Calcium-binding protein s100b: a potential biomarker of cerebral tissue injury during general anaesthesia in piglets?

Introduction
Moderate and severe hypotension (HT) and hypocapnia (HC) might cause neuro-morbidity following general anaesthesia (GA) in infants. Increased serum levels of calcium-binding protein s100b have been associated with cerebral injury (head trauma, perinatal intraventricular haemorrhage and asphyxia). Our objective was to investigate if s100b can be used as a biomarker of cerebral cell injury during GA in an animal model.

Method
A total of 57 sevoflurane-midazolam anaesthetized piglets (4-6 weeks of age) were randomised to normotension (C), mHT or sHT (n=27; group ‘HT’) or mHC, sHC or mHC/mHT combined (HTC) (n=30; group ‘HC’). Monitoring included ECG, pulse oxymetry, rectal temperature, invasive blood pressure measurement, end-tidal anaesthetic volatile analysis, capnography, spirometry and repeated arterial blood gas analysis. Hypotension was induced by blood withdrawal (10 ml/kg) and nitroprusside infusion (target MAP: 35-38 (mHT) and 27-30 (sHT) mmHg). Ventilation was adjusted as per protocol to target PaCO2 of 35-45 (normocapnia), 28-30 (mHC) or 23-25 (sHC) mmHg. S100b was measured by chemiluminescent immunoassay of serum samples taken at baseline (B), before (Tr0), after treatment (Tr60) and recovery (postTr60) maintained for 60 min each. Simultaneously, serum concentration of albumin was analysed to exclude dilutional artefacts induced by maintenance fluid (Ringer’s acetate + glucose 1%, rate 5ml/kg/hour).

Data were analysed using mixed repeated measures ANOVA followed by Sidak post-hoc tests (p<0.05). Results: All 57 piglets completed the study without non-intended adverse events. In both ‘HT’ and ‘HC’, serum levels of s100b decreased significantly from B to postTr60 (p(HT) =0.037; p(HC) <0.001). Within groups, s100b values at specific time points did not differ between the treatment arms (p(HT)=0.118; p(HC)=0.536). S-Albumin decreased with time in all treatment groups. Mean values with standard deviations (SD) are shown (figure 1: s100b; figure 2: albumin).

Discussion
Neuronal dysfunction and ischemia caused by hypotension and/or hypocapnia during sevoflurane anaesthesia has previously been demonstrated in an identical piglet study setting by magnetic resonance imaging. In the current study, s100b did not reflect cerebral damage caused by moderate and severe hypotension/hypocapnia during GA in piglets. Since sampling of liquor was not part of our model it is unclear, whether the blood-brain-barrier remained intact preventing release of s100b. Further, the glial rather than neuronal origin of the protein might explain the lack of increase. Explanation by accelerated renal clearance of s100b seems less likely in the setting of global hypotension and regional hypoperfusion.

Conclusion
In the current study s100b does not reflect cerebral tissue injury caused by circulatory and respiratory instability during GA in piglets. Whether these results apply to a human setting is unknown and awaits further clarification.

References
Abstract H

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Medforfattere Tietze A, Aanerud J, Öettingen G, Juul N, Sørensen JC, Nikolajsen L, Østergaard L, Rasmussen M
Titel Influence of vaso pressors and inotropes on brain oxygenation and cerebral microcirculation

Background
Both beta agonist in trope ephedrine and alpha agonist vasopressor phenylephrine are commonly used to raise the mean blood pressure (MABP) in order to maintain cerebral perfusion pressure (CPP) during craniotomy. Recent studies suggest that, despite an increase in MABP cerebral oxygenation decreases after phenylephrine but remains unchanged after administration of ephedrine(1,2). This difference may be caused by different influence on brain microcirculation and capillary transit time heterogeneity (CTH)(3). The effects of ephedrine and phenylephrine on brain oxygenation and cerebral microcirculation are unknown.

Aim and hypothesis
The objective of this study was to compare the effects of ephedrine and phenylephrine on brain oxygenation and cerebral microcirculation on patients undergoing surgery for cerebral tumors. We hypothesized that the use of phenylephrine was associated with a reduction in brain oxygenation and cerebral microcirculation by altering CTH and decreasing the oxygen extraction fraction (OEF) compared to ephedrine.

Methods
The study is an investigator-initiated, single-center, double blinded randomized study. Twenty four patients with brain tumors scheduled for craniotomy were randomized to receive either ephedrine or phenylephrine infusion during general anesthesia. Cerebral microcirculation and brain oxygenation were studied with magnetic resonance imaging (MRI) before and after administration of either ephedrine or phenylephrine. Surgery was initiated after the MRI examination.

