Abstracts - foredragskonkurrence DASAIMs Årsmøde 2014

Abstract 12

Korresponderende forfatter Troels Haxholdt Lunn

Email	lunn@dadlnet.dk
Afdeling	Department of Anesthesiology and Orthopedic Surgery, The Lundbeck Centre for Fast-track Hip and Knee Arthroplasty, Neurobiology Research Unit, Center for Integrated Molecular Brain Imaging and Section of Surgical Pathophysiology
Hospital/institution	Hvidovre Hospital, Gentofte Hospital, Holstebro Hospital, Vejle Hospital and Rigshospitalet
Medforfattere	Vibe G. Frokjaer, Torben B. Hansen, Per W. Kristensen, Thomas Lind, Henrik Kehlet

Titel Analgesic effect of perioperative escitalopram in high pain catastrophizing patients after total knee arthroplasty, a randomized, double-blind, placebo-controlled trial

Introduction
Sufficient pain treatment remains a challenge after total knee arthroplasty (TKA), especially in high pain catastrophizing patients. Selective serotonin reuptake inhibitors (SSRI's) are widely used for major depression and anxiety disorders, and serotonergic signaling may be involved in pain processing. However, to our knowledge, the effect of SSRI on well-defined postoperative pain has not previously been investigated. We hypothesized that perioperative escitalopram would reduce pain after TKA in high pain catastrophizing patients.

Methods
The study was approved by the regional ethics committee, the Danish Medicines Agency, and the Danish Data Protection Agency. It was monitored by the Danish Good Clinical Practice Monitoring Units. The study was conducted at 3 high volume knee arthroplasty centers in Denmark (Gentofte, Holstebro and Vejle Hospital). Patients scheduled for TKA were assessed for eligibility using the Pain Catastrophizing Scale as preoperative screening tool. High pain catastrophizing patients were randomized (1:1) to either 10 mg escitalopram or placebo daily from pre-anesthesia to postoperative day 6. In addition, all patients received a standardized analgesic regime including oral acetaminophen and celecoxib and intra-operative local infiltration analgesia. Rescue analgesics consisted of oral morphine. The primary outcome was pain upon ambulation (walking 5 meters) 24 hours after surgery, assessed with the visual analog scale. Secondary outcomes were overall pain during well-defined m obilizations and at rest from 2-48 hours and from day 2-6, morphine equivalents, anxiety, depression and side effects.

Results
A total of 1110 patients were assessed for eligibility, 120 randomized and 114 included in the intention-to-treat analysis of the primary outcome. Pain upon ambulation [mean (95% CI)] 24 hours after surgery in the escitalopram vs. placebo group was: 58 (53-64) vs. 64 (58-69), the mean difference being -5 (-13–3), p=0.20. Overall pain upon ambulation and at rest from day 2-6 were significantly lower in the escitalopram vs. placebo group, both p=0.02 (Bonferroni corrected), as were depression score at day 6 (p<0.01). Side effects were insignificant except for reduced tendency to sweat and prolonged sleep in the escitalopram group. No other between-group differences were observed.

Discussion
Our findings of significant effects of escitalopram only on secondary pain outcomes (from day 2-6) make them exploratory in nature, precluding firm conclusions. However, they raise the intriguing question that if initiating the SSRI intervention earlier, it may exert an analgesic effect immediately after surgery, where pain is more pronounced.

Conclusion
Escitalopram did not reduce pain upon ambulation 24 hours after TKA in high pain catastrophizing patients. However, pain was significantly reduced from day 2-6 calling for future studies on effect, optimal timing and duration of treatment.

Clinical Trials: NCT01430520

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Korresponderende forfatter Ask Daffy Kvisselgaard

Email	akvisselgaard@me.com
Afdeling	Dansk Anæstesi Allergi Center (DAAC) – Klinik for allergi
Hospital/institution	Gentofte Hospital
Medforfattere	Krøigaard M, Mosbech H, Garvey LH

Titel Er lokalanæstetika hyppigt årsag til perioperative allergiske reaktioner?

Introduktion
Lokalanæstetika (LA) mistænkes ofte at som årsag til mulige allergiske reaktioner i forbindelse med indgreb i lokalanæstesi. Ved større operationer bruges LA ofte som supplement til generel anæstesi bl.a. ved perifere blok, epiduralblokade eller lokal infiltration. Derudover bruges

LA til spinalanæstesi ved visse indgreb f.eks. sectio og hoftealloplastik. Dansk Anæstesi Allergi Center (DAAC) har landsfunktion for udredning af patienter med mistænkte perioperative allergiske reaktioner. Det er ikke tidligere undersøgt, hvor hyppigt perioperativ eksponering for LA findes som årsag til allergiske reaktioner. Formålet med dette studie var således at undersøge hyppigheden af LA som årsag til perioperative allergiske reaktioner.

