

Pain management in COVID-19 pediatric patients—An evidence-based review

ABSTRACT


Despite our growing knowledge about the COVID pandemic, not much concern has been focused upon the effective pain management in pediatric patients suffering from this SARS CoV2 virus. Symptoms with pain like myalgia (10%–40%), sore throat (5%–30%), headache (14%–40%) and abdominal pain (10%) are common in children suffering from COVID. (3-5) We conducted a systematic review regarding analgesia for COVID positive pediatric patients. Cochrane, PubMed, and Google scholar databases were searched for relevant literature. Owing to the novel status of COVID-19 with limited literature, we included randomized controlled trials (RCTs), observational studies, case series and case reports in the descending order of consideration. Articles in languages other than English, abstract only articles and non-scientific commentaries were excluded. The Primary outcome was evaluation of pain related symptoms and best strategies for their management. Our review revealed that a multidisciplinary approach starting from non-pharmacological techniques like drinking plenty of water, removing triggers like inadequate sleep, specific foods and psychotherapy including distraction, comfort and cognitive behavioural strategies should be used. Pharmacological approaches like acetaminophen, NSAIDS, spasmolytics etc. can be used if non-pharmacological therapy is inadequate. As per the current strength of evidence, acetaminophen and ibuprofen can be safely administered for pain management in children with COVID-19. Undertreated pain is a significant contributor to increased morbidity and poor prognosis. Integration of evidence based non-pharmacotherapies in the multidisciplinary pain management will contribute towards improved functioning, early recovery and better quality care for pediatric patients suffering from COVID.

Key words: Analgesia; analgesic safety; COVID-19; pain management; pediatric

Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious zoonotic disease which has recently been declared as a global health emergency by World Health Organization (WHO). Within a very short span of time, a multitude of research and data has cropped about different aspects of this illness

caused by SARS-CoV2 virus, including its spread, clinical features, and management. It is already known that the disease is associated with respiratory, gastrointestinal (GI), neurological, and cardiovascular illness in humans.^[1] Though there are researches regarding management of COVID-positive pediatric patients but the chief focus stays on the anti-viral

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treatment, respiratory care, and infection control. As for now, the disease has shown to affect children to a lesser extent as compared to elderly and adults, nearly accounting for 1–2% of the total cases. Even after an extensive research, we were unable to find any comprehensive data regarding management of pain in pediatric patients suffering from COVID-19. The illness severity in a study including over 2,143 COVID-positive pediatric patients, ranged from asymptomatic (4%), mild (51%), moderate (39%), severe (5%), and critical illness in 0.6%.^[2] As the majority of pediatric patients suffer from mild to moderate disease, supportive therapy becomes the mainstay of treatment in them. An array of symptoms were witnessed in the three case series done on children with SARS CoV2, like fever (91–100%), myalgia (10–40%), sore throat (5–30%), headache (14–40%), and abdominal pain (10%).^[3-5] These figures effectively highlight the importance of analgesic treatment in supportive therapy for pediatric patients suffering from COVID.

Despite the expanding realms of pain management in current practice, the pediatric population has always presented grave challenges. There has been consistent evidence that the complaints of pain continue to receive sub-optimal treatment among hospitalized children. In the current scare of COVID, with more emphasis on treatment of severe illness patients in hospitals, reluctance to outreach hospitals for mild to moderate pain among patients re-enforces the considerable probability of pain component going under-noticed and under-treated in the COVID-positive children. Adequate treatment of pain is not only essential to optimize recovery, but also to reduce morbidity and mortality. It also contributes to allay the child's fear and anxiety, distress among family, and makes the overall health care more satisfactory. We are doing this systematic review to fill up the lacuna in efficient analgesia for COVID-positive children and to optimize the health care practice in this challenging group.

