

Opioids for Pediatric Pain Management

RV HRIDYA, MG GEETA, P GEETHA, VT AJITHKUMAR, A RIYAZ

From Institute of Maternal and Child Health, Government Medical College, Calicut, Kerala.

Correspondence to: Dr RV Hridya,
Senior Resident, Department of
Pediatrics, Government Medical
College, Calicut, Kerala.
rv.hridya@yahoo.co.in
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Objectives: To study the efficacy and adverse effects of opioids in management of pain in children. **Methods:** A descriptive study was conducted in children aged below 15 years with moderate to severe pain, and response to opioids and adverse effects were assessed at 24, 48 and 72 hours after administration. **Results:** 100 children (68% males) with median (IQR) age of 6.5 (3.5,10) years were studied. 81% ($n=81$) children with moderate pain and 78.9% ($n=15$) with severe pain responded to opioids in 72 hours. Among children with severe pain of non-malignant origin, 80% ($n=8$) responded in 48 hours compared to 11.1% ($n=1$) with malignancy and this difference was statistically significant at 24 hours ($P=0.005$). Of children with severe pain 73.7% ($n=14$) developed adverse reactions compared to 30.9% ($n=25$) with moderate pain. **Conclusions:** Children with moderate-severe pain, either of malignant or non-malignant origin could be managed effectively with opioids without severe adverse effects.

Keywords: Analgesia, Analgesic ladder, Malignancy.

Despite the relatively high prevalence of pain and its distressing implications for children and their families, it is often under-recognized and under-treated. Lack of awareness and misconceptions regarding use of opioids has led to suboptimal use of this class in children [1]. Opioids are indicated for moderate to severe pain when other measures have failed. The present study was conducted to ascertain the efficacy of opioids in both malignant and non-malignant conditions in children.

METHODS

This study was conducted after Institutional Ethics Committee clearance, among children under 15 years with moderate to severe pain at a tertiary centre in India over 24 months from January, 2012. Critically ill children with unstable vital parameters, obtunded sensorium, intellectual disability and whose parents refused consent were excluded. Severity of pain was assessed using age appropriate tools (3 years and below - FLACC scale, 3-7 years - Wong Baker Faces Scale, 7 years and above - Numerical Rating Scale) and grading was done as 0 - no pain, 1-3: mild pain, 4-6: moderate pain, 7-10: severe pain [2-4].

Children with moderate pain were treated with a weak opioid (codeine) and those with severe pain were given a strong opioid (morphine) along with step 1 analgesics and adjuvants, when indicated according to WHO three step ladder [5]. Follow up by one of the four trained observers was done at 24, 48 and 72 hours, when the severity of pain

and adverse effects were carefully assessed and dose of drug titrated. Reduction in severity of moderate-severe pain to no pain/mild pain was considered as response to treatment.

Statistical analysis: Data were entered into a semi-structured proforma, and statistical analysis was done by SPSS 16.0 software. The analysis of the data was done by Pearson chi-square test and a P value <0.05 was taken as significant.

RESULTS

Of the 100 children enrolled in the study with median (IQR) age of 6.5 years (3.5, 10), 68% were boys and 40% were between 5 and 10 years of age. Moderate pain was seen at presentation in 81 children and severe pain in 19. Among the 56 children with cancer, 66% ($n=37$) had acute lymphoblastic leukemia. Hemophilia (36.4%) and burns (31.8%) were the common non-malignant conditions. Nociceptive pain predominated in our study ($n=96$), while 4 children had additional neuropathic component, which included a child with leukemia with brain metastasis, and three hemophilia patients having nerve compression.

Codeine was prescribed for 81 children with moderate pain. At 48 hours, 93.6% ($n=44$) with malignancy ($n=47$) and 94.1% ($n=32$) with non-malignant conditions ($n=34$) responded. All children with moderate pain responded within 72 hours. There was no statistically significant difference in opioid response of moderate pain in malignant and non-malignant conditions. The dose requirement of

Table I Adverse Effects in Children Receiving Opioids for Pain in Malignant and Non-malignant Conditions

Adverse effects	Severe pain (n=19)		Moderate pain (n=81)	
	Malignant (n=9)	Non malignant (n=10)	Malignant (n=47)	Non malignant (n=34)
Constipation	2 (10.5)	4 (21.0)	10 (12.3)	10 (12.3)
Constipation with sedation	2 (10.5)	1 (5.3)	0	0
Constipation with nausea /vomiting	2 (10.5)	0	4 (4.9)	0

Constipation with nausea/vomiting and sedation in 1 child with severe malignant condition, and pruritus in one child with moderate pain in malignant condition were also noted. Only 2 children in malignant condition had only sedation as side effect.

codeine given 4-hourly was 0.5 mg/kg/dose for 96.3%, while 3.7% required 1mg/kg/dose.