Metoder
I perioden 2004 - 2013 blev i alt 409 patienter (244 kvinder/165 mænd; median alder 49 år, range 1-86 år) udredt i DAAC på mistanke om allergi i forbindelse med anæstesi og operation. Udredning omfattede en kombination af hudtests, in vitro tests og provokationer med alle stoffer patienten var eksponeret for, før reaktionen.
I alt var 165 (40%) patienter eksponeret for ét eller flere LA. Udredning med lokalanæstetika omfattede: priktest, intrakutan test og subkutan provokation med de mistænkte præparater. Patienter med hudtests, som opfyldte kriterierne for positivitet, fik alligevel foretaget subkutan provokation, da falsk positive hudtests kan forekomme.

Resultater
I alt 207 testserier blev udført på 165 patienter (89 kvinder/76 mænd; median alder 54 år, range 2-85 år) fordelt på præparaterne: Lidocain n=80 (49%), bupivacain n=84 (51%), ropivacain n=31 (19%) og mepivacain n=12 (7%). Alle 165 patienter havde negativ subkutan provokation for alle testede LA. Kun to patienter havde positive hudtests. De tålte begge efterfølgende subkutan provokation med samme præparat og hudtest resultat blev tolket som falsk positivt. I alt 55 ud af 165 (33,3%) patienter blev diagnosticeret med allergi overfor et andet allergen, hyppigste årsager var: klorhexidin n=12, cefuroxim n=8 og Patent Blue n=7.

Konklusion
Ingen af de 165 patienter med mistænkte perioperative allergiske reaktioner og eksponering for LA reagerede ved subkutan provokation. Der er således ikke konstateret allergi overfor LA hos patienter udredt i DAAC i perioden 2004-2013 og allergi overfor LA må anses for sjælden i en sådan population.

Den reelle hyppighed af allergi overfor LA ved undersøgelser eller små indgreb udført i LA alene, er ukendt, men bør undersøges yderligere ved opgørelse af resultater af allergiudredning af disse patienter.

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Korresponderende forfatter Simon Tilma Vistisen

Email	vistisen@clin.au.dk
Afdeling	Research Centre for Emergency Medicine
Hospital/institution	Aarhus University Hospital/Aarhus University, Institute of Clinical Medicine

Titel Fluid responsiveness is predicted by analysis of extra systoles following cardiac surgery

Introduction
Fluid responsiveness prediction is an unsettled matter for intensive care patients. We hypothesised that systolic blood pressure (SBP) at the extra systolic post-ectopic beat, which is associated with increased preload, could be analysed in relation to surrounding sinus beats and that the magnitude of the SBP change (ΔSBP) could predict fluid responsiveness.

Methods
Post cardiac surgery patients scheduled for a 500 ml volume expansion by the attending physician were observed. In the time frame, 0-30 min prior to volume expansion, ECG was analysed for occurrence of isolated extra systoles (at least 10 preceeding and following sinus beats). During this period and during volume expansion, other hemodynamic interventions, significant concurrent bleeding (> 100 ml) and prolonged fluid infusion times (30 minutes for crystalloids and 75 minutes for colloids) excluded the recordings.

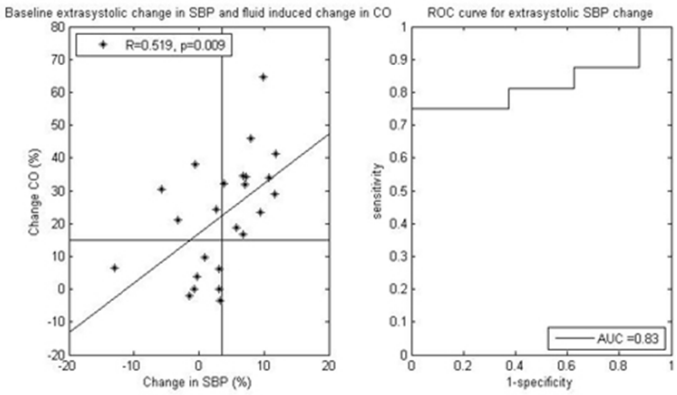
ΔSBP was defined as the change from average SBP at surrounding sinus beats to SBP at the extra systolic post-ectopic beat. A cardiac output increase >15% following volume expansion defined fluid responsiveness. ΔSBP's ability to predict fluid responsiveness was analysed with receiver operating characteristic (ROC) analysis and linear regression analysis.

