Does the use of non-steroidal anti-inflammatory drugs in children with varicella increase the risk of soft tissue infections?

**CLINICAL SCENARIO**

A 3-year-old is seen in Accident & Emergency with a rash and fever. On examination, there are vesicular lesions consistent with chicken pox. His parents are concerned about his fever and distress despite regular paracetamol, and ask you if they can give ibuprofen as well.

**STRUCTURED CLINICAL QUESTION**

In children with varicella (population), does the use of non-steroidal anti-inflammatory drugs (NSAID) (exposure) increase the risk of infectious complications of varicella (outcome)?

**SEARCH STRATEGY**

Ovid Medline was searched using the search terms (Varicella (mapped to Chicken Pox)) AND (NSAID OR ibuprofen OR non-steroidal anti-inflammatory). The search resulted in 64 articles and all available abstracts were reviewed. Review articles, studies not addressing the question, case studies, letters and articles not published in English were excluded at this point. Ten studies were included for full text review.

**Table 1** Does the use of non-steroidal anti-inflammatory drugs in children with varicella increase the risk of soft tissue infections?

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Outcome</th>
<th>Key results</th>
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| Dubos et al,
  2008, France | All children with varicella infection or varicella complication admitted to 11 hospitals in a district of France over 1 year (n=159) | Multicentre prospective study Level 3b | Bacterial skin infection (clinically diagnosed) within 4 weeks of onset of varicella | OR 4.8 (1.6–14.4) Statistically significant association between NSAID exposure and bacterial skin infection | No attempt to define time of exposure to NSAIDs to show causality (eg, NSAIDs could have been given after symptoms of skin infection developed) |
| Mikaeloff et al,
  2007, UK   | Cases and controls drawn from a group of patients of all ages who visited the GP with varicella (identified from the UK GP research database) | Nested case–control study Level 3b     | Diagnostic codes of SSTI within 2 months of varicella exposure (n=386) | ARR 4.9 (2.1–11.4) Statistically significant association between NSAID exposure and diagnosis of SSTI | Did attempt to define timeline by limiting it to NSAIDs prescribed 2 days before SSTI was diagnosed, but we do not know when these NSAIDs were given Only included patients whose NSAID was prescribed by the GP, which is not uniformly done in the UK (only 3% of cases in this study had NSAIDs prescribed) |
| Lesko et al,
  2001, USA   | Cases identified by network of paediatric ID specialists | Multicentre prospective case–control study Level 3b | NSTI or GAS within 2 weeks of primary varicella (n=52) | OR for any infectious complication with NSAID exposure was 3.9 (1.3–12) OR for NSTI with NSAID exposure was 1.3 (0.33–5.3) OR for invasive GAS with NSAID exposure was 2.9 (1.1–7.5) Not worse with more doses of NSAID (OR remained 3.4 with escalating doses or 3/4 doses) | robust system for identifying timing of onset of infectious complications and timing of NSAID administration (potential to demonstrate causality) Statistically and clinically significant risk of infectious complication with exposure to NSAID However, in subanalysis this exposure was only significant for patients with invasive GAS (not NSTI), and who had taken both ibuprofen and acetaminophen (paracetamol) Authors say ‘this unexpected result is unclear’ Two sponsors: paracetamol/ ibuprofen manufacturers |
| Zerr et al,
  1999, USA   | Hospital study: participants identified by discharge codes + surveillance | Case–control (mixed retrospective and prospective) Level 4 (poor quality) | Cases (n=19): NF within 3/2 varicella NF = fever + surgery | OR, 10.2, 95% CI 1.3 to 79.5 Statistically significant association between NSAID exposure and NF | 7 out of 9 cases who used ibuprofen did so after symptoms of secondary infection Very large CIs with very different clinical implications Used controls with SSTI rather than uncomplicated varicella |
| Choo et al,
  1997, USA   | ICD-9 codes from a healthcare provider database | Not named but nested case–control study Level 3b | Cases: all skin infections within 30 days of diagnosis of varicella (n=89) | OR 5.1 (0.1–32.5) for ibuprofen use in preceding 30 days OR 1.9 (0.3–6.5) for ibuprofen use in preceding 180 days There was no statistically significant association between the use of ibuprofen and the development of skin infections | About half the included superinfections did not require systemic antibiotics, so were they really superinfections? Large CIs No statistically significant results Only three cases with ibuprofen exposure |

GAS, group A streptococcal infection (soft tissue or otherwise); GP, general practitioner; ICD, International Classification of Diseases; ID, infectious diseases; NF, necrotising fasciitis; NSAID, non-steroidal anti-inflammatory drugs; NSTI, necrotising soft tissue infection; SSTI, skin and soft tissue infection; ARR, absolute risk reduction.
articles were relevant. On review of the full text, five of these ten articles did not address the clinical question and were excluded, leaving a total of five studies. Each article was appraised using a structured approach (table 1).

COMMENTARY

There have been a number of studies trying to determine whether exposure to NSAIDs in patients with varicella increases the risk of developing secondary infections. However, the studies differ in their exposures and outcomes: some looked at all NSAIDs and some just at ibuprofen. Two studies looked at any skin and soft tissue infection (SSTI) or invasive group A streptococcal infection (iGAS). Zerr et al’s outcome of interest was only necrotising fasciitis (NF) and in fact used patients with other SSTIs postvaricella as their control group.

In every study, the results pointed towards an association with NSAID exposure and postvaricella complications, with all but one achieving statistical significance. This finding was confirmed in the most recent study, a 2008 publication looking at 159 children hospitalised in France. There was a statistically significant association between NSAID exposure and subsequent bacterial skin infection (OR 4.8, 95% CI 1.6 to 14.4). They did not, however, ask whether the NSAID exposure occurred before or after the onset of signs of a skin infection.

In fact, only two studies made an attempt to differentiate between exposure and causality. It could be that children with more severe chicken pox are more likely to need symptom relief and are also more likely to develop a secondary skin infection. It could also be that NSAIDs are being used to treat fever caused by an already-established skin infection, rather than contributing to its development. This is exemplified in Zerr et al’s paper, where seven of their nine cases were first exposed to ibuprofen after the development of symptoms of NF. Lesko et al also found that parents were likely to choose to use ibuprofen if their children had higher temperatures, chills, somnolence or seemed severely ill.

The paper that best addressed this potential confounder was Lesko et al, who developed a structured method for assessing the time of onset of skin or iGAS infection (index hour) and did not include NSAID exposure in the 12 hours before the index hour. Their primary outcome achieved statistical significance, with cases who had used an NSAID being more likely to develop the compound outcome of NSTI or iGAS (OR 3.9, 95% CI 1.3 to 12). However, they are hesitant to attribute causation. They note that when the results are broken down, this association is with iGAS rather than NSTI and is only observed in the group of patients who have used an NSAID in combination with paracetamol. They also note that the association does not strengthen with increasing doses of NSAID. This study benefited from industry sponsorship from manufacturers of children’s acetaminophen (paracetamol equivalent) and ibuprofen.

This series of studies demonstrates clearly that there is an association between NSAID exposure and the development of secondary infections in varicella. Lesko et al’s study, the only one to adequately look for a causative association, found a statistically significant association. They conclude that this is the result of unknown confounders and have not specifically recommended avoiding NSAIDs in patients with varicella. However, none of the studies have satisfactorily demonstrated that NSAIDs are safe to use in patients with varicella. In the absence of further information, it is difficult to endorse the use of NSAIDs in varicella.

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