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The PANSAID Randomized Clinical Trial: A pre-planned 1-year follow-up regarding harm.

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Short title: 1-year follow-up from the PANSAID trial
Abstract

Background: Limiting harm from postoperative pain treatment is important. However, long-term follow-up from acute pain trials are rare. The aim of the study is to provide long-term follow-up data regarding harm from the ‘Paracetamol and Ibuprofen in Combination’ (PANSAID) trial.

Methods: In this preplanned long-term follow-up study from the PANSAID trial, we used data from Danish national health registries (the Danish National Patient Registry and the Danish Civil Registration System) in addition to the 90-day follow-up in the original trial. The primary outcome was 1-year proportion of patients with one or more serious adverse events.

Results: 1-year follow-up was complete for 551 patients (99%). We found three additional patients with one or more serious adverse events in the 1-year follow-up compared with the 90-day follow-up. The relative risk of having one or more serious adverse event when randomized to ibuprofen compared with paracetamol was 1.40 (95% CI: 0.84 to 2.33, P = 0.20).

Conclusion: We found no statistically significant difference in 1-year serious adverse events between patients randomized to ibuprofen compared with paracetamol in patients having planned primary total hip arthroplasty. There were few additional events from the 90-day follow-up to the 1-year follow-up.

Editorial Comment:

For this clinical trial of acute pain management after total hip replacement surgery, an additional planned assessment for long term follow-up for harm is presented here. No difference in serious adverse events between the 2 treatments, paracetamol vs ibuprofen, were observed at 1 year after surgery.
Introduction

Postoperative pain treatment without long term adverse events is of utmost importance to have safe treatments, but long term follow-up regarding harm in trials investigating postoperative pain treatment is largely non-existing. Given the possible association between short term treatment with nonsteroidal anti-inflammatory drugs (NSAID) and long term harm, long term follow-up from acute pain trials are highly needed.

We recently reported the main results, including a 90-day follow-up, from the ‘Paracetamol and Ibuprofen in Combination’ (PANSAID) trial in patients having planned total hip arthroplasty randomized to ibuprofen versus paracetamol. In this pre-planned follow-up study we present the pre-planned 1-year follow-up on serious adverse events.

We hypothesized that patients randomized to ibuprofen compared with paracetamol would have increased risk of serious adverse events.
Methods

A detailed description of both the trial protocol and the statistical analysis plan are available,\textsuperscript{5,6} and the main results have been published.\textsuperscript{4} In brief, the Paracetamol and NSAID in combination (PANSAID) trial (clinicaltrials.gov identifier NCT02571361) randomized 559 patients to 4 different combinations of paracetamol, ibuprofen and placebo for the first 24 hour after elective primary total hip arthroplasty. The trial medication was given four times the first 24 hours and consisted of A) paracetamol 1000 mg and ibuprofen 400 mg, or B) paracetamol 1000 mg, or C) ibuprofen 400 mg, or D) paracetamol 500 mg and ibuprofen 200 mg.
Regarding harm, groups with ibuprofen were collated and compared with the paracetamol alone group. The co-primary outcome regarding harm was 90-day proportion of patients with one or more serious adverse events (SAEs). SAEs were defined using a modified ICH-GCP definition (defined as any untoward medical occurrence that results in death; is life threatening; requires hospitalization; or results in significant or persistent disability or incapacity; birth defects; or a medical intervention to prevent one of the before-mentioned outcomes).

In this preplanned 1-year follow-up, we followed participants through national registries (the Danish National Patient Registry and the Danish Civil Registration System) in addition to the 90-day follow-up in the original trial.

All analyses were performed by STATA version 16. For relative risk we used a generalized estimating equating model with hospital as a cluster variable. A two-sided p-value of less than 0.05 was considered statistically significant.
Results

We included 556 randomized patients in the intention to treat population, 142 were randomized to paracetamol treatment alone and 414 were randomized to a treatment including ibuprofen. One-year follow-up was complete for 551 participants (99%). Three participants had died (all in groups including ibuprofen).