Results
By August 5 2014, 24 patients were included. Among 16 responders and 8 non-responders, ΔSBP predicted fluid responsiveness in 20 patients correctly with 100% specificity and 75% sensitivity (Optimal ΔSBP threshold: 3.5%), ROC area: 0.83, (figure 1). Additionally, ΔSBP correlated statistically significantly with the changes in CO (figure 1).

Discussion and conclusion
Analysis of SBP at extra systolic post-ectopic beats can predict fluid responsiveness in post-cardiac surgery patients with good accuracy. The method needs to be validated in other patient groups that are not paced and/or mechanically ventilated, and the appliability of the method (the occurence of eligible extra systoles) needs to be elucidated for the intensive care patient group.

Conflicts of interest: The present method is protected by an international patent application (PCT/DK2014/050094)

Figure 1 (abstract 25)



Abstract 26

Korresponderende forfatter Anders Kehlet Nørskov

Email	anderskehlet@hotmail.com
Afdeling	Anæstesiologisk afdeling
Hospital/institution	Nordsjællands Hospital - Hillerød
Medforfattere	Charlotte V. Rosenstock, Jørn Wetterslev, Arash Afshari, Grethe Astrup, Lars H. Lundstrøm and the DIFFICAIR trial group.

Titel The effect of using the Simplified Airway Risk Index compared with usual care airway assessment on the frequencies of unanticipated difficult and easy intubation: A cluster randomized trial with 64,273 patients - The DIFFICAIR trial

Introduction
Prediction of intubation difficulties registered in the Danish Anaesthesia Database (DAD) is based on the anaesthesiologist's clinical assessment. The Simplified Airway Risk Index (SARI) is a multivariable risk score for prediction of difficult intubation (DI)[Fig 1]. The use of systematic and uniform airway assessment (AA) may reduce the incidence of unanticipated DI.
Aim: To compare the effect of using the SARI for AA with usual clinical care.

Methods
From 01.10.2012 to 31.12.2013, 26 departments of anaesthesia, stratified on 2011 proportions of unanticipated DI, were cluster-randomized to AA by SARI or by usual care.
Anticipation of DI was registered in the DAD pre-operatively by the anaesthesiologists. The SARI registration enabled the prediction of DI to be based on this assessment in the SARI group. An intubation score in the DAD graded the severity of the intubation conditions.
Primary outcomes: Fractions of unanticipated difficult and easy intubation.
The primary outcomes were tested using generalized estimating equations adjusted for the stratification and cluster variable according to the ITT principle.
A trial protocol[1] and a detailed statistical analysis plan[2] were published prior to obtaining clean files.

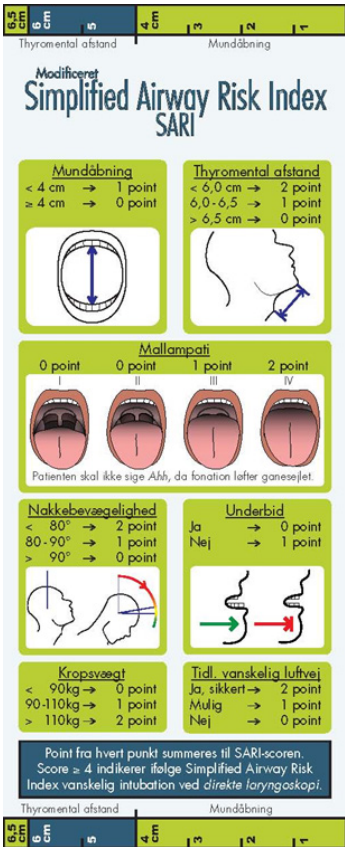
Results
A total of 64,273 patients were included with their first entry. Primary outcomes were measured on 59,514 patients not scheduled for advanced intubation (SARI: 29,209; Control: 30,305).
Unanticipated DI was 2.38% in the SARI vs. 2.39% in the control group. Adjusted odds ratio (OR) was 1.03 (0.77–1.38), P=0.84. Unanticipated easy intubation was 1.41% in the SARI vs. 0.96% in the control group, adjusted OR was 1.26 (0.68–2.34), P=0.47.
There was a 58% increase, 4.32% (1,397) vs. 2.73% (871), in patients anticipated difficult to intubate in the SARI group compared to the control group.
In the SARI group there was an 84% increase in patients scheduled for an advanced intubation compared to the control group, 10.33% (3,342) versus 5.62% (1,794).
In order to exclude patients intubated with advanced techniques due to educational purposes, we assumed that when DI was anticipated this was indeed the reason for choosing an advanced intubation technique. In the SARI group the number of anticipated DI intubated by an advanced method increased with 87% to 2.21% (714) vs. 1.18% (378) in the control group.

