BONUS DIGITAL CONTENT

Medicine by the Numbers

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Ibuprofen vs. Acetaminophen for Fever or Pain in Children Younger Than Two Years

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Details for This Review

Study Population: 241,138 patients younger than two years from 18 studies who received acetaminophen or ibuprofen for fever or pain

Efficacy End Points: Reduction in temperature or pain within four hours and four to 24 hours

Harm End Points: Serious adverse events, renal impairment, gastrointestinal bleeding, liver injury, severe soft tissue infection, empyema, and asthma or wheezing

Narrative: Fever and pain are common in childhood. Acetaminophen and ibuprofen are the most widely used medications to treat these conditions, with up to 95% of children receiving acetaminophen by nine months of age.[1] The decision to use ibuprofen or acetaminophen for fever or pain typically varies based on purported benefits and harms, and recommendations regarding these medications differ in terms of age and dosing.[2,3]

Several older studies suggest that acetaminophen is safer because ibuprofen was associated with an increased risk of acute kidney injury and serious bacterial infection or soft tissue infection.[4-9] However, more recent evidence suggests early acetaminophen exposure may be associated with childhood asthma.[10,11] Previous meta-analyses have suggested that ibuprofen is likely more effective than acetaminophen for fever and at least as effective as acetaminophen for pain relief, with no difference in adverse events.[12,13] These earlier reviews had significant heterogeneity and included ages one month to 18 years, limiting the applicability to children younger than two years.

The meta-analysis in this review included studies of any design and children younger than two years; directly compared acetaminophen with ibuprofen; and reported antipyretic, analgesic, and/or safety outcomes.[14] Primary outcomes were fever (continuous variable) or pain within four hours of treatment. Secondary outcomes included the proportion of patients who were fever-free or pain-free within four hours of treatment and at four to 24 hours (categorical variable). Safety outcomes comprised serious adverse events, renal impairment, gastrointestinal (GI) bleeding, liver injury, severe soft tissue infection, empyema, and asthma or wheezing. The authors did not place limits on total duration of follow-up.

The meta-analysis included 18 studies with 241,138 patients from seven countries and multiple health care settings. The studies consisted of 11 randomized studies (n = 28,450) and seven nonrandomized studies (n = 212,688). Of these nonrandomized studies, two were prospective cohort, two were retrospective cohort, one was case-control, one was cross-sectional, and one was retrospective cross-sectional. Based on data from four randomized controlled trials only, children who received ibuprofen had lower temperatures within four hours compared with those who received acetaminophen

IBUPROFEN VS. ACETAMINOPHEN FOR CHILDREN YOUNGER THAN TWO YEARS

Benefits	Harms
Ibuprofen lowered temperature (standardized mean difference = 0.38°C [0.21°F]) more than acetaminophen within four hours	No one was harmed
1 in 8 receiving ibuprofen vs. acetaminophen was afebrile within four hours	
1 in 6 receiving ibuprofen vs. acetaminophen was afebrile at four to 24 hours	
1 in 4 receiving ibuprofen vs. acetaminophen had reduced pain at four to 24 hours	
12.5% reduction in fevers within four hours with ibuprofen vs. acetaminophen	
18.5% reduction in fevers at four to 24 hours with ibuprofen vs. acetaminophen	
25.2% reduction in pain at four to 24 hours with ibuprofen vs. acetaminophen	

The NNT Group Rating System

Green	Benefits greater than harms
Yellow	Unclear benefits
Red	No benefits
Black	Harms greater than benefits

(standardized mean difference = 0.38°C [0.21°F]; 95% CI, 0.08 to 0.67; moderate-quality evidence). Based on data from five randomized controlled trials, ibuprofen was associated with a higher likelihood of the child being afebrile at four hours (odds ratio = 1.86; 95% CI, 1.01 to 3.44; absolute risk reduction = 12.5%; number needed to treat [NNT] = 8) and at four to 24 hours (odds ratio = 2.22; 95% CI, 1.55 to 3.17; absolute risk reduction = 18.5%; NNT = 6).[14]

No study reported pain outcomes within four hours of treatment. Two randomized studies found reduced pain based on a variety of scales (standardized mean difference = 0.20; 95% CI, 0.03 to 0.37) and higher likelihood of the child being pain-free (absolute risk reduction = 25.2%; NNT = 4) at four to 24 hours. There were low rates of adverse events reported in the randomized studies, with most studies reporting no adverse events during the follow-up period. Seven studies with moderate-quality evidence reported similar potential harms within 28 days, including renal impairment, liver injury, and asthma or wheezing, whereas low-quality evidence suggested similar rates of GI bleeding. No severe soft tissue infections or empyema was reported. Two randomized trials reported similar rates of asthma or wheezing and no serious adverse events in the long term (greater than 28 days).

Caveats: There are several limitations associated with this meta-analysis. Studies differed in setting, drug dosages, sample size, and duration of therapy. Only four studies with 796 patients evaluated analgesia, and there were no studies reporting on pain within four hours of therapy. Pain scales were heterogeneous and included the Children's Hospital of Eastern Ontario Pain Scale, facial expression, a discomfort scale, an irritability score, and the Non-communicating Children's Pain Checklist. Sample sizes were small in most studies, limiting the comparison of adverse events. Only nine studies evaluated medication safety as a primary outcome, and measurement bias may have affected evaluation of adverse events. Most randomized studies provided adverse event data for less than 28 days, with most of the long-term adverse events reported only by observational studies.

Conclusion: The American Academy of Pediatrics recommends against the use of acetaminophen in infants younger than three months or ibuprofen in those younger than six months without clinical evaluation, although it states that both medications are safe and effective when used appropriately.[2] Based on the available evidence, the meta-analysis found that ibuprofen is more effective in reducing temperature and pain at various follow-up periods compared with acetaminophen.[14]

These findings are consistent with previous studies, but the meta-analysis found no differences in adverse events. Thus, we have assigned a color recommendation of green (benefits outweigh harms) for the use of ibuprofen compared with acetaminophen in children younger than two years. Further study is needed to evaluate combination therapy, specific dosing, and use in those younger than six months.

This series is coordinated by Christopher W. Bunt, MD, *AFP* assistant medical editor, and Daniel Runde, MD, from the NNT Group.

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