

A Model-Based Approach for Joint Analysis of Pain Intensity and Opioid Consumption in Postoperative Pain

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Introduction

Joint analysis of pain intensity and opioid consumption is encouraged in trials of postoperative pain [1]. However, previous approaches have not appropriately addressed the complexity of their interrelation in time [2,3]. We hypothesized that adequate joint data analysis of pain intensity and opioid consumption required description of four key phases: A) pain intensity in time, B) probability of threshold pain, C) probability of opioid request and D) opioid effects on pain intensity.

Aim

It was the aim of this study to demonstrate the application of a joint analysis approach spanning the four key phases using non-linear mixed effects modeling.

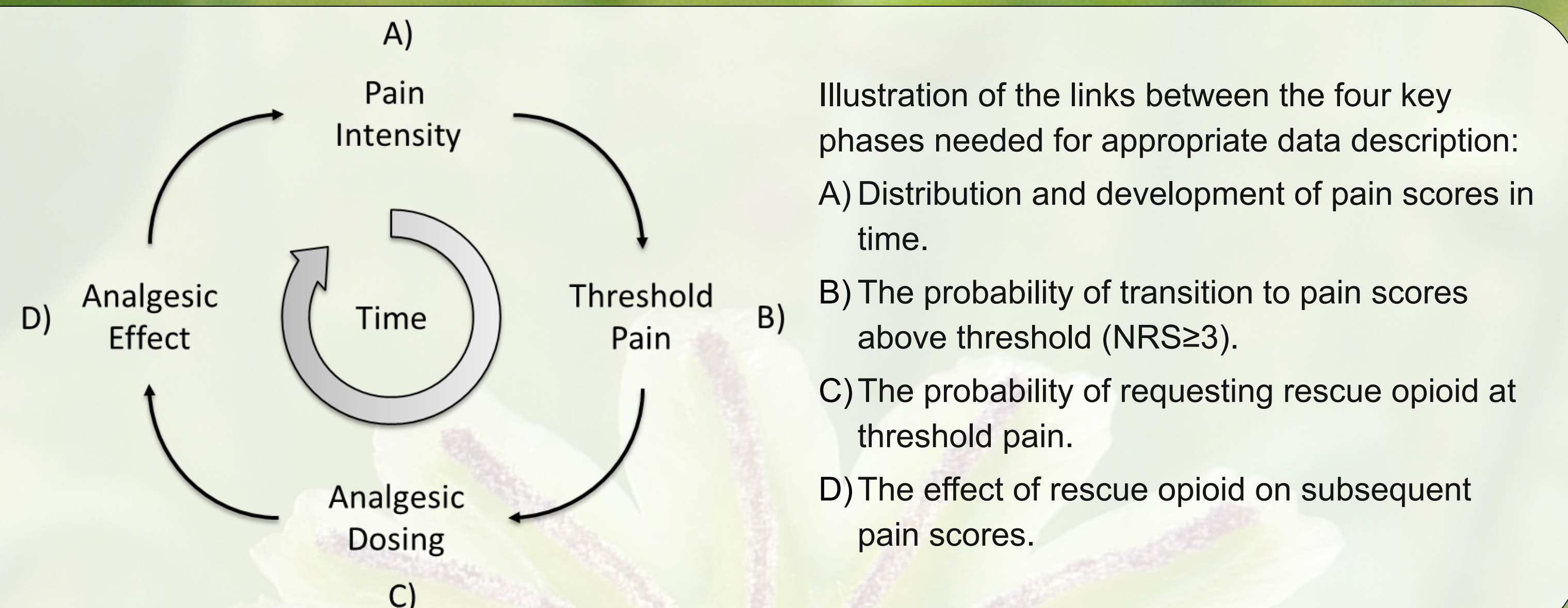
Methods

Study

- 44 patients undergoing percutaneous kidney stone surgery
- Randomised to receive oxycodone or morphine (0.1 mg/kg, IV)
- Study period: 4 hours
- Pain intensity: every 15 minutes, using Numerical Rating Scale (NRS)
- Rescue doses: available if NRS ≥ 3