Results
We are still in the process of data-analysis.

Conclusion
At the DASAIM conference we will present data concerning the effects of ephedrine and phenylephrine on CTH, OEF, mean transit time (MTT) and cerebral blood flow (CBF).

References
Abstract 22

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Titel Cerebral oximetry during preoperative resuscitation in elderly patients with hip fractures: A prospective observational study

Introduction
Elderly hip fracture patients often show postoperative delirium and mortality is high, and before surgery patients may be hypovolemic. In a prospective observational design this study explored whether cerebral oxygenation (ScO2) taken as an index for systemic circulatory integrity predicts postoperative outcome.

Methods
Forty elderly (>65 years) patients with hip fracture were included in a prospective study using an observational design as approved by the regional ethics committee. Using Near-infrared spectroscopy ScO2 was determined during initial resuscitation at admission and during surgery, respectively. Up to seven days after surgery the Memorial Delirium Assessment Scale and the Confusion Assessment Method assessed postoperative delirium. Mortality was defined as all-cause death within 30 days of admission.

Results
Ten patients (25 %) developed postoperative delirium within the first seven postoperative days. At initial resuscitation ScO2 was 60.5% (IQR; 58.0-75.0) in patients with subsequent delirium versus 68.5% in patients without subsequent delirium (p=0.331). Intraoperative ScO2 values were similar in the two groups. All-cause 30-day mortality was 10 % (4 out of 40 patients). At initial resuscitation ScO2 was 57.0 [IQR; 51.5-60.0] in patients who died versus 66.0 [IQR; 58.0-70.0] in surviving patients (p=0.042) and the corresponding ScO2 nadir values were (49.0 [IQR; 42.5-52.0] versus 59.0 [IQR; 49.5-65.0], p = 0.047). Low ScO2 during initial resuscitation (defined as an incidence with ScO2 < 55) was also significantly associated with 30-day mortality (p=0.015). There were no associations between low blood pressure at initial resuscitation or surgery and postoperative delirium or mortality.

Conclusion
Low preoperative ScO2 is associated with 30-day mortality in elderly patients undergoing surgery for hip fracture.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event of low ScO2</th>
<th>P value</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0%)</td>
<td>4 (10.0%)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>25 (63.5%)</td>
<td>11 (27.5%)</td>
<td>3.27 (2.00-5.36)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative delirium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (10.0%)</td>
<td>6 (15.0%)</td>
<td>0.135</td>
</tr>
<tr>
<td></td>
<td>21 (52.5%)</td>
<td>9 (22.5%)</td>
<td>0.40 (0.13-1.19)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Events of low ScO2 (<55) during initial preoperative resuscitation in hip fracture patients in relation to 30-day mortality and delirium. Values are numbers (%).
Abstract 29

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Titel  
The association between preoperative sepsis and the mortality after hip fracture surgery

Background
Postoperative sepsis is a well-known cause of mortality(1), but the extent of preoperative sepsis in hip fracture patients and its consequences are sparsely elucidated. The aim of this study was to assess the association between preoperative sepsis and 30-day mortality after hip fracture surgery.

Methods
We conducted a retrospective analysis of 1,901 patients who underwent hip fracture surgery in the Capital Region of Denmark between January 1, 2014 and December 31, 2014 (NCT03201679). Data from an Early Warning Score register(2) as well as all cultures and laboratory data were obtained. Preoperative sepsis was defined as presence of systemic inflammatory response syndrome together with a positive culture within 72 hours before surgery. Primary outcome was 30-day mortality, and secondary outcomes included length of hospital stay and admission to intensive care unit. The chi-squared test and Wilcoxon rank sum test were used to determine statistical significance.