Discussion
This is the first major RCT comparing two strategies for prediction of DI. We have employed state of the art methodology for conducting cluster RCTs including predefined adjustments to sample size, data analyses and reporting[3].

Conclusion
Implementing the SARI as a strategy for pre-operative AA led to an increase in the anticipation of DI and a change in airway management behaviour favouring more advanced intubation techniques. However, it did not reduce the incidence of unanticipated DI or unanticipated easy intubation.

1. Trials 2013, 14:347 - 2. Trials 2014, 15:173 - 3. BMJ 2012, 345:e5661 Abstract 27

Figure 1 (abstract 26)



The diagnostic accuracy of the anaesthesiologists' prediction of difficult intubation
Primary analysis - Patients primarily attempted intubated with direct laryngoscopy

The SARI group

		Difficult intubation		
		Yes	No	
Anticipated difficult intubation	Yes	85	415	497
	No	696	28016	28712
		778	28431	29209

Sensitivity	=	0.11	(0.09-0.13)
Specificity	=	0.99	(0.98-0.99)
Positive predictive value	=	0.16	(0.13-0.20)
Positive likelihood ratio	=	7.22	(5.76-9.05)

The Control group

		Difficult intubation		
		Yes	No	
Anticipated difficult intubation	Yes	71	302	373
	No	723	29209	29932
		794	29511	30305

Sensitivity	=	0.09	(0.07-0.11)
Specificity	=	0.99	(0.99-0.99)
Positive predictive value	=	0.19	(0.15-0.23)
Positive likelihood ratio	=	8.74	(6.81-11.20)

Abstract 27

Korresponderende forfatter Morten Thingemann Bøtker

Email moboet@rm.dk
Afdeling Forskningsafdelingen
Hospital/institution Præhospitalet, Region Midtjylland
Medforfattere Carsten Stengaard, Erika Frischeknecht Christensen, Hans Kirkegaard, Christian Juhl Terkelsen

Titel Unresolved dyspnea is a dangerous symptom in the prehospital setting

Introduction
Electrocardiogram (ECG) based telemedicine is a cornerstone in prehospital triage of patients with suspected ST-elevation myocardial infarction (STEMI). In Denmark, an ECG transmitted from the ambulance is reviewed by a cardiologist on-call in case of 1) chest pain 2) re-suscitation from cardiac arrest 3) unresolved dyspnea and 4) other suspicion of myocardial infarction. However, dyspnea is rarely caused by myocardial infarction, but can be caused by many other etiologies. We hypothesize that unresolved dyspnea is an independent predictor of mortality in this prehospital setting and that the mortality is higher in patients with unresolved dyspnea than in patients with chest pain.

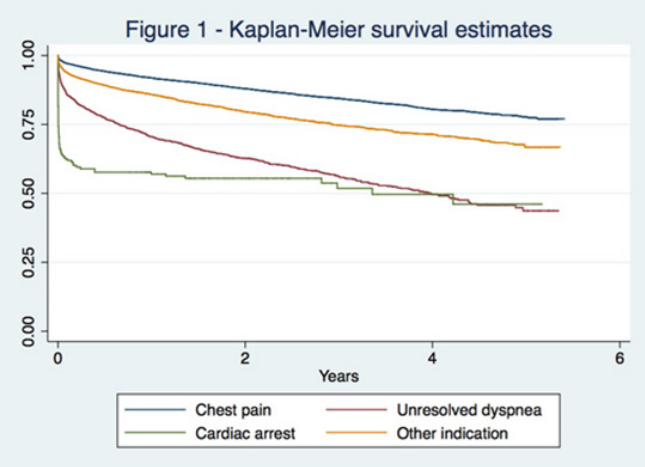
Methods
Population based follow-up study from 1st of June 2008 to 1st of January 2013. Participants were 17.361 patients triaged using ECG based telemedicine in the Central Denmark Region. Mortality-data was obtained from the Danish Civil Registration System. Cox multiple regression analysis was used to determine whether unresolved dyspnea is an independent predictor of mortality. Log-rank test was used to compare survival curves.