Objectives

We have performed this systematic review to address the lack of a clear consensus in pain management and provide clarity for efficient analgesia in COVID-positive children. The goals of our review include elucidating the clinical situations warranting pain management in pediatric COVID patients, exploring the evidence regarding safety of various analgesics and identifying the best available practices for efficient analgesia. The aim of this review is not to give an exhaustive description of each symptom and its treatment, but rather to provide a brief overview of the specific therapies for pain in pediatric COVID-positive patients, highlight the significance of integrated pain

management, and explore the evidence base of commonly utilized analgesics in current scenario.

Literature Search Strategy

We conducted our initial search for published literature regarding COVID-19 among children between December 2019 and May 2020. However, due to very limited literature over this brief period and keeping into consideration, the novel status of COVID-19 and the similarities with other acute respiratory illnesses, we also included the studies related to SARS infection over a period between 2000 and 2020 in our review. Two researchers independently searched through the literature, collected all the relevant articles, and one other researcher reviewed all the selected abstracts. Literature for this review was identified by searching the following online databases: Cochrane, PubMed, and Google scholar. We used a well formulated PICOS framework to conduct the research [Table 1]. The keywords used for the search were- “COVID-19” AND “children,” “Coronavirus” AND “children,” “COVID-19” AND “pediatric,” “COVID-19” AND “analgesia,” “COVID-19” AND “pain management,” “COVID-19” AND “NSAIDS,” “SARS-CoV2,” “SARS” AND “children,” “pediatric” AND “acute viral infection,” “COVID-19” AND “TREATMENT,” “COVID-19” AND “DRUG INTERACTIONS.” We also screened the WHO database of publications on novel corona virus for any potentially relevant articles.

Data Analysis

The search was conducted with systematic reviews and meta-analysis with highest consideration, followed by randomized controlled trials (RCTs), observational studies, finally case series, and case reports. We excluded the non-scientific commentaries, reports, and news articles from this analysis. We also excluded the articles published

Table 1: PICOS framework

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|---------------|---|
| Population | Children and adolescents (<19 y) with confirmed severe acute respiratory syndrome coronavirus 2 infection |
| Interventions | Approaches for pain management |
| Controls | Comparison with alternative treatment approaches |
| Outcomes | Primary objective- 1. Evaluation of pain symptoms 2. Therapeutic strategies for pain Secondary objective- 1. Safety profile of analgesics in these patients |
| Study design | Randomized controlled trials Case –control studies Case series Case reports |

in languages other than English and abstract only articles. From the initial 7,555 publications, we finally included 40 articles in our systematic review. Details regarding the data selection are given in Figure 1. Only 18 of these publications had direct evidence related to coronavirus, while the rest 22 provided indirect evidence. Based on the main research objectives, articles were classified into one of the following research domains clinical manifestations, treatment including pharmacological and non-pharmacological approaches and the evidence of safety of analgesics.

Pain Assessment in Children

Pain is also known as the “fifth vital sign” and it is essential to assess and record it as often as other vital signs. The assessment of pain in children is difficult to perform as they often cannot accurately describe the discomfort. The aim of pain assessment is identification of the site, quality, intensity, and duration of their pain along with the aggravating and relieving factors.^[6] There are various pain assessment tools available for use in pediatric population. These include Premature Infant Pain Profile (PIPP) for preterm and full-term neonates, COMFORT scale (0–3 yr, Toddler and pre-school children), Oucher (≥ 3 yr). In the older children above 5 years of age, self-reporting is the preferred method of assessing pain. Wong-Baker faces scale and Visual analog scale (VAS) can be used in this group of children. Children having communication disability or cognitive impairment

can be assessed for pain by Non- Communicating Children’s Pain Checklist—R (NCCPC-R).^[7] Effective pain management in children involves identification and assessment of pain, followed by prompt pain control through a multifaceted approach, while attempting for resolution of the underlying cause.

Selection of an appropriate therapy is critical in designing an individual treatment plan for the child. This can be targeted for the specific subset of pain symptoms to improve prognosis. A multidisciplinary approach to pain management should be taken to treat pain in pediatric patients. As sore throat, headache, myalgia and abdominal pain are the most commonly encountered pain symptoms in COVID illness, hence, we will try to elucidate on them specifically.

