Abstract 7

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**Titel**
The effect of preoperative intraarticular methylprednisolone on pain after total knee arthroplasty - a double-blinded, randomized, placebo controlled trial in patients with high-pain knee osteoarthritis and sensitization

**Introduction**
Acute pain after total knee arthroplasty (TKA) remains a considerable clinical problem with 75% of patients having moderate-severe pain on the first postoperative day and 30-40% after 2 weeks with implications for recovery and the development of persistent postsurgical pain conditions [2]. Intense preoperative pain and central sensitization have been associated to acute post-TKA pain, and intraarticular inflammation suggested as the underlying pathogenic mechanism [1]. Intraarticular methylprednisolone (MP) is well-established to reduce pain in knee osteoarthritis, and intraarticular administration in arthroscopic surgery reduces postoperative pain [3]. A preoperative downregulation of the intraarticular inflammation in patients with high-pain osteoarthritis and sensitization could potentially serve as a stratified preventive analgesic strategy in this subgroup of patients. Thus, we hypothesized that a single intraarticular dose of 40 mg MP administered one week prior to TKA would reduce acute postoperative pain in patients with preoperative high-pain knee-osteoarthritis and central sensitization.

**Methods**
48 patients with high pain osteoarthritis (NRS ≥ 5) and signs of central sensitization (pressure algometry) were included in this double-blinded, randomized, placebo-controlled trial. Primary outcome was proportion of patient with moderate/severe pain during a 5 meter walk test 24 hours postoperatively. Secondary outcomes included pain during a 5 meter walk test at 48 hours, pain and opioid consumption during the first 14 postoperative days and quantitative sensory testing (QST) of change in pressure pain threshold and temporal summation to mechanical stimulation (wind-up) from prior to administration of MP until two days after surgery.

**Results**
There was no difference between MP/placebo groups in proportion of patients with moderate/severe pain at 24 hours (67% vs 74% respectively, p=0.63), at 48 hours (p=0.46) or during the first 14 postoperative days in pain (p=0.44) or opioid consumption (p=0.16) (table 1 and 2). MP did not reduce QST signs of sensitization (p>0.41). In conclusion, our study does not support the use of methylprednisolone administered 1 week preoperatively to reduce moderate-severe post-TKA pain in patients with high pain osteoarthritis and signs of central sensitization. The need for an improved analgesic strategy in this subgroup of patients is emphasized, and other mechanism based treatment options should be explored.

**Reference List**

**Table 1: Moderate-severe pain during standardized 5 meters walk test**

<table>
<thead>
<tr>
<th></th>
<th>NRS &gt; 3 MP group</th>
<th>NRS &gt; 3 Placebo group</th>
<th>χ² (p-value)</th>
<th>Risk-difference (95%CI)</th>
<th>Odds ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hrs. after TKA</td>
<td>67%</td>
<td>74%</td>
<td>0.2 (p=0.63)</td>
<td>-7% (-35% to 21%)</td>
<td>0.7 (0.2 to 2.8)</td>
</tr>
<tr>
<td>48 hrs. after TKA</td>
<td>57%</td>
<td>68%</td>
<td>0.5 (p=0.46)</td>
<td>-11% (-41% to 18%)</td>
<td>0.6 (0.2 to 2.3)</td>
</tr>
</tbody>
</table>

Data are reported as percentage of patients with moderate-severe pain (NRS > 3) and difference between groups tested with a chi square test.

Risk-difference: the risk of having moderate-severe pain being in intervention group (methylprednisolone) compared to placebo group. MP = methylprednisolone, χ² = chi square.
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Titel
Predictive performance of SAPS II and initial SOFA score in acutely ill ICU patients

Introduction
Severity scores including the Simplified Acute Physiology Score (SAPS) II[1] and the Sequential Organ Failure Assessment (SOFA) score[2] are used in intensive care units (ICUs) to assess disease severity, predict mortality and in research. We assessed the predictive performance of SAPS II and the initial SOFA score for in-hospital and 90-day mortality in a contemporary international cohort.

Methods
This was a post-hoc study of the Stress Ulcer Prophylaxis in the Intensive Care Unit inception cohort study[3], which included acutely ill adults from general ICUs across 11 countries (n=1034). The relevant ethical committees in each country waived informed consent.

We compared the discrimination of SAPS II and initial SOFA scores, compared the discrimination of SAPS II in our cohort with the original cohort, assessed the calibration of SAPS II customised to our cohort, and compared the discrimination for 90-day mortality vs. in-hospital mortality for both scores. Discrimination was evaluated using areas under the receiver operating characteristics curves (AUROC). Calibration was evaluated using Hosmer-Lemeshow’s goodness-of-fit Č-statistic.

