The relationship between postoperative opioid consumption and the incidence of hypoxemic events following total hip arthroplasty: a post hoc analysis

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Background: Postoperative opioid analgesia may cause respiratory depression. We assessed whether following total hip arthroplasty, placebo-adjusted reductions in morphine consumption at 48 hours with parecoxib (47.0%), propacetamol (35.1%) or parecoxib plus propacetamol (67.9%) translated into a reduction in hypoxemic events.

Methods: This was a post hoc analysis of a randomized, placebo-controlled, non-inferiority study. Patients were randomly assigned to receive intravenous parecoxib (40 mg twice daily), propacetamol (2 g 4 times daily), parecoxib plus propacetamol (40 mg twice daily + 2 g 4 times daily) or placebo. Dose, date and time of morphine administration via patient-controlled analgesia were monitored throughout the study. In patients not receiving supplemental oxygen, peripheral blood oxygenation was assessed continuously for 48 hours after surgery. Hypoxemia was defined as peripheral oxygen saturation less than 90%. The times and oximeter readings of hypoxemic events were recorded. Pearson correlation coefficient was used to assess for correlations between cumulative morphine consumption at 48 hours and mean number of hypoxemic events.

Results: A significantly smaller proportion of patients who received the combined treatment with parecoxib and propacetamol had hypoxemia versus placebo (2.8% vs. 13.2%, p < 0.05), and the mean number of hypoxemic events was significantly smaller for parecoxib (0.12), propacetamol (0.06) and parecoxib plus propacetamol (0.03) versus placebo (0.36; all p < 0.05). There was no correlation between the reduction in cumulative morphine consumption at 48 hours and the mean number of hypoxemic events in any treatment group (all p > 0.1).

Conclusion: Following total hip arthroplasty, a greater than 70% reduction in morphine consumption may be necessary to translate into a corresponding reduction in hypoxemic events.

Contexte : L’utilisation d’analgésiques opioïdes en période postopératoire peut provoquer une dépression respiratoire. Nous avons voulu déterminer si, après une arthroplastie totale de la hanche, une réduction de la consommation de morphine à 48 heures par l’administration de parécoxib (47,0 %), de propacétamol (35,1 %) ou d’une combinaison des deux (67,9 %) — avec ajustement selon un groupe placebo — se traduirait par une réduction du nombre d’épisodes d’hypoxémie.

Méthodes : Nous avons effectué une analyse post hoc d’une étude randomisée de non-infériorité avec témoins sous placebo. Après une répartition aléatoire, chaque patient a reçu par voie intraveineuse du parécoxib (40 mg 2 fois par jour), du propacétamol (2 g 4 fois par jour), une combinaison de parécoxib et de propacétamol (40 mg 2 fois par jour + 2 g 4 fois par jour) ou un placebo. Tout au long de l’étude, la dose, la date et le moment de l’administration de morphine contrôlée par le patient ont été notés. Chez les patients qui ne recevaient pas d’oxygène d’appoint, la saturation périphérique en oxygène a été surveillée de manière continue pendant les 48 heures suivant l’opération. L’hypoxémie a été définie comme une saturation inférieure à 90 %. Le moment et les données d’oxymétrie ont été notés pour chaque épisode d’hypoxémie. Le coefficient de corrélation de Pearson a été utilisé pour évaluer la présence de correlations entre la consommation cumulative de morphine durant les premières 48 heures et le nombre moyen d’épisodes d’hypoxémie.

Résultats : Une proportion significativement plus faible de patients ayant reçu le traitement combiné de parécoxib et de propacétamol ont connu des épisodes...
Although opioids are commonly used in postoperative multimodal analgesia, other analgesics and techniques are increasingly being used to minimize opioid consumption and opioid-related adverse effects, including respiratory impairment. Respiratory depression can be clinically measured as episodes of hypoxemia using pulse oximetry. Parecoxib (PAR), a cyclooxygenase-2 selective nonsteroidal anti-inflammatory drug, and propacetamol (PROP), the prodrug of paracetamol, reduce postoperative opioid consumption in a variety of clinical settings.