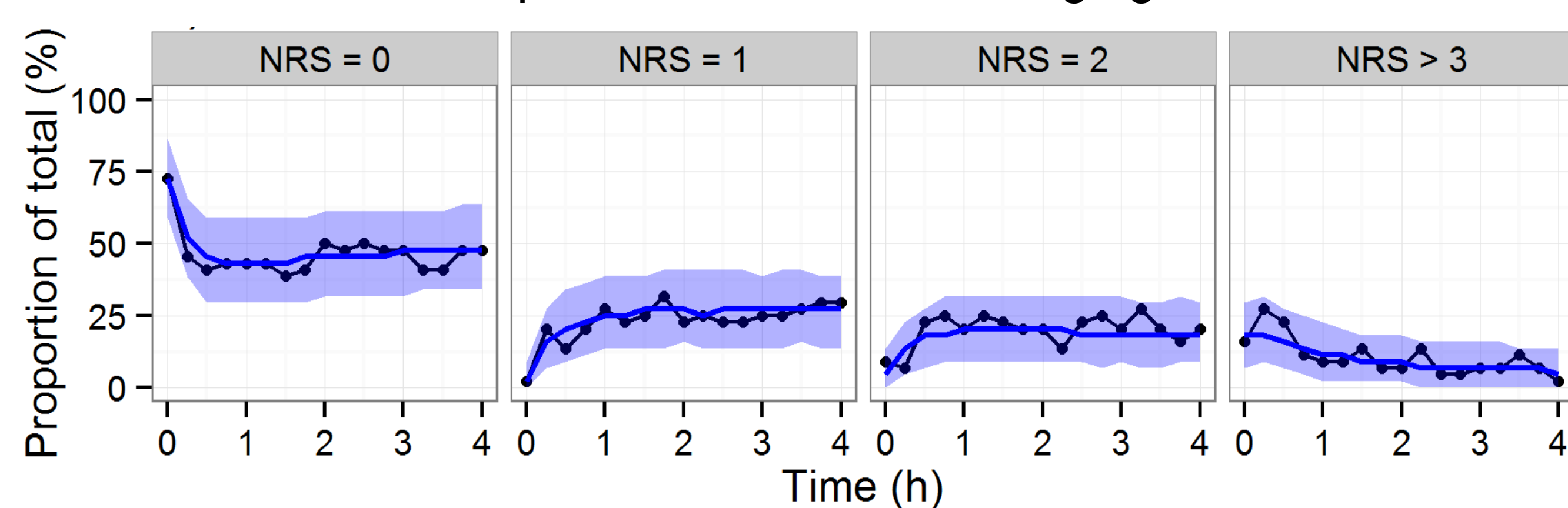
Data analysis

- Non-linear mixed-effects modeling (NONMEM 7.3)
- Truncated, zero-inflated Poisson distribution to describe pain scores
- First order Markov chains to describe dependence between pain scores



Distribution and time course of pain scores

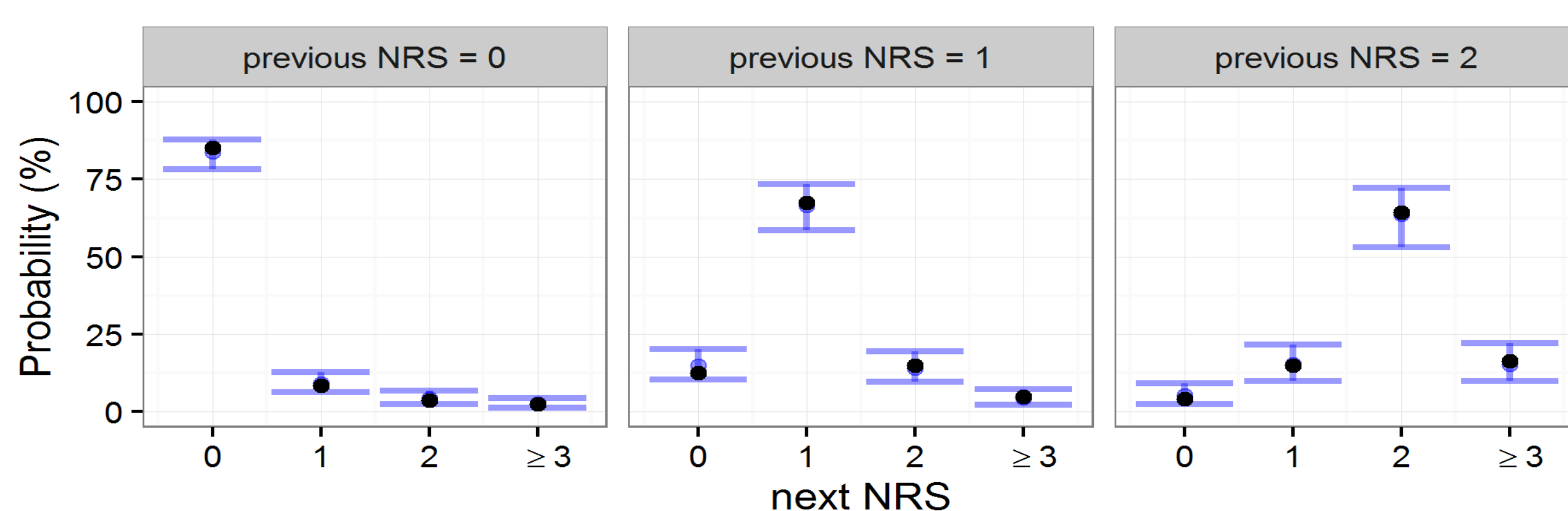
Pain intensity scores followed a zero-inflated, truncated Poisson distribution with time-dependent mean score ranging from 0.93 to 2.45



