates $p>0.5$, no statistical difference between the two groups.

### Table 2: Pain scores in Patients receiving Ketoprofen and Pethidine

<table>
<thead>
<tr>
<th>Time</th>
<th>Group I</th>
<th>Group II</th>
<th>Mann-Whitney U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0hr</td>
<td>0 (0-0)</td>
<td>0 (0-1)</td>
<td>658</td>
<td>0.003</td>
</tr>
<tr>
<td>2hr</td>
<td>1 (0-1)</td>
<td>1 (0-2)</td>
<td>734</td>
<td>0.077</td>
</tr>
<tr>
<td>6hr</td>
<td>2 (1-2)</td>
<td>1.5 (1-2)</td>
<td>916</td>
<td>0.936</td>
</tr>
<tr>
<td>24hr</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>810</td>
<td>0.165</td>
</tr>
</tbody>
</table>

Note: The scores represent median. Figures in parentheses indicate range of scores obtained.
The number of children with more than two episodes of vomiting were significantly lower in group I than in group II (2 and 16 in group I and II respectively, p<0.05). The number of patients requiring anti-emetic was also significantly lower in the group I (8 in group I vs 24 in group II, p<0.05, Figure 2).

Discussion

VR and RD surgeries are associated with severe pain. In adults, many of the short-duration ophthalmologic surgeries are undertaken under regional anaesthesia. As this is not feasible in children and young adults, VR and RD surgeries are essentially carried out under general anaesthesia. Till recently, only narcotic agents such as pethidine have been used for intra-operative pain relief for ophthalmic surgical procedures in children under general anaesthesia. These agents are known to have adverse effects that include nausea and vomiting. The patients undergoing ophthalmologic surgery that involves extensive manipulation of extra-ocular muscles are even more prone to develop post-operative nausea and vomiting because of the oculo-emetic reflex.

Excessive nausea and vomiting may interfere with post-operative care. They lead to increase in the intra-ocular pressure (IOP), which in turn may cause ocular morbidity. In addition, VR surgery often requires intra-operative administration of air, air-gas or silicon oil into the vitreous cavity for prevention of post-operative tamponade. These patients need to be nursed in prone position. Presence of PONV does not allow the patients to be in prone position.

The oculo-emetic reflex further aggravates PONV. Given the detrimental effects of PONV and the inherent risk of this complication related to ophthalmologic surgeries, any factor that would decrease the incidence or prevalence of PONV would be highly useful. Ketoprofen is a non-steroidal anti-inflammatory drug with central and peripherally mediated analgesic activity. The central analgesic effect of ketoprofen has elevated it as a reference drug in the management of post-operative pain. Ketoprofen exhibits a good relative safety profile, and can be injected intravenously as well. It is associated with a low incidence of serious reactions. Like other NSAID agents ketoprofen decreases platelet aggregation and may increase bleeding time and may impair renal function. However, these effects are usually mild, infrequently encountered and are clinically insignificant. More importantly, it is devoid of the common side effects of opiate analgesics. Features such as rapid onset of pain relief, longer duration of action and good analgesic efficacy have led to an increase in use of ketoprofen. It has been safely and effectively used for acute pain including post-operative pain as well as peri-operative pain. Rorarius et al used a constant infusion of intravenous ketoprofen (200mg/24 hr) and diclofenac (150 mg/24 hr); and compared these drugs with placebo after elective caesarean section performed under spinal or extra-dural block. They reported comparable pain relief with both the drugs. The patients in treatment groups required first rescue analgesia after significantly longer time compared to the placebo group. The patients in the treatment groups were more comfortable than those in the placebo group and required less dose of rescue analgesia in 24 hours. Hommeril et al used ketoprofen (200mg IV) followed by infusion of 12.5mg/hr over 13 hours after hip and knee arthroplasty and compared the effects with those of extra-dural morphine (4mg). They reported comparable pain relief in both the groups. These were hardly any side effects noted in ketoprofen group but extra-dural morphine administration was associated with adverse side-effects such as urinary retention and hypercapnia requiring naloxone treatment. They concluded that ketoprofen is an efficient alternative to extra-dural morphine. Tai et al have demonstrated the superior efficacy of ketoprofen over diclofenac in post-operative patients. Similarly Cooper et al have shown ketoprofen to be nearly six times as potent as...
ibuprofen in equianalgesic doses. Elhakim in a study has compared intraoperative ketoprofen with pethidine for post-operative pain relief involving sixty patients undergoing nasal surgery and reported lower pain scores and less post-operative analgesic requirement in those patients who received ketoprofen than those who received pethidine. Kokki et al showed that ketoprofen reduces the postoperative analgesic requirement in children undergoing strabismus surgery. These studies show that ketoprofen has significant efficacy in the management of post-operative pain.

NSAIDs are associated with less PONV as compared to opioids. Mendel and associates compared ketorolac with fentanyl in children undergoing strabismus surgery. The incidence of vomiting in the ketorolac group was 17% compared to 72% in fentanyl group. Ketoprofen 1mg/kg administered IV during strabismus surgery followed by 1mg/kg infusion over 2 hours produced analgesia and reduced opioid consumption and decreased the incidence of vomiting after strabismus surgery.

This is the first study that has compared the efficacy of ketoprofen with that of pethidine for use in peri-operative period in vitreous and retinal surgery. It has demonstrated that ketoprofen has significant analgesic activity and that intravenous ketoprofen during anaesthesia offers satisfactory analgesia. The number of doses of intra-operative rescue analgesics required was comparable. Children who received pethidine had an unacceptably high incidence of vomiting as compared to those who received ketoprofen. Ketoprofen had a fairly low incidence of early as well as late PONV. This should favourably influence the course and duration of hospital stay. In addition, there were no major side effects during administration of ketoprofen. This has been demonstrated in other studies as well.

Omission of narcotics in the study group may cause concern regarding awareness during anaesthesia, as opioids contribute to the net sedation effect. Although opioids in normal doses do not affect bispectral analysis (BIS), monitoring of BIS would have served to highlight differences, if any, in anesthetic depth between the two groups. It is important that the problem of awareness be addressed, as subtle post-operative behavioural problems may be traced back to explicit memory, which the child may not be able to express. The additive MAC was kept at 1.2-1.3 (monitored with a Datex – Engstrom monitor) in all children using an appropriate inspired concentration of isoflurane, which we felt would eliminate this problem. Addition of BIS as an adjunct to monitoring should be kept in mind while designing a similar study.

References