Results
A total of 146 (7.7%) of the hip fracture patients met the criteria for preoperative sepsis. The 30-day mortality was 13.7% in

<table>
<thead>
<tr>
<th>Preoperative resuscitation</th>
<th>All patients</th>
<th>Dead at 30 days</th>
<th>Alive at 30 days</th>
<th>p value</th>
<th>Postoperative delirium = Yes (n=10)</th>
<th>Postoperative delirium = No (n=30)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ScO2 value, median (IQR).</td>
<td>65.5 (58.0-70.0)</td>
<td>57.0 (51.5-60.0)</td>
<td>66.0 (58.0-70.0)</td>
<td>0.042</td>
<td>58.5 (57.0-70.0)</td>
<td>66.0 (59.0-70.0)</td>
<td>0.246</td>
</tr>
<tr>
<td>ScO2 value, nadir, median (IQR).</td>
<td>57.5 (49.0-64.5)</td>
<td>49.0 (42.5-52.0)</td>
<td>59.0 (49.5-65.0)</td>
<td>0.047</td>
<td>51.5 (46.0-63.0)</td>
<td>58.5 (50.0-65.0)</td>
<td>0.396</td>
</tr>
<tr>
<td>ScO2 value, baseline median (IQR).</td>
<td>65.5 (60.0-73.8)</td>
<td>58.5 (56.5-62.0)</td>
<td>68.5 (60.5-74.5)</td>
<td>0.060</td>
<td>60.5 (58.0-75.0)</td>
<td>68.5 (61.0-73.0)</td>
<td>0.331</td>
</tr>
<tr>
<td>Lowest MAP, mmHg, Median (IQR).</td>
<td>71 (64-80)</td>
<td>73 (64-121)</td>
<td>71 (63-80)</td>
<td>0.913</td>
<td>75 (65-95)</td>
<td>67 (59-72)</td>
<td>0.357</td>
</tr>
<tr>
<td>MAP, median, mmHg (IQR).</td>
<td>86 (75-101)</td>
<td>76 (66-110)</td>
<td>86 (78-101)</td>
<td>0.419</td>
<td>85 (73-108)</td>
<td>86 (77-99)</td>
<td>0.988</td>
</tr>
<tr>
<td>Heart frekvens, median, beats/min (IQR).</td>
<td>82 (72-92)</td>
<td>88 (81-94)</td>
<td>81 (72-92)</td>
<td>0.419</td>
<td>91 (75-103)</td>
<td>78 (72-89)</td>
<td>0.131</td>
</tr>
</tbody>
</table>

Table 1: Cerebral oxygenation and hemodynamic values in hip fracture patients at initial resuscitation and surgery in relation to 30-day mortality and postoperative delirium.
patients with preoperative sepsis as compared to 9.0% in those without (HR 1.60, 95% CI [0.97;2.64], p = 0.06). Patients with preoperative sepsis had longer hospital stays (median 10 days vs. 9 days, mean difference 2.4 (SD 9.4) days, p = 0.02), and higher frequency of ICU admission (11.0% vs. 2.8%, HR 4.47, 95% CI [2.47;8.11], p < 0.0001).

Conclusion
Preoperative sepsis is associated with an increased hospital burden in hip fracture patients, and may increase mortality. Hip fracture patients with preoperative sepsis are a vulnerable group in which treatment may be intensified.

Ethical approval: The study is approved by the Danish Health Authority and the Danish Data Protection Agency. The Ethics Committee deemed that no formal approval was needed under Danish law.


Abstract B

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Titel: Challenging the multimodal analgesic principle: Data from a cohort of total hip arthroplasty patients in five different hospitals.

Introduction
The available literature does not present a “gold standard” for postoperative pain treatment after total hip arthroplasty. Our knowledge about benefit and harm of multimodal analgesia in daily clinical practice is limited.

Methods
This prospective, multicenter, observational cohort study of 501 total hip arthroplasty patients was performed at five different hospitals at the Capital Region and at Region Zealand in Denmark from April 2014 to April 2016. The study was approved by The Danish Data Protection Agency and the Research Ethics Committee at Region Zealand. The study had two co-primary outcomes: Numeric rating scale (NRS) (0-10) pain during mobilisation at 6 hours postoperatively, and morphine consumption 0 - 24h postoperatively.

Results
A large variety of non-opioid analgesic treatment routines were used at the included hospitals and no hospital used the same basic analgesic regimen. For all patients at all hospitals, the NRS-pain level during mobilisation at 6h was 5 (3-6), (median (IQR)), and the 24-hour intravenous morphine-equivalent consumption was 25 mg (18-35), with no major differences between hospitals. In general, pain levels at rest were low to moderate, and pain during mobilisation was moderate to severe. For further details, see table 1.

Discussion
Although the analgesic non-opioid and opioid treatment routines varied between the five included hospitals, we found only marginal differences in pain and 24 h morphine consumptions between hospitals and routines. Alas, no multimodal analgesic regime showed relevant superior efficacy in clinical practice. Therefore, we find it important to register such pragmatic clinical data, to qualify and supplement results from randomized clinical trials and systematic reviews for postoperative pain treatment.