Sore Throat

Sore throat is a frequent symptom in COVID-19 patients. Sore throat in children can prompt reluctance to eat or drink which can further aggravate the clinical condition. However, myriad of causes can present with the sore throat. During the course of this viral illness, sore throat may improve on its own. The need to alleviate the pain in throat in such patients comes from the goal to improve patient’s comfort, the ability to eat and drink and hence, decrease overall morbidity. Management of sore throat can be done using both pharmacological and non-pharmacological approaches.

Non-pharmacological approaches

Therapy can be initiated with the non-pharmacologic components, especially since many children (with mild-moderate severity) may not require pharmacologic treatment. Supportive measures like drinking plenty of water, using throat lozenges, and steam inhalation may prove beneficial.^[8] During the course of illness, hydration status of the children should be checked frequently, warm water or beverages should be offered as dehydration may lead to dryness which can further exacerbate the throat pain.^[9]

Pharmacological approach

Acetaminophen is usually well tolerated in children. It may be administered every six hourly as needed in doses of 10–15 mg/kg per oral. Most common single dose range of children is around 40–480 mg depending on the age and weight, not exceeding five doses per day. It should not be used in children younger than 3 months of age without consultation with a health care provider due to risk of toxicity. Ibuprofen can also be used to relieve sore throat, in doses of 5–10 mg/kg, every 4–6 h in children. The maximum doses should not exceed 40 mg/kg per day.^[10] Ibuprofen is better tolerated with less adverse effects.^[11] Aspirin should be

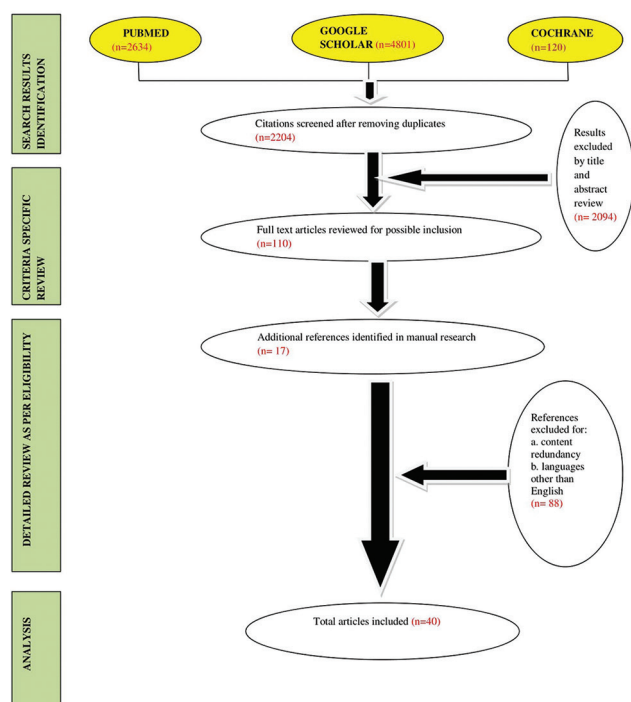


Figure 1: Literature search algorithm

avoided in children with acute febrile illness as it has been found to be associated with a potentially serious condition known as Reye syndrome in children less than 16 years of age with viral illness.^[12] Sprays containing topical anesthetic agents are also available to manage throat pain, but found to be less effective. Moreover, many throat sprays contain benzocaine, which is a common anesthetic agent and it can cause hypersensitivity reactions in children. Thus, they should be used with caution in children.

Headache

Headache is reported as one of the manifestations of COVID-19.^[13] However, whenever presented, we should rule out other potential differentials before labeling it as secondary to COVID infection. It can be managed by using acetaminophen or ibuprofen, with acetaminophen being the drug of choice for headache treatment in COVID-19.^[14] Remove any associated trigger factors like inadequate hydration, lack of sleep, specific foods and beverages and inappropriate physical exercise.