Of the 19 children with severe pain started on morphine, none responded in 24 hours. At 48 hours, 80% ($n=8$) with non-malignant conditions responded compared to 11.1% ($n=1$) with malignancy. Severe pain took a statistically significant longer duration for response in both malignant and non-malignant cases. The dose requirement of morphine given 4 hourly was 0.3 mg/kg/dose for 57.9%, while the rest required 0.5 mg/kg/dose.

Of the children with moderate pain, 48.1% ($n=39$) had reduced severity at 24 hours, against 68.4% ($n=13$) with severe pain. Reduction in severity at 48 hours occurred in 93.8% ($n=76$) children with moderate pain against 94.7% ($n=18$) with severe pain. Thus, reduction in severity was faster in severe pain than moderate pain but this was not statistically significant.

Adverse effects occurred in 39 (39 children) and were increased in children with severe pain on morphine (73.7%, $n=14$), compared to moderate pain on codeine (30.9% $n=25$) ($P=0.001$) (**Table I**). The major adverse effect was constipation (36%). Adverse effects were more in malignancy, females (64.1%), under-five children (43.3%) and those with pain lasting beyond 2 weeks (50%).

All children were co-prescribed with bisacodyl anticipating constipation; 6% required cremaffin in addition. Those on morphine were co-prescribed with domperidone. Ketamine was given in a dose of 0.15 mg/kg sublingually to reduce incident pain in children with burns. Amitriptylline was given to reduce neuropathic pain in four children.

There were no misconceptions about opioids in 77% parents, whereas 20% were concerned about addiction and 3% considered that they were to be only used terminally.

DISCUSSION

Opioids are important in management of pain of both malignant and non-malignant causes in children. Although seldom used in non-malignant conditions, this study

showed that they are equally efficacious. Children with acute lymphoblastic leukemia and hemophilia, accounted for the male preponderance [6]. Among children with moderate pain, all responded to codeine in 72 hours, with no significant difference between malignant and non-malignant conditions. Children with severe malignancy-related pain responded more slowly, possibly due to comorbid conditions, therapeutic procedures and adverse effects of chemotherapy [7]. Severe pain treated with a strong opioid was more rapidly ameliorated than moderate pain, although it took longer for complete response. Although not statistically significant, this has immense clinical relevance.

Adverse effects were commoner in severe pain treated with morphine, than moderate pain treated with codeine similar to previous studies [8,9]. Increased adverse effects in younger children may be due to delayed clearance by immature hepatic enzyme systems. Parental misconceptions including fear of addiction and the belief that opioids were end stage drug, were overcome by timely counseling and guidance from physicians trained in pain management.

Limitations of the study include small sample size, lack of a control group and no follow-up beyond 72 hours. Besides, different age-appropriate tools were used to assess severity of pain, which may not be representative.

The World Health Organization has recently replaced the three-step analgesic ladder by two-step ladder since variable expressions of enzymes involved in biotransformation of codeine (CYP2D6) can lead to substantial differences in plasma concentration of the active metabolite, morphine [10]. However, in our study, codeine was found to be uniformly safe and efficacious in management of moderate pain. Hence, use of the three-step ladder in populations where it has been shown to work may be reconsidered, although this may require larger studies.

Contributors: MGG: conceptualized the study, supervised the study, contributed to review of literature, statistical analysis, critically analyzed and reviewed the manuscript; PG,VTA, AR: data analysis, critical review of manuscript; RVH: collection of

WHAT THIS STUDY ADDS?

- Opioids are efficacious in malignant and non-malignant pain in children, with frequent but non-serious adverse effects.

data, analysis, preparation of manuscript, review of literature. All authors were involved in the assessment and management of patients and approved the final version of manuscript.

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