Prescribing of Nonsteroidal Anti-inflammatory Drugs, Tramadol, and Opioids in Children: Patterns of Its Utilization

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Background: Analgesics is commonly used in children but little is known about its patterns of utilization. This study explored the patterns of analgesic prescribing in children. Materials and Methods: This cross-sectional study used prescription databases of tertiary hospital settings in Malaysia from 2010 to 2016. Prescriptions for nine NSAIDs (diclofenac, ketoprofen, etoricoxib, celecoxib, ibuprofen, indomethacin, mefenamic acid, meloxicam, and naproxen), tramadol, and five other opioids (morphine, oxycodone, fentanyl, buprenorphine, and dihydrocodeine) prescribed for children aged <18 years were included. Number of annual patients and prescriptions were measured and analyzed using Stata v15. Results: During a 7-year study period, a total of 5040 analgesic prescriptions of the nine NSAIDs, tramadol, and five other opioids were prescribed for 2460 pediatric patients (81.8% NSAIDs patients, 17.9% tramadol patients, and 0.3% opioid patients). Ibuprofen was the primary analgesic in young children less than 12 years old (≤2 years old [y.o.] [75%], 3–5 y.o. [85%], and 6–12 y.o. [56.3%]). However, there was a wide range of analgesics used in older children (>12 y.o.) with the majority for naproxen (13–15 y.o. [28.2%] and 16–17 y.o. [28.2%]). Other frequently prescribed analgesics for older children included ibuprofen (20.6%) and diclofenac (18.2%) for 12–15 y.o. and diclofenac (26.7%) and tramadol (17.6%) for 16–17 y.o. Conclusion: Ibuprofen was the primary analgesic for children less than 12 y.o., whereas there was a wide range of analgesics prescribed for children age >12 y.o. including naproxen, diclofenac, and tramadol.

Keywords: Analgesics, children prescribing, Malaysia, NSAIDs, opioids, tramadol

INTRODUCTION

Analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed in children for relieving pain in various painful conditions. However, most analgesics have not been systematically studied in children population,[1,2] and most of the efficacy and safety studies were conducted in adults. Children are not small adults and their pharmacokinetics profiles including drug distribution, absorption, excretion, and metabolism are different from adults at all levels. This pharmacokinetics issue is already complicated in adults and has become compounded in children, particularly in neonatology, in which their pharmacokinetic data are not available in clinical trials.[3]

The lack of evidence on the benefits and harms of analgesics in children is not only of NSAIDs but also for other analgesics, including opioids. Owing to this, the Centre for Disease Control and Prevention does not recommend the use of opioid in children and adolescents <18 years.[4] Specifically, the use of

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The dependent variable was analgesic (either yes or no to be prescribed with a particular analgesic). The independent variable was age (stratified for young children (≤12 years old) and older children (>12 years old). The reference group comprised young children. Odd ratios (ORs) and 95% confidence intervals (CIs) were used to summarize the association. Two-sided P values (significance: P < 0.05) were used for statistical tests. All data analyses were performed using Stata v15.1 (Stata Corp. Stata Released, College Station, Texas).\(^6\)

### RESULTS

During the 7-year study period, a total of 5040 analgesic prescriptions were identified. The nine NSAIDs, tramadol, and five other opioids were prescribed for 2460 pediatric patients (81.8% NSAIDs patients, 17.9% tramadol patients, and 0.3% opioid patients). Of these analgesics users, 54.0% are male and 46% are female. The mean (SD) age was slightly older for male children (14.0 ± 3.65 years old) compared to that for female children (13.77 ± 3.54 years old) [Table 1].

Among the three types of analgesic, NSAIDs was the most commonly prescribed in all children age groups. Children in the oldest age group (>15 and <18 years) were the predominant group (37.8%) prescribed with analgesics followed by children in the age group of >12 and ≤15 (32.9%), >5 and ≤12 (24.9%), >2 and ≤5 (3.8%), and ≤2 (0.5%) years [Figure 1].