Pain intensity scores in time. The panels describe the proportion of total observations at each NRS score with time. In all panels, observed data (black points and lines) are compared with simulated median and 95% confidence interval (blue line and ribbon) based on 1000 simulations with the final model

Dependence between pain score observations

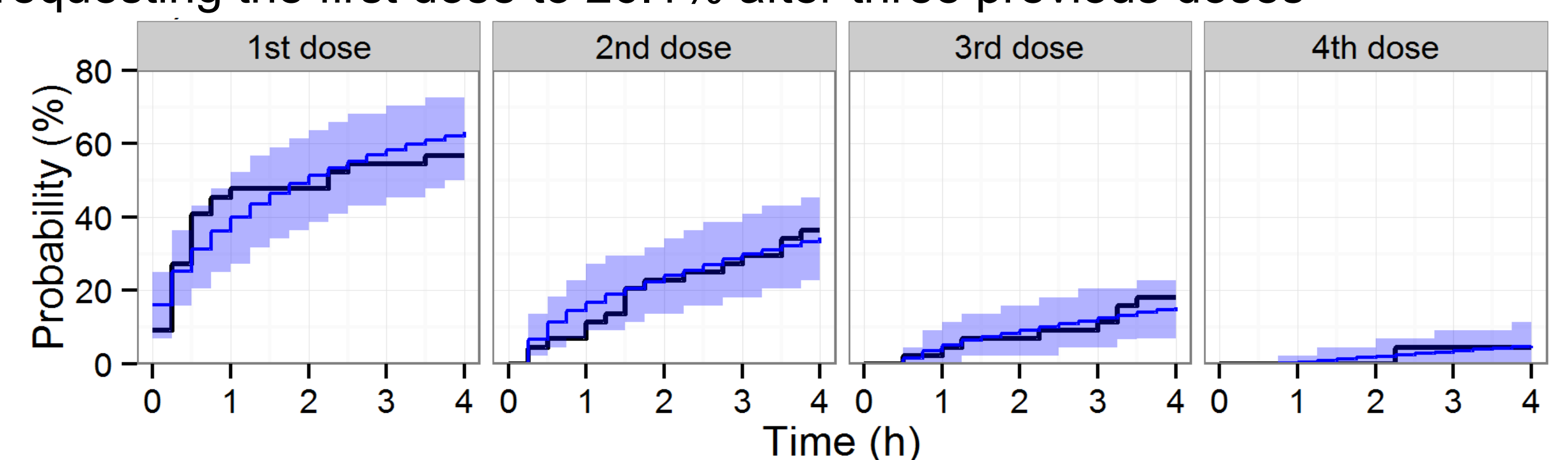
Probability of transition to threshold pain (NRS ≥ 3) was strongly dependent on previous pain levels ranging from 2.8-15.2% after NRS of 0-2



Probability of scoring a particular NRS value based on the previously scored NRS value from the same patient.