Conclusion
We found a large heterogeneity in pain treatment following THA, but no firm clinical relevant differences in outcomes between the five included hospitals. The concept of multimodal analgesia may be challenged when used in daily practice.
Abstract I

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Medforsøgte

Titel

Introduction

Laparoscopic ventral hernia repair is a common surgical procedure. However, muscle tensions may impair surgical overview and cause difficulties suturing the hernia defect. Deep neuromuscular blockade (NMB) paralyses the abdominal wall muscles and employment of deep NMB may ease the surgical conditions.1

We aimed at investigating if deep NMB compared with no NMB improved the surgical overview and/or the surgical conditions when suturing of the hernia defect during laparoscopic ventral hernia repair.

Methods

This study was approved by Research Ethics Committee of Copenhagen and the Danish Health and Medicines Authority and was carried out from May 2014 until February 2017. Patients were computer randomised 1:1 in an investigator-initiated, assessor-blinded crossover design to receive either no NMB followed by deep NMB or deep NMB followed by no NMB. Eligible patients were adults scheduled for elective laparoscopic ventral hernia repair.

A blinded surgeon assessed both surgical overview and surgical conditions during suturing of the hernia defect using a 5 point rating scale. The general surgical overview was evaluated both during deep NMB and with no NMB in all patients in the beginning of the laparoscopy. The surgical conditions during the laparoscopic suturing of the hernia defect were evaluated in patients either receiving deep NMB or no NMB according to randomisation. Deep NMB was established with rocuronium and reversed with sugammadex. Anaesthesia was performed with propofol and remifentanil.

Results

A total of 34 patients (mean 56 years of age, BMI 29, ASA 1-3, gender M/F 25/9) were included. Deep NMB compared to no NMB improved the surgeons’ ratings of surgical conditions during suturing the hernia defect (p=0.012, Mann-Whitney U test)(Table 1). We found no difference in improvement in surgical overview comparing deep NMB with no NMB; mean -0.1 (95% confidence interval -0.4 - 0.2) (p=0.521, paired t test).

No differences were found in either total length of surgery (p=0.755) or hernia suturing time (p=0.808)(Table 2).

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Table 1. Non-opioid analgesics and analgesic methods used for periparative pain treatment, pain and morphine consumption

<table>
<thead>
<tr>
<th>Hospitals</th>
<th>A (N=95)</th>
<th>B (N=100)</th>
<th>C (N=100)</th>
<th>D (N=101)</th>
<th>E (N=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic premedication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PCM + extended release morphine</td>
<td>95%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extended release oxycodone</td>
<td>78%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PCM + GABA + tramadol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>94%</td>
</tr>
<tr>
<td>PCM</td>
<td>98%</td>
<td>100%</td>
<td>98%</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
<td>90%</td>
<td>91%</td>
<td>27%</td>
<td>9%</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
<td>93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td>Chlorzoxazone</td>
<td>7%</td>
<td></td>
<td></td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Local infiltration analgesia</td>
<td>20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCN block</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>Morphine IV (mg) [median (IQR)]</td>
<td>20 (13-30)</td>
<td>18 (8-26)</td>
<td>28 (20-41)</td>
<td>27 (22-34)</td>
<td>31 (19-49)</td>
</tr>
<tr>
<td>Pain (6th) Rest [median (IQR)]</td>
<td>5 (3-6)</td>
<td>4 (3-5)</td>
<td>3 (2-4)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Pain (6th) Mobilisation [median (IQR)]</td>
<td>5 (3-6)</td>
<td>4 (3-5)</td>
<td>3 (2-4)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Pain (24th) Rest [median (IQR)]</td>
<td>5 (3-6)</td>
<td>4 (3-5)</td>
<td>3 (2-4)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
</tr>
<tr>
<td>Pain (24th) Mobilisation [median (IQR)]</td>
<td>5 (3-6)</td>
<td>4 (3-5)</td>
<td>3 (2-4)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
</tr>
</tbody>
</table>

PCM = pethidol, NSAID = non-steroidal anti-inflammatory drugs, GABA = gabapentin, LFCN= Lateral Femoral Cutaneous Nerve. Pain measured in NRS = Numeric Rating Scale, NS = not significant, morphine = morphine equivalent, IV = intravenous.

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Discussion
Deep NMB compared to no NMB did not improve surgical overview. Deep NMB improved surgical conditions during laparoscopic suturing of the hernia defect. A similar finding was also seen in a previous study where deep NMB improved surgical conditions during suturing of the abdominal fascia.