Compared with the 90 follow-up, three additional participants had one or more SAEs at 1-year follow-up (Table 1 and 2). The relative risk for SAEs comparing patients treated with ibuprofen with those treated with paracetamol alone was 1.40 (95% CI: 0.84 to 2.33, P = 0.20).
Discussion

In this preplanned 1-year follow-up from a large randomized clinical trial investigating paracetamol and ibuprofen for postoperative pain, we found few additional participants having one or more SAEs within 1 year compared with within 90 days after surgery, and there was no statistically significant difference between participants randomized to either ibuprofen or paracetamol treatment. However, the power to detect a clinically relevant relative risk increase of patients with one or more SAEs within 1 year was, obviously, low in this trial. We observed an increase in patients with one or more medical SAE after 1 year that was also present at the 90-day follow-up. This increase, from 3% to 7%, if related to NSAID use within the first 24 hours, would be of clinically relevance.

Only few additional patients with one or more SAEs were observed in the 1-year follow-up compared with the 90-day follow-up. For the 1-year follow-up, we used registry data only and all events were hardly captured. Contrary, analyses have shown very small differences in treatment effects between data from adjudication committees and data from Danish registries.

This 1-year follow-up has several limitations. First, the short intervention period of 24 hours may not be an appropriate length of intervention in the clinical setting, however, randomized data regarding long term follow-up of harm is sparse in acute pain research. NSAID have been associated with harm even with short term use and the optimal length of follow-up remains undetermined. Second, we do not have data on the use of analgesics, including use of NSAIDs, in the period from day 91 to 1 year. However, there were no differences in NSAID use in the four intervention groups within 90 days (68% to 80% of participants using NSAIDs). The lack of detailed information on the use of analgesics in the follow-up...
period (especially from day 91 to 1 year) is a major concern regarding causality between the intervention and the outcome.

In conclusion, there was no statistically significant difference in 1-year serious adverse events between patients randomized to ibuprofen compared with paracetamol in patients having planned primary total hip arthroplasty. There were few additional events from the 90-day to the 1-year follow-up.

Acknowledgements

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Conflicts of interests

The authors have no conflicts of interests. Ole Mathiesen is an associate editor at Acta Anaesthesiologica Scandinavica.
References

Table 1 Serious adverse events within one year post-randomization

<table>
<thead>
<tr>
<th></th>
<th>Paracetamol</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with one or more SAE, N (%)</td>
<td>16 (11.3)</td>
<td>65 (15.7)</td>
</tr>
<tr>
<td>No SAE, N (%)</td>
<td>125 (88.0)</td>
<td>345 (83.3)</td>
</tr>
<tr>
<td>Missing data, N (%)</td>
<td>1 (0.7)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

SAE, serious adverse events
Table 2, Types of serious adverse events within one year post-randomization

<table>
<thead>
<tr>
<th>Related to surgery, n (% of randomized patients)</th>
<th>Paracetamol, n = 142</th>
<th>Ibuprofen, n = 414</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical site infection, n</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Mechanical problems with the prosthesis, n</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Medical problems after surgery, n (% of randomized patients)</td>
<td>4 (3%)</td>
<td>29 (7%)</td>
</tr>
</tbody>
</table>
- Pneumonia, n | 0 | 3
- DVT, n | 1 | 4
- PE, n | 1 | 1
- Low hemoglobin, n | 0 | 3
- Delirium, n | 0 | 1
- Syncope, n | 0 | 1
- Vertigo, n | 0 | 2
- Cardiological, n | 1 | 7
- Dyspepsia, n | 1 | 1
- Renal, n | 0 | 1
- Constipation, n | 0 | 2
- Abdominal pain, n | 0 | 2

"Not" related to the surgery, n (% of randomized patients) | 4 (3%) | 15 (4%)
- Infection: not anatomical related, n | 1 | 4
- Fracture, not anatomical related, n | 0 | 1
- Unknown, n | 3 | 10

Deaths, n (% of randomized patients) | 0 (0%) | 3 (1%)

Total, n (% of randomized patients) | 17 (12%) | 70 (17%)

Numbers may not add up for table 1 and table 2, as table 1 is “patients with one or more SAE” and for table 2 all events are counted. Regarding the three deaths, two participants had a serious adverse event preceding the death (one had acute myocardial infarction and one had an infection). n, number of participants; DVT, deep venous thrombosis; PE, pulmonary embolism.