In young children aged <12 years, ibuprofen was the primary analgesics prescribed (75% for children ≤2, 85% for >2 and ≤5 and 56.3% for >5 and ≤12 years old). In older children aged >12 years, the majority were prescribed naproxen (28.2% for children >12 and ≤15 and 28.2% for >15 and ≤18 years old). There was also a wide range of other analgesics used in children aged >12 years, including ibuprofen, diclofenac sodium, ketoprofen, celecoxib, and mefenamic acid. It was also observed that tramadol was prescribed in most of the age groups with the highest in children >15 and <18 years old (17.6%), followed by >2 and ≤5 (9.3%), >12 and ≤15 (9.1%), and ≤2 (8.3%). The overall prevalence of opioids prescribed for children in all age groups was very low.

Results of the logistic regression analysis revealed a significant decrease in the chances of ibuprofen (OR = 0.10, 95% CI 0.086–0.115) being prescribed for older children. In contrast, the likelihood of naproxen (OR = 1.34, 95% CI 1.17–1.55), tramadol (OR = 3.99, 95% CI 3.01–5.31), celecoxib (OR = 6.95, 95% CI 3.76–12.82), diclofenac (OR = 4.23, 95% CI 3.39–5.27), ketoprofen and codeine for pain relief in children of less than 12 years, which is contraindicated due to the association with the risk of respiratory depression.\(^3\)

It is timely to examine children prescribing to help us better understand the many important aspects of analgesic use in children. This study aimed to evaluate the prescribing patterns of NSAIDs, tramadol, and opioids analgesics in children of different age groups.

### MATERIALS AND METHODS

The results of this study are reported in an aggregated manner using de-identified data. An informed consent was not required because the patients were not directly involved in this study. The Medical Research Ethical Committee, Ministry of Health, Malaysia has granted an ethical approval for this study to be conducted (NMRR-16-2135-33068).

### Study design and setting

This cross-sectional study was conducted at two tertiary outpatient hospital settings in Malaysia. Various facilities are available at these ~800–1000-bedded hospitals, including renal services, pain services, anesthesiology, and surgery. The prescription databases of these hospitals were assessed from January 1, 2010 to December 31, 2016. The data extracted from the databases included drug names, quantities, strengths, frequencies, duration, prescription dates, and issuing departments. All available prescriptions for NSAIDs (ketoprofen, celecoxib, diclofenac, etoricoxib, indomethacin, ibuprofen, meloxicam, naproxen, and mefenamic acid), tramadol, and five other opioids (morphine, oxycodone, fentanyl, buprenorphine, and dihydrocodeine) were included.

This study incorporated patients aged <18 years who have been prescribed with at least one analgesic prescription during the study period. The age of each patient was calculated based on the date of first opioid prescription entry in the database. All the patients were then stratified into five age groups: ≤2, >2 and ≤5, >5 and ≤12, >12 and ≤15, >15, and ≤18 years old. Patients have also been stratified into young children (≤12 years old) and older children (>12 years old) to assess the difference in analgesic prescribing between these two groups. The total number of patients and analgesics prescriptions for each age group and the departments that issued the analgesics were enumerated.

Patient demographics were measured using mean, standard deviation (SD), and range. Simple logistic regression was used to measure the association between prescribed analgesics (e.g., ibuprofen, naproxen, celecoxib, and tramadol) and age variables.
Table 1: Patient demographics

| Descriptions         | NSAIDs | Opioids | Tramadol | Total |
|----------------------|--------|---------|----------|-------|
| No. of patients (n)  | 2012   | 42      | 406      | 2460  |
| %                    | 81.8   | 1.7     | 16.5     | 100   |
| Age                  |        |         |          |       |
| Mean                 | 13.6   | 14.7    | 15.2     | 13.9  |
| Median               | 15     | 15      | 16       | 15    |
| Mode                 | 17     | 17      | 17       | 677   |
| Range                | 0–17   | 0–17    | 1–17     | 0–17  |
| Std                  | 3.7    | 2.3     | 2.8      | 3.6   |
| Age group            |        |         |          |       |
| ≤ 2 years old (n)    | 18     | 0       | 2        | 20    |
| %                    | 0.9    | 0       | 0.5      | 0.8   |
| >2 and ≤5 years old (n) | 84    | 0       | 10       | 94    |
| %                    | 4.2    | 0       | 2.5      | 3.8   |
| >5 and ≤12 years old (n) | 449   | 5       | 27       | 481   |
| %                    | 22.3   | 11.9    | 6.6      | 19.5  |
| >12 and ≤15 years old (n) | 614   | 20      | 109      | 743   |
| %                    | 30.5   | 47.6    | 26.8     | 30.2  |
| >15 and <18 years old (n) | 847   | 17      | 258      | 1122  |
| %                    | 42.1   | 40.5    | 63.5     | 45.6  |
| Gender               |        |         |          |       |
| Female               | 958    | 21      | 152      | 1131  |
| %                    | 47.6   | 50      | 37.4     | 46    |
| Male                 | 1054   | 21      | 254      | 1329  |
| %                    | 52.4   | 50      | 62.6     | 54    |