Results
AUROC for in-hospital mortality was 0.80 for SAPS II and 0.73 for the initial SOFA score (P<0.001 for comparison, Fig. 1). Discrimination of SAPS II was significantly reduced compared with the original SAPS II validation sample (P=0.001, Fig. 2). Calibration of the customised SAPS II for predicting in-hospital mortality was adequate (P=0.60). AUROC for 90-day mortality was 0.79 (P=0.74 for comparison with in-hospital mortality) for SAPS II and 0.71 (P=0.66 for comparison with in-hospital mortality) for the initial SOFA score (Fig. 1).

Discussion
We found that SAPS II was superior in predicting mortality compared with the initial SOFA score, which was not developed for this purpose. The performance of SAPS II has deteriorated over time, and re-calibration showed that the score was associated with a lower mortality risk in our contemporary cohort compared with the older, original cohort. Discrimination was comparable for 90-day vs. in-hospital mortality for both scores.

Conclusion
The predictive performance of SAPS II was superior to that of the initial SOFA score, comparable for in-hospital and 90-day mortality, but appears to have decreased over time. Use of a contemporary severity score with improved predictive performance may be indicated.
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Medforfattere  Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB, Mathiesen O
Titel  Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: A randomized, blinded trial

Introduction
Perioperative handling of surgical patients with opioid dependency represents an important clinical problem. Animal studies suggest that ketamine attenuates central sensitization and hyperalgesia and thereby reduces postoperative opioid tolerance. We therefore hypothesized that intraoperative ketamine would reduce immediate postoperative opioid consumption compared to placebo in chronic pain patients with opioid dependency undergoing lumbar spinal fusion surgery.

Methods
One hundred and fifty patients undergoing spinal fusion surgery were randomly assigned to intraoperative S-ketamine bolus 0.5 mg/kg and infusion 0.25 mg/kg/h or placebo. Postoperatively patients received their usual opioids, paracetamol and IV Patient Controlled Analgesia (PCA) with morphine. Primary outcome was morphine consumption 0-24 h postoperatively. Secondary outcomes were acute pain at rest and during mobilization 2-24 h postoperatively (VAS), adverse events and persistent pain 6 months postoperatively.

Results
In the final analyses 147 patients were included (Table 1). PCA IV morphine consumption 0-24 hours postoperatively was significantly reduced in the ketamine group compared to the placebo group: 79 (47) vs 121 (53) mg IV, mean difference 42 mg (95% CI -59 to -25), P<0.001. Sedation was significantly reduced in the ketamine group 6 h and 24 h postoperatively. There were no significant differences regarding acute pain, nausea, vomiting, hallucinations or nightmares. Back pain at 6 months postoperatively compared to preoperative pain levels was significantly improved in the ketamine group compared to the placebo group, P=0.005 (Table 2).

Discussion
Recently, intraoperative ketamine has been suggested as an ideal candidate for managing perioperative pain treatment in opioid...
dependent chronic pain patients. Our finding on reduced opioid consumption supports this. The results on reduced 6 months pain levels must be considered exploratory secondary outcomes, as the sample size calculation was not based on these outcomes.

Conclusion
In conclusion, intraoperative ketamine significantly reduced morphine consumption 0-24 h after lumbar fusion surgery in opioid dependent patients. The trend regarding less persistent pain 6 months postoperatively needs further investigation.

### Table 1
Patient characteristics and perioperative data.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Ketamine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>74</td>
<td>73</td>
</tr>
<tr>
<td>Gender, female/male</td>
<td>46/28</td>
<td>52/21</td>
</tr>
<tr>
<td>Age, years</td>
<td>57 (14)</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77 (14)</td>
<td>78 (18)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 (9)</td>
<td>170 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preoperative data</th>
<th></th>
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</tr>
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<tbody>
<tr>
<td>Preoperative VAS at rest, mm</td>
<td>53 (25)</td>
<td>57 (23)</td>
</tr>
<tr>
<td>Preoperative VAS during mobilization, mm</td>
<td>67 (22)</td>
<td>68 (20)</td>
</tr>
<tr>
<td>Daily use of opioids, mg*</td>
<td>60 (33 – 80)</td>
<td>58 (30 – 78)</td>
</tr>
<tr>
<td>Type of opioids, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Tramadol</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Ketobemidone</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

| Hospital Anxiety and Depression Scale (HADS) |           |         |
| Anxiety score                      | 19 (3)    | 19 (3)  |
| Depression score                   | 17 (2)    | 18 (2)  |
| Total score                        | 36 (3)    | 35 (4)  |

| Brief Pain Inventory (BPI)         |           |         |
| Pain score                         | 6 (2)     | 6 (2)   |
| Interference score                 | 6 (2)     | 6 (2)   |
| Total score                        | 6 (2)     | 6 (2)   |