Myalgia

Myalgia resulting from COVID-19 may precede the respiratory symptoms in children. Kawasaki like illness has also been found associated in coronavirus positive children presenting with non-purulent conjunctivitis, polymorphic rash, mucosal changes, and swollen extremities.^[15] The muscle and body pains are usually self-limiting, managed by the supportive measures and symptomatic treatment.^[16] We can use acetaminophen or ibuprofen as discussed above for pain. In addition to these, adequate rest and stress relief exercises such as yoga and meditation to relieve muscle tension can be advised to provide relief. Drinking plenty of fluids can also help in alleviating the muscle pains. If the child is running fever, bringing temperature down to decrease shivering and hence relieving the excessive muscle exhaustion should be also emphasized. Mild–moderate body pains improve over time with adequate rest, rehydration and analgesics.

Abdominal Pain

Gastrointestinal symptoms like diarrhea, vomiting, and abdominal pain has been seen in majority of children suffering from COVID.^[17] This can be really distressing in pediatric patients. We should start the empirical treatment with the suppression of acid in children with upper abdominal pain. If the child is taking ibuprofen for pain, we should change the medicine to acetaminophen. Anti-emetics like ondansetron, anti-motility and spasmolytic (drotaverine, Mebeverine)

agents should be used in case of vomiting, diarrhea and abdominal cramps.^[18] Zinc supplementation can help to reduce the severity of diarrhea and hence, relieve abdominal pain. Supportive treatment given to the children includes plenty of warm fluids and sufficient calorie intake. We should also try the non-pharmacological therapies like dietary interventions, probiotics and biopsychosocial modifying therapies, that is, hypnotherapy, cognitive behavioral therapy, and physiotherapy.^[19]

Alternatively, we can also use the Unani medicinal agents which are plant-based medicines and with no side effects. Plants like *Glycyrrhiza glabra* has shown antiviral properties against many viruses including SARS related coronavirus. Homeopathic medicines are also an alternative in the management. Children should be encouraged to take sufficient amounts of fruits and nuts, which act as immunity boosters.^[20]

Role of Psychological Approach and Education

Incorporation of integrative non-pharmacological approaches in multifaceted pediatric pain management has been demonstrated to be both feasible and helpful.^[21,22] In recent years, psychotherapy has been identified as an integral component of pain management. Parents can provide distraction and comfort with physical touch (e.g., cradling and cuddling), books, and music therapy. Favorite toys, singing, storytelling, and engaging in conversation can also be used for distraction. The child should be encouraged to choose the distraction, as this will provide better engagement by giving them a sense of control.^[23] Education about their illness or injury, information like why it hurts and when it will possibly resolve, is also useful in helping both the child and their parents feel more in control. Cognitive behavioral strategies involving the use of breathing techniques, relaxation approaches, education, and self-regulation have been found to be effective in providing pain relief on their own or in combination with pharmacological pain management. Advise the parents to frequently wash the toys that the child plays with and also take care of environmental sanitation.

Safety of Analgesics in Pediatric COVID Patients

NSAIDs constitute the most commonly used drugs for pain management in both children and adults. There is a raised concern for higher risk of adverse effects with their use in patients having acute viral respiratory diseases including COVID-19 and an increased risk of contracting COVID-19 from the use of NSAIDs. Due to paucity of evidence

specific to COVID patients, the judgment to use NSAIDs for the pain management in COVID-19 infections needs to be based on both the scarce available COVID specific direct evidence and an indirect evidence from the existing literature regarding the use of these drugs in other acute respiratory infections.