n = number

Figure 1: Number of prescriptions for NSAIDs, tramadol, and opioids and total number of all analgesic prescriptions in children with different age groups

(OR = 3.98, 95% CI 2.55–6.21), and mefenamic acid (OR = 3.74, 95% CI 2.64–5.28) being prescribed was significantly greater for older children. Other analgesics were not included in the logistic regression analysis as the prescriptions were less than 3%.

In children aged ≤2 years, analgesics were mainly prescribed by an emergency department (62.5%), whereas in other four children age groups the pediatric department was the main contributor to the analgesics prescriptions in children (60.6% for >2 and ≤5, 75.5% for >5 and ≤12, 63.5% for >12 and ≤15 and 48.6% for >15 and <18 years old).

**DISCUSSION**

This study showed that ibuprofen was the primary NSAIDS prescribed for young children <12 years of age at the outpatient tertiary hospital settings in Malaysia.
This finding is consistent with other studies,\textsuperscript{[7-9]} which also found the use of ibuprofen as a preferred analgesic in children. According to these previous studies, ibuprofen has a superior analgesic potency for treatment of many clinical conditions, such as sprains, fractures, and postoperative pain. The side-effect profile of gastrointestinal disturbance of ibuprofen is found to be comparable to acetaminophen, making it preferable to acetaminophen for the treatment of mild-to-moderate pain conditions.\textsuperscript{[10]} Another factor that may contribute to the high use of ibuprofen is the availability of ibuprofen in various dosage forms, such as oral suspension, infant drops, tablet, and intravenous formulations. It was also reported that ibuprofen was commonly used for feverish illnesses in younger children, which may likely contribute to a high use of ibuprofen.\textsuperscript{[7]}

In children aged 12 years old and above, this study found the use of a wide range of analgesics (ibuprofen, diclofenac sodium, ketoprofen, celecoxib, tramadol, and mefenamic acid), which may reflect the flexibility of prescribing analgesics in older children. Naproxen was the most commonly used analgesic in this group, similar to the finding of a study conducted in Netherland, which showed naproxen being primarily prescribed in girls. This study, however, was conducted in girls aged younger than 12 years.\textsuperscript{[7]}

Ibuprofen was the preferred analgesic in children, which is in line with the recommendation on analgesic use in children. The use of tramadol may need to be reviewed as it is contraindicated to be used in children. Although most analgesics are typically well tolerated in children, they pose the risks of gastric irritation, increased bleeding, and acute kidney injury.\textsuperscript{[13]} Future studies need to look at the appropriate prescribing of analgesics in children particularly in children of less than 2 years of age, due to unavailability of pharmacokinetic data for this population in clinical trials. Moreover, this population also has greatest differences in their pharmacokinetic profiles compared to adults.

**Conclusion**

Taken together, this study provides insights into the prescribing of analgesics in children at outpatient tertiary hospital settings in Malaysia. Ibuprofen was the preferred analgesic in children, which is in line with the recommendation on analgesic use in children. The use of tramadol may need to be reviewed as it is contraindicated to be used in children. Although most analgesics are typically well tolerated in children, they pose the risks of gastric irritation, increased bleeding, and acute kidney injury.\textsuperscript{[13]} Future studies need to look at the appropriate prescribing of analgesics in children particularly in children of less than 2 years of age, due to unavailability of pharmacokinetic data for this population in clinical trials. Moreover, this population also has greatest differences in their pharmacokinetic profiles compared to adults.

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**Conflicts of interest**

There are no conflicts of interest.

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