Conclusion
Deep NMB compared to no NMB improved surgical conditions during suturing of the hernia defect in laparoscopic ventral hernia repair.

Funding: Supported by a research grant from the Investigator Initiated Studies Program of MSD. Trial registration: At clinicaltrials.gov NCT02247466 in September 2014.

References
1) Madsen MV. Acta Anaesthesiol Scand. 2015; 59: 1-16
2) Madsen MV. Dan Med J. 2017; 64: A5364

Table 1
<table>
<thead>
<tr>
<th>Rating of suturing</th>
<th>NMB (n=19)</th>
<th>No NMB (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: extremely poor conditions</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2: poor conditions</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3: acceptable conditions</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>4: good conditions</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5: optimal conditions</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>p=0.012, Mann-Whitney U test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2
<table>
<thead>
<tr>
<th>Allocation</th>
<th>Mean (SD) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total length of surgery</td>
<td></td>
</tr>
<tr>
<td>No NMB during surgery</td>
<td>64 (31)</td>
</tr>
<tr>
<td>Deep NMB during surgery</td>
<td>61 (24)</td>
</tr>
<tr>
<td>Hernia suturing time</td>
<td></td>
</tr>
<tr>
<td>No NMB during suturing of the defect</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Deep NMB during suturing of the defect</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Total surgery time: p=0.755, Hernia suturing time: p=0.808, Mann-Whitney U test</td>
<td></td>
</tr>
</tbody>
</table>

Abstract 33

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Titel INVERT: Bedre neuromuskulær monitorering ved hjælp af e-læring – et prospektivt multicenter studie

Introduktion


**Metoder**
Vi designede et prospektivt multicenterstudie, som udnyttede, at data om brug af neuromuskulær monitorering rutinemæssigt registreres i den elektroniske anæstesijournal MetaVision (iMDsoft®, Düsseldorf, Germany). De Videnskabsetske Komiteter bekræftede, at studiet ikke krævede videnskabsetisk godkendelse. Studiet er godkendt af Styrelsen for Patientsikkerhed og Datatilsynet, og er registreret clinicaltrials.gov (NCT02925143).


**Resultater**

**Diskussion**
Denne præliminære analyse tager ikke højde forskelle imellem afdelingerne og en evt. naturlig variation i brug af neuromuskulær monitorering over tid. Generelt vanskeliggør det non-randomiserede design vurdering af kausalitet, men det begrænsede antal afdelinger umuliggjorde et (cluster-)randomiseret studie. Vi har planlagt at udføre segmenteret regressionsanalyse, som vil kunne tage højde for naturlig variation og forskelle mellem afdelingerne.

**Konklusion**
Frekvensen af neuromuskulær monitorering var højere efter indførsel af et obligatorisk e-læringsmodul om neuromuskulær monitorering.

**COI:** Studiet er støttet af MSD’s Investigator Initiated Studies Program.
Abstract 34

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Titel
Brug af muskelrelaksantia og neuromuskulær monitorering i Region Sjælland – et tværsnitsstudie baseret på data fra den elektroniske anæstesijournal MetaVision

Introduktion

Metoder

Resultater
I løbet af den 25 måneder lange periode blev der givet 77.754 generelle anæstesier, hvoraf patienten i 54.312 tilfælde blev intuberet. Af dem fik 30.126 (55%) relaksans enten i forbindelse med intubation eller under proceduren, fordelt på 13.698 (45%) med kun depolariserende og 16.428 (55%) med non-depolariserende. Neuromuskulær monitorering blev anvendt i 4.196 (31%) af tilfældene med depolariserende alene og i 14.379 (88%) af tilfældene med non-depolariserende relaksantia.

Diskussion
Anæstesipersonalet monitorerer næsten konsekvent den non-depolariserende blokade, men ikke den depolariserende. Studier fra Dansk Kolinesterase Kartotek har ellers dokumenteret vigtigheden af konsekvent neuromuskulær monitorering af alle patienter der relakseres, uanset type af relaksans.

Konklusion
Næsten halvdelen af alle intubationer i Region Sjælland gennemføres uden brug af muskelrelaksantia. Ved brug af non-depolariserende muskelrelaksantia anvendes neuromuskulær monitorering i næsten 9 ud 10 tilfælde, mens det ved depolariserende blokade alene kun er anvendes i 3 ud af 10 tilfælde.