Renal function estimations and dose recommendations for Gabapentin, Ibuprofen and Morphine in acute hip fracture patients

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Aims: Optimization of pain management is essential for fast-track surgery and safety in acute hip fracture (AHF) patients. Kidney function determines the doses of several postoperative painkillers, but previous studies have shown the standard Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation overestimate glomerular filtration rate (GFR) in elderly and underweight patients. The optimized Cockcroft Gault (CGop) equation might be more accurate in this patient group. The study aims to (1) investigate the differences in estimated GFR (eGFR) based on CKD-EPI and CGop and (2) to simulate this impact on recommended dosing of standard painkillers in AHF patients.

Methods: Patients admitted with AHF from January to April 2015 were included. eGFR was calculated for each patient by CKD-EPI and CGop based on the lowest measured serum creatinine between 1 and 4 days postoperatively. CKD-classification (1–5) was performed based on both eGFR values. If patients were classified differently based on the two eGFR values, then drug dosages were simulated for Morphine, Ibuprofen and Gabapentin according to prescribing recommendations in Renbase®. Two-sided Mann–Whitney test was used to compare median values between groups.

Results: 176 patients (62% women) with a median age of 76 years were included. CKD-EPI (78.0 mL/min/m^2) estimated eGFR significantly higher compared with GGop (58.9, $P < 0.001$). Depending on the equation used to estimate GFR, CKD ≥ 3 (eGFR < 60 mL/min/m^2) occurred in 23–53% all patients. Using CGop to estimate GFR resulted in CKD re-classification for 63% of all patients. Using CKD-EPI to estimate GFR resulted in significantly higher doses of Morphine, Ibuprofen and Gabapentin ($P < 0.0001$) in re-classified patients.

Conclusions: GFR estimates are significantly higher when calculated by CKD-EPI compared to CGop, and this difference results in significantly higher recommended doses of painkillers in AHF patients. Future studies should include a gold standard for measuring GFR and maybe alternative biomarkers for the renal function.

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Evaluating the ability of non-rectangular electrical pulse forms to preferentially activate nociceptive fibers by comparing perception thresholds

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Aims: Selective activation of nociceptive fibers is difficult using electrical stimulation as the activation threshold is higher than for non-nociceptive fibers. It remains unclear to what extent accommodation of non-nociceptive fibers during slowly rising electrical pulses can be utilized to reverse this activation order. The aim of this study was to evaluate the ability of different pulse forms to activate nociceptive fibers with minimal co-activation of non-nociceptive fibers by comparing subjective perception thresholds (PT).

Methods: Electrical pulses were applied on the volar forearm of 25 subjects with (1) small diameter pin electrodes providing high current density in the skin epidermis, where primarily nociceptive fibers terminate and (2) standard patch electrodes (2.63 cm^2). PTs were obtained for exponential current increase, linear current increase, increasing form of exponential current decay (ED), and standard rectangular current pulses. All pulse forms were tested at two relatively long durations (5 and 50 ms). The PT ratio between patch- and pin electrode was calculated as an estimate of the ability of a pulse form to preferentially activate nociceptive fibers. The short form McGill pain questionnaire (SF-MPQ) was used to assess perceived quality of pain for all pulse forms.

Results: For the pin electrode, PT tended to decrease with increasing pulse area. Patch electrode PT tended to increase for increasing pulse area for non-rectangular 50 ms pulses, in contrast to 5 ms pulses, indicating accommodation of non-nociceptive fibers. Largest PT ratio was obtained for the 50 ms ED. SF-MPQ scores were higher for the pin- compared to the patch electrode. Pin electrode pain qualities were mainly described as stabbing and sharp. SF-MPQ scores did not differ between pulse forms.

Conclusions: Long duration ED pulses seem to activate nociceptive fibers better than regular, short duration pulses; most likely reflecting accommodation of non-nociceptive fibers.

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Detection of systemic inflammation in severely impaired chronic pain patients, and effects of a CBT-ACT-based multi-modal pain rehabilitation program

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Aims: A few previous studies indicate an ongoing of low-grade systemic inflammation in chronic pain patients (CPP) [1,2]. In the present study we investigated the plasma inflammatory profile in severely impaired chronic pain patients. In addition we studied if there were any alterations in inflammation patterns at one-year

follow up, after the patients had taken part in a CBT-ACT based 4 weeks in-hospital pain rehabilitation program (PRP).

Methods: Blood samples were collected from 52 well characterized chronic pain patients. Plasma from matched healthy blood donors were used as controls. At one year after the treatment program, 28 of the patients were available for follow up. Instead of only analyzing single inflammation-related substances, we used a new multiplex panel enabling the simultaneous analysis of 92 inflammation-related proteins, mainly cytokines and chemokines (Proseek Inflammation, Olink, Uppsala, Sweden). Multivariate statistics were used for analysis.

Results: Clear signs of increased inflammatory activity were detected in the pain patients. Accepting a false discovery rate (FDR) of 5%, there were significant differences in 43 of the 92 inflammatory biomarkers. The expression of 8 biomarkers were 4 times higher in patients compared to controls. Three biomarkers, CXCL5, SIRT2, AXIN1 were more than 8 times higher. The conventional marker for inflammation, CRP, did not differ. Of the 28 patients available for follow up one year after the intervention, all showed lower levels of the inflammatory biomarker initially raised.

Conclusions: The results indicate that CPP suffer from a low grade of chronic systemic inflammation, not detectable by CRP analysis. This may have implications for the general pain hypersensitivity, and other symptoms, often described in this group of patients. We conclude that inflammatory plasma proteins may be measureable molecular markers to distinguishes CPP from pain free controls, and that a CBT-ACT pain rehab program seem to decrease this inflammatory activity.

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Fixed or adapted conditioning intensity for repeated conditioned pain modulation

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Aims: Conditioned pain modulation (CPM) is used to assess descending pain modulation through a test stimulation (TS) and a conditioning stimulation (CS). Due to potential carry-over effects, sequential CPM paradigms might alter the intensity of the CS, which potentially can alter the CPM-effect. This study aimed to investigate the difference between a fixed and adaptive CS intensity on CPM-effect.

Methods: On the dominant leg of 20 healthy subjects the cuff pressure detection threshold (PDT) was recorded as TS and the pain tolerance threshold (PTT) was assessed on the non-dominant leg for estimating the CS. The difference in PDT before and during CS defined the CPM-effect. The CPM-effect was assessed four times using a CS