| Pain Catastrophizing Scale (PCS)   |           |         |
| Total score                        | 24 (11)   | 27 (11) |

| Perioperative data                 |           |         |
| Duration of surgery, min           | 130 (99 – 170) | 135 (109 – 180) |
| Propofol, mg                       | 1100 (890 – 1480) | 1100 (818 – 1410) |
| Remifentanil, mg                   | 7.7 (6 – 9.7) | 7.6 (6 – 10) |
| Morphine at end of surgery**, mg IV| 30 (24 – 35) | 30 (25 – 35) |
| Sufentanil at end of surgery***, µg IV | 0 (0 – 19) | 0 (0 – 19) |
| Bleeding, ml                       | 410 (250 – 750) | 390 (253 – 650) |
| Crystalloids, ml                   | 1500 (1050 – 2000) | 1400 (1075 – 2025) |
| Spine segments operated on, n      | 1 (1 – 2)   | 1 (1 – 2) |
| Fusion technique, instrumented/non-instrumented | 66/9 | 64/9 |
| Time in postoperative care unit, min | 205 (140 – 353) | 200 (145 – 360) |

Data are mean (SD), median (lower and upper quartiles) or frequencies. *All opioids converted to oral morphine equivalents. **Morphine 0.4 mg/kg 45 min before end of surgery. ***Sufentanil bolus 5 µg in case of unacceptable pain upon awakening.
Abstract

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Titel	Prediction of difficult mask ventilation using a systematic assessment of risk factors versus existing practice – a cluster randomised clinical trial in 94 006 patients

Introduction
Anaesthesiologists’ prediction of difficult mask ventilation is poor. [1] In the Danish Anaesthesia Database (DAD), prediction of difficult mask ventilation is left at the discretion of the individual anaesthesitist. Preoperative assessment of risk factors for difficult mask ventilation may reduce the incidence of unanticipated difficulties.
We compared systematic assessment of risk factors for difficult mask ventilation with existing practice for airway assessment on accuracy in predicting difficulties.

Methods
26 departments were cluster-randomised to assess 11 risk factors for difficult airway management (intervention) or existing airway assessment (control). Prediction of mask ventilation and intubation difficulties, and actual airway management conditions were registered in the DAD. In order to adjust for the clustered nature of data we examined the diagnostic accuracy of predicting difficult mask ventilation and the combination of difficult mask ventilation and difficult intubation using generalized estimating
equations. Primary outcome was the proportions of unanticipated difficult mask ventilation.

**Results**
Among 94006 patients undergoing mask ventilation the incidence of unanticipated difficult mask ventilation was 427/46804 (0.91%) in the intervention group and 414/47202 (0.88%) in the control group, OR 0.98 (95% CI: 0.66–1.44), p=0.90. The number of patients predicted difficult to mask ventilate, but in fact found to be easy (unanticipated easy) was 298 (0.64%) versus 164 (0.35%), OR 1.56 (1.01-2.42), p=0.045. In the intervention group 427 of 495 (86.3%) cases of difficult mask ventilation were unpredicted, compared with 414 of 454 (91.2%) in the control group, OR 0.61 (0.41-0.91), p=0.016. In 44337 patients undergoing both mask ventilation and tracheal intubation the incidence of combined difficult mask ventilation and difficult intubation was 0.3% in both groups. In the intervention group 71 of 365 (19.5%) difficult mask ventilations were also difficult to intubate versus 65 of 318 (20.4%) in the control group.

Had the anaesthetist predicted one or both of these modalities as difficult we considered it correctly predicted. In patients with combined difficulties 56 of 71 (78.9%) were unanticipated in the intervention group compared with 53 of 65 (81.5%) in the control group, OR 0.76 (0.41-1.41), p=0.39.

**Discussion**
This is the first cluster randomised trial comparing two strategies for prediction of difficult mask ventilation. In the same trial we also assessed prediction of difficult intubation. These results have been published previously.[2]

**Conclusion**
The intervention did not reduce the overall incidence of unanticipated difficult mask ventilation, but better prediction was found in the intervention group when isolating cases with difficult mask ventilation. In both group the risk of difficult intubation increases in cases with difficult mask ventilation.

Flowchart results
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Titel Prehospital triage of patients suffering severe dyspnea using N-terminal pro-Brain Natriuretic Peptide, the PreBNP trial: a randomized controlled clinical trial

Introduction
Patients suffering dyspnea in the ambulance have high mortality. Early identification of the underlying cause of dyspnea to facilitate correct triage and treatment may improve outcome. The aim of this study was to examine whether addition of brain natriuretic peptide measurement to the routine diagnostic work-up by prehospital critical care team physician improves triage in patients with severe dyspnea.