Results
Of the 17.361 patients, 1.428 was triaged because of unresolved dyspnea. Overall, 30-day mortality among patients triaged by use of telemedicine was 4,6% (CI 4.3 – 5.0). Thirty-day mortality was 13.3% (CI 11.6-15.1) in patients with unresolved dyspnea, 2.7% (CI 2.4-3.0) in patients with chest pain, 37.4% (CI 29.9-44.9) in patients resuscitated from cardiac arrest and 5.9% (CI 5.2 – 6.7) in patients with other suspicion of myocardial infarction. See figure 1 for long-term mortality curves. Unresolved dyspnea was an independent predictor of mortality when adjusting for age, sex and Charlson Comorbidity Index ($p<0.001$). The mortality was higher in patients with unresolved dyspnea than in patients with chest pain (log-rank $p<0.001$).

Discussion
We have demonstrated that dyspnea is a dangerous symptom in the prehospital setting and the mortality is higher than in patients with chest pain. A systematic approach both prehospital and inhospital combined with primary percutaneous coronary intervention in case of STEMI has improved survival of patients with chest pain. A similar systematic approach using point-of-care testing and a focus on improving prehospital treatment of patients with dyspnea may improve survival in these patients.

Conclusion
Unresolved dyspnea in the prehospital setting is an independent predictor of mortality and the mortality is higher than in patients with chest pain. Future research should focus on possibilities for improving early diagnosis and treatment of these patients.

Figure 1 (abstract 27)



Abstract 29

Korresponderende forfatter Anne Juul Wikkelsø

Email	wikkelso@gmail.com
Afdeling	Anæstesiologisk afdeling
Hospital/institution	Herlev Hospital
Medforfattere	HM Edwards, A Afshari, J Stensballe, J Langhoff-Roos, C Albrechtsen, K Ekelund, G Hanke, EL Secher, HF Sharif, LM Pedersen, A Troelstrup, J Lauenborg, AU Mitchell, L Fuhrmann, J Svare, MG Madsen, B Bødker, AM Møller
Titel	Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: a randomised controlled trial

Introduction
At the early stage of postpartum haemorrhage (PPH) a low level of fibrinogen is associated with excessive subsequent bleeding and blood transfusion. We hypothesized that pre-emptive treatment with fibrinogen concentrate (FC) may reduce the need for red blood cell (RBC) transfusion in patients with PPH(1).

Methods
The Danish National Committee on health research ethics and the Danish Medicines Agency approved this trial(1). Written informed consent was obtained from all patients. In this investigator-initiated multicentre, double-blinded parallel randomised controlled trial, we assigned patients with caesarean section and perioperative blood loss ≥1000 ml or vaginal delivery with either: blood loss ≥ 500 ml and intended manual removal of placenta; or blood loss ≥ 1000 ml and intended manual exploration of the uterus. Exclusion criteria were: Known inherited coagulation deficiencies, antenatal anti-thrombotic treatment, pre-pregnancy weight below 45 kg, and refusal to receive blood transfusion. Patients were randomized to 2 g of FC or placebo (saline). A fixed dose was given to all patients independent of body weight and fibrinogen level at inclusion. The primary outcome was RBC transfusion up to 6-weeks postpartum.

Results
Of the 249 randomised patients 244 were included in the intention-to-treat analysis. At inclusion the patients had severe PPH with a mean blood loss of 1459 ml (SD 476) and a mean fibrinogen level of 4.5 g/L (SD 1.2). The intervention group received a mean dose of 26 mg/kg FC, thereby significantly increasing the fibrinogen level by 0.46 g/L (95%CI, 0.17 to 0.75, p= 0.002) compared to the placebo group. Postpartum blood transfusion occurred in 25 (20%) of the fibrinogen group and 26 (22%) of the placebo group (relative risk, 0.95; 95% CI, 0.58 to 1.54, p= 0.88). We found no difference in any predefined secondary outcomes, per-protocol, or adjusted analyses. No thromboembolic events occurred.

Discussion
This trial is the largest randomised controlled trial investigating FC(2). It is investigator-initiated, the first trial in obstetric patients, and the only trial where patients were randomised in an emergency setting. The pragmatic multicentre trial set-up and few exclusion criteria strengthen the external validity, with the randomised design reducing selection and performance bias. However, our results are limited by the low number of included patients with an initial low fibrinogen and the wide confidence intervals on the primary result. This probably reflects the difficulty to provide informed written consent to patients with massive and rapid bleeding. Some colleagues recommend early treatment with 2-4 g of FC in cases of 1500 ml PPH(3). However, this represents off-label use in most countries. Based on our findings further pre-emptive use of FC in PPH is not justified.

Conclusion
We found no evidence for the use of 2 g FC as pre-emptive treatment for severe PPH with normofibrinogenaemia.

References

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