Opioid request

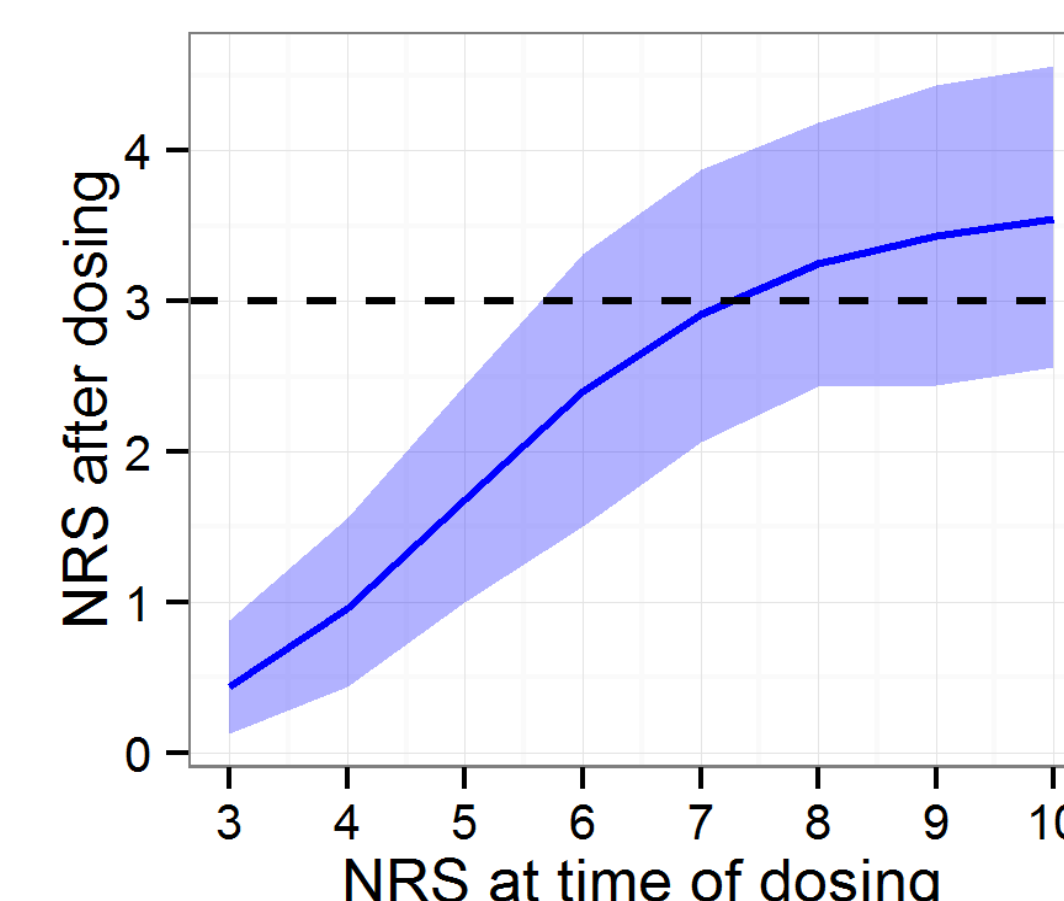
Probability of requesting opioid when allowed (NRS ≥ 3) was strongly correlated with the number of previous doses, ranging from 89.8% for requesting the first dose to 26.1% after three previous doses



Opioid consumption data in time. The panels describe the probability of having requested 1 to 4 opioid doses in time.

Reduction in pain intensity after opioid dosing

Reduction in pain scores after opioid dosing was significantly related to the pain intensity at time of opioid request.



Expected NRS following opioid dosing versus the pain intensity value at time of opioid dosing.

Conclusion

- This study highlights the importance of analyzing pain intensity and opioid consumption in an integrated manner
- Non-linear mixed effects modelling proved a valuable tool for analysis of interventions that affect pain intensity, probability of rescue dosing or the effect of opioids in the postoperative pain period
- Published in The AAPS Journal 2016 [4]

References

- [1] US Food Drug Administration. Guidance for industry analgesic indications: developing drug and biological products., 2014
- [2] McQuay HJ, Derry S, Eccleston C, Wiffen PJ, Andrew Moore R. Evidence for analgesic effect in acute pain - 50 years on. *Pain* 2012;153(7):1364-1367.
- [3] Woolf CJ. Overcoming obstacles to developing new analgesics. *Nature medicine* 2010;16(11):1241-1247.
- [4] Juul, RV, Knøsgaard, KR, Olesen, AE, Pedersen, KV, Kreilgaard, M, Christrup, LL, Lund, TM. (2016). A Model-Based Approach for Joint Analysis of Pain Intensity and Opioid Consumption in Postoperative Pain. *The AAPS Journal*. <http://doi.org/10.1208/s12248-016-9921-2>

Acknowledgements

The study was supported by an unrestricted grant from Norpharma A/S. Mech-Sense, Aalborg University Hospital has received funding from Innovation Fund Denmark for Strategic Research in Individuals, Disease and Society.