Methods
Randomized controlled trial with ClinicalTrials.gov identifier NCT02050282. Prehospital critical care team physicians included unselected patients >18 years with severe dyspnea according to pre-specified criteria to routine diagnostic work-up or diagnostic work up with incorporated point-of-care N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) measurement. The primary endpoint was the proportion of patients suffering dyspnea of cardiac origin triaged directly to a department of cardiology. An endpoint-adjudication committee determined the primary cause of dyspnea as heart disease, lung disease, or other disease. The Central Denmark Region Committee on Biomedical and Research Ethics approved the study as an emergency research project (approval nr 1-10-72-317-13).

Results
A total of 747 patients were randomized and 711 patients with a median age of 75 years (interquartile range: 75-82) consented to participate. Of these, 350 patients were randomized to the NT-proBNP group and 361 patients to the routine work-up group. A statistically non-significantly higher proportion of patients suffering dyspnea of cardiac origin were triaged directly to a department of cardiology in the NT-proBNP group than in the routine work-up group (75 % vs. 69 %, p = 0.22). No differences in hospital length of stay, intensive care unit admission rates or mortality were observed. We observed increased negative predictive value for heart disease (87% vs. 75%, p = 0.010) and increased positive predictive value for lung disease (74% vs. 60%, p = 0.032) in the NT-proBNP group.

Discussion
Inclusion of unselected patients rendered a population that was older than in previously conducted studies in emergency department settings. Contrary to our expectations, the value of point-of-care NT-proBNP measurement in these elderly patients with dyspnea seemed to lie in rule-out of heart disease rather than rule-in. Other point-of-care modalities may be needed for early recognition of high-risk patients among this heterogeneous group of mainly elderly patients.

Conclusion
Supplementary point-of-care measurement of NT-proBNP in patients suffering severe dyspnea did not improve triage or patient outcome, but improved rule-out of heart disease and rule-in of lung disease. Our results encourage further research evaluating the impact of prehospital biomarker panel measurement or other point-of-care diagnostics on early management of patients suffering dyspnea.

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Abstract 41

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Titel  Sugammadex versus Neostigmine in reversing neuromuscular blockade

Introduction
This Cochrane review compares Sugammadex, the first selective relaxant-binding agent with Neostigmine, an acetylcholinesterase inhibitor with well-recognized potential side-effects.

Methods
Our objective was to investigate whether Sugammadex is more effective and more safe in reversing neuromuscular blockade than Neostigmine. The primary outcome was recovery time to TOF > 0.9 measured by acceleromyography. The secondary outcome was prevalence of adverse events and serious adverse events.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) MEDLINE and EMBASE until 01. May 2016. We included all RCTs, irrespective of publication status, blinding status, date of publication or language, performed on adult ASA I-IV patients receiving non-depolarizing muscle blocking agents, scheduled for elective in-patient or day-case surgical procedures. We contacted the corresponding authors of included studies to retrieve relevant and missing data.

We assessed risk of bias in 10 methodological domains using the Cochrane Collaboration risk of bias tool and risk of random error through trial sequential analysis. We used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) approach to provide an overall assessment of evidence related to all of our outcomes. We present pooled estimates of the effects of interventions as mean differences (MDs) and risk ratios (RRs) with 95% confidence intervals (CIs).

Results
Overall, 56 relevant studies were identified, of which 43 RCTs (n=4470) met our inclusion criteria. Eleven studies were eligible for meta-analysis of the primary outcome (n=1006), 26 studies of the secondary outcome (n=2162) and 13 studies (n=2013) were ineligible for meta-analysis.

Meta-analysis of the results showed the following:
- Sugammadex 2 mg/kg was on average 9.84 minutes (95% CI, 8.23-11.46, p < 0.00001, I² = 82 %, n = 892) faster than Neostigmine 0.04-0.05 mg/kg in reversing the neuromuscular blockade at T2 reappearance (Fig.1).
- Sugammadex 4 mg/kg was on average 45.78 minutes (95% CI, 39.41-52.15, p < 0.00001, I² = 0 %, n = 114) faster than Neostigmine 0.07 mg/kg in reversing the neuromuscular blockade at PTC 1-5 reappearance.
- There were significantly less subjects with one or more adverse events (RR 0.60, 95% CI 0.45-0.79, p = 0.0003, I² = 0%, n = 1659) as well as significantly less composite adverse events (RR 0.66, 95 CI 0.54-0.81, p < 0.0001, I² = 20 %, n = 2162) in the Sugammadex group when compared to Neostigmine (Fig. 2).
- There was no significant difference between Sugammadex and Neostigmine regarding subjects with one or more serious adverse events as well as composite adverse events (RR 0.54, 95% CI 0.13-0.2.25, p = 0.4, I² = 0%, n = 938).

Conclusions
Sugammadex reverses neuromuscular blockade faster then Neostigmine regardless of the depth of the block and is generally associated with fewer adverse events.