Recently, a multicentre, double-blind, randomized, non-inferiority, placebo-controlled study assessed the efficacy and safety of combined PAR and PROP treatment, as well as treatment with each drug alone, for postoperative pain following total hip arthroplasty. Combined treatment, and both treatments alone, significantly reduced morphine consumption versus placebo. This study also captured pulse oximetry data, and there were significantly fewer hypoxemic events for combined PAR and PROP treatment versus placebo. The aim of this post-hoc analysis was to assess whether the treatment-related reduction in morphine consumption translated into a corresponding reduction in the incidence of hypoxemic events.

**METHODS**

Details of the study have been described elsewhere. Briefly, the study was conducted in 18 centres in 5 countries in accordance with the International Conference on Harmonization’s Guideline for Good Clinical Practice, the Declaration of Helsinki and the institutional review board and/or independent ethics committee of each participating centre. The company protocol number of the study is PARA-0505-080. Each patient provided written informed consent before entering the study. The study took place before the requirement for clinical studies to be registered was established, so no ClinicalTrials.gov identifier is available.

Men and women aged 18 years and older were included if they were undergoing routine unilateral total hip arthroplasty performed under spinal anesthesia and were expected to experience moderate or severe postoperative pain in the absence of postoperative analgesia. Patients were randomly assigned to receive 1 of 4 intravenous treatments: PAR 40 mg twice daily; PROP 2 g 4 times daily; PAR 40 mg twice daily plus PROP 2 g 4 times daily; or placebo. The first dose of study medication was administered after the last surgical stitch was completed (time 0). The duration of study treatment was 48 hours from the first dose of study medication. After surgery, all patients were immediately connected to a patient-controlled analgesia (PCA) system (1 mg/mL morphine) and could self-administer morphine for pain via the PCA system as needed. Dose, date and time of morphine administration during the study were recorded, as was the cumulative amount of morphine administered. Peripheral blood oxygen saturation levels (SpO₂) were measured continuously using pulse oximetry, for 48 hours after surgery, a period during which patients were not allowed to ambulate. Times and readings of percent oxygen saturation were recorded for all episodes during which SpO₂ fell below 90%, considered to be an adverse event. Patients who experienced hypoxemia were given supplemental oxygen immediately.

The proportion of patients who experienced hypoxemic events in each of the treatment groups was analyzed using a Cochran–Mantel–Haenszel test adjusted for centre. The number of hypoxemic events in each of the treatment groups was analyzed using a general linear model with fixed effects for treatment and centre. The Pearson correlation coefficient between the reduction in morphine consumption at 48 hours and the mean number of hypoxemic episodes by treatment group was calculated. A significance level of 0.05 was used for all statistical tests.

**RESULTS**

In total, 253 patients were enrolled (38 in the placebo group, 72 in the PAR group, 71 in the PROP group, 72 in the PAR + PROP group). Of these, 17 patients experienced hypoxemic events (5 in the placebo group, 7 in the PAR group, 3 in the PROP group, 2 in the PAR + PROP group), and 29 hypoxemic events were reported (12 in the placebo group, 9 in the PAR group, 5 in the PROP group, 3 in the PAR + PROP group). Among patients experiencing hypoxemic events, only 1 patient in the placebo group had a preexisting respiratory pathology. A significantly smaller proportion of patients who received the combined...
PAR and PROP treatment had hypoxic events versus placebo (Fig. 1A, *p < 0.05). In patients treated with either PAR or PROP alone, the proportion experiencing hypoxic events was similar to the proportion in the placebo group. The mean number of hypoxic events was significantly smaller in the group treated with PAR plus PROP than in the placebo group (Fig. 1B, *p < 0.01), and it was also significantly smaller in the groups treated with PAR alone and with PROP alone than in the placebo group (both *p < 0.05).

To evaluate whether the treatment-related reduction in morphine consumption translated into a reduction in hypoxic events, we analyzed the correlation between the cumulative morphine dose at 48 hours and the mean number of hypoxic events in each treatment group (Table 1). As shown previously,14 morphine consumption at 48 hours was significantly reduced for all treatment groups compared with placebo (47.0% reduction in the PAR group; 35.1% in the PROP group; 67.9% in the PAR + PROP group; all *p < 0.001). The reduction in cumulative morphine dose at 48 hours was not significantly correlated with the mean number of hypoxic events in any treatment group (all *p > 0.1).