Direct evidence

There were reports of worsening of COVID-19 symptoms with use of ibuprofen in children in France.^[24] In the literature published by Fang *et al.* they have claimed that administration of ibuprofen to COVID-19 infected patients may worsen their clinical condition.^[25]

However, WHO has issued a scientific brief concluding that there is no clear evidence of severe adverse effects with use of NSAIDs in COVID patients, after a comprehensive review of evidence.^[26]

Indirect evidence

Krenke *et al.* concluded in their study that both ibuprofen and acetaminophen are potential risk factors for aggravation of community acquired respiratory infections in children.^[27] There are few other studies in past showing negative impact of NSAIDs on patients having acute respiratory infections.^[28,29] A randomized trial concluded that indomethacin acts as an inhibitor of coronavirus replication and could be beneficial as an anti-inflammatory agent in SARS infection.^[30]

We realize that a randomized trial is not feasible in the current scenario. Hence, large population based observational studies should be conducted to provide strong evidence regarding association of NSAIDs and COVID symptoms. Till then, as per the recommendations of WHO, guided by the current strength of evidence, acetaminophen and ibuprofen can be safely administered for pain management in children with COVID-19.^[31]

An Overview of Probable Drug Interactions

There is currently no specific antiviral treatment available for COVID-19. Hence, the mainstay of treatment is symptomatic including respiratory therapy, cardiovascular support, and nutritional therapy. Remdesivir, chloroquine (CQ) and hydroxychloroquine (HCQ) are the most popularly used drugs for anti-viral and immunotherapy but none is still approved for coronavirus. Lopinavir, ritonavir, Ribavirin and many other antivirals are being tried for treatment.^[32] Keeping this in mind, we also need to explore any possible interactions between these commonly used drugs and analgesics.

Co-administration of diclofenac with chloroquine and hydroxychloroquine has been found to result into an increased risk of elevation of liver enzymes.^[33] Studies have documented that paracetamol inhibits the autophagy by CQ and HCQ and leads to an increase in plasma concentration of unchanged paracetamol.^[34,35] Although these studies were conducted with anti-rheumatic doses of CQ and HCQ, these doses (3–6 mg/kg) are comparable to those used for prophylaxis and treatment of SARS CoV2 infection.^[36] Though, these inferences call for caution while co-administration of these drugs, but this indirect evidence should not be taken as a guide for use of NSAIDs in patients receiving CQ and HCQ and comprehensive research is required in this aspect to provide more evidence. There is still no evidence of any drug interactions with remdesivir which is a broad spectrum antiviral drug.^[37] Concurrent administration of acetaminophen with ritonavir may result in elevated acetaminophen and aspirin plasma concentrations as they inhibit the enzyme CYP3A4 responsible for metabolism of these NSAIDs.^[38] Caution and close monitoring is advised if the opioid analgesics like oxycodone, hydrocodone and morphine are administered together with lopinavir; ritonavir. These antiviral drugs are potent inhibitors of CYP3A4 and hence, may increase opioid plasma concentrations and increased adverse reactions.^[39] Hydroxychloroquine and Lopinavir/ritonavir should not be co-administered due to increased levels of hydroxychloroquine and subsequent toxicity like QT prolongation and hypoglycemia.^[40]

Strengths

An important strength of our systematic review is the absence of population bias (all pediatric patients tested SARS-CoV-2 positive). Also, to the best of our knowledge, this is the first systematic review that summarizes the current evidence on pain management in children infected with SARS-CoV-2 infection, while filling the substantial lacuna in acknowledgment and information about this critical part of treatment.

Limitations

We acknowledge that a major limitation of our research was that it included direct evidence regarding COVID over a brief period of five months with substantial indirect evidence. Hence, Secondly, the included data were observational designs, and simple case series or case reports. Hence, there is a considerable heterogeneity in our studies.

Conclusion

With the prime focus of health care shifting toward prevention of COVID transmission and care of critically ill

patients, children with mild–moderate illness are potentially vulnerable to inadequate treatment. This in addition to the fear, anxiety, different coping mechanisms and lack of social support can further aggravate the clinical condition in children. Undertreated pain is a significant contributor to increased morbidity and poor prognosis. Hence, an effective pain management in pediatric age group should be given equal priority with due recognition to physical and psychological components of pain. Integration of evidence based non-pharmacotherapies in the multidisciplinary pain management will contribute toward improved functioning, reduced morbidity, early recovery, and better quality care.

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Conflicts of interest

There are no conflicts of interest.

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