**Discussion**

This post hoc analysis shows that in patients undergoing total hip arthroplasty who received supplemental morphine, a significantly smaller proportion of patients in the group that received combined treatment with PAR and PROP experienced hypoxic events than in the placebo group, there were significantly fewer hypoxic events in all active treatment groups compared with placebo, and there was no correlation between cumulative morphine consumption at 48 hours and the mean number of hypoxic events in any treatment group.

| Treatment group            | Correlation coefficient (r) | p value |
|----------------------------|-----------------------------|---------|
| Placebo                    | 0.25                        | 0.18    |
| Parecoxib                  | 0.17                        | 0.20    |
| Propacetamol               | 0.04                        | 0.78    |
| Parecoxib plus propacetamol| 0.19                        | 0.15    |

The finding of no correlation between cumulative morphine consumption at 48 hours and the mean number of hypoxic episodes suggests that the reduction in cumulative morphine consumption may need to be greater than that observed to translate into a corresponding reduction in hypoxic events. This is somewhat surprising given that the reduction in cumulative morphine consumption at 48 hours was 47.0% and 35.1% for treatment with PAR alone and PROP alone, respectively, and 67.9% for combined treatment with PAR and PROP.14 This analysis suggests, therefore, that reductions in morphine consumption greater than 70% may be required before a corresponding reduction in hypoxic events is observed. The lack of an apparent correlation between cumulative morphine consumption at 48 hours and the number of hypoxic events may also be due to the relatively small sample of patients in the current study. Only 17 patients experienced hypoxic events, and only 29 hypoxic events were reported. Additional studies with larger patient samples may help to clarify any relationship between reductions in opioid consumption and incidences of hypoxic events. It should also be borne in mind that this study evaluated up to 2 combined nonopioid analgesics that had different modes of action. The use of additional nonopioid analgesics with different modes of action, or nonopioid analgesic techniques, as part of a multimodal analgesic approach may
help to reduce opioid consumption further to achieve a corresponding reduction in hypoxemic events.

Limitations

Although the type of spinal anesthesia was standardized across the study, this analysis had several limitations. Hypoxemia is only 1 manifestation of opioid-induced respiratory depression, and it could be that use of a different measure of respiratory impairment, or a different technique to measure hypoxemic events, may have revealed an effect of reduced opioid consumption on respiratory depression. The original study was not powered to detect differences between treatment groups in the incidence of hypoxemic events. As suggested above, larger studies are needed to further explore the relationship between opioid consumption and the occurrence of hypoxemia. Although most patients had only 1 hypoxemic event, some patients had more than 1 event, which may complicate any analysis. Finally, the pharmacodynamics of morphine in individual patients may be 1 of the most important factors determining occurrences of hypoxemia, but this issue was not assessed as part of the study.

Conclusion

The incidence and proportion of patients reporting hypoxemic events was significantly lower with combined PAR and PROP treatment following total hip arthroplasty than with placebo. However, the reduction in cumulative morphine consumption at 48 hours did not translate into a corresponding reduction in hypoxemic episodes. A reduction in hypoxemic events may only be apparent with reductions in morphine consumption greater than 70%. These findings may help to inform future studies of postoperative analgesics.

Acknowledgement: Medical writing support was provided by Dr. David Cope of Engage Scientific Solutions and was funded by Pfizer.

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Funding: This study was sponsored by Pfizer.

Competing interests: M. Essex, P. Salomon and S. Pan are employees of Pfizer and have stock or stock options with Pfizer. F. Camu has acted as consultant to pharmaceutical companies and health authorities, outside the submitted work. R. Cheung was an employee of Pfizer at the time of study conduct. No other competing interests were declared.

Contributors: M. Essex, F. Camu and R. Cheung designed the study. M. Essex, F. Camu, S. Pan and R. Cheung acquired the data, which all authors analyzed. M. Essex, P. Salomon and R. Cheung wrote the article, which all authors critically reviewed. All authors gave final approval of the version to be published.

Data sharing: Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the United States and/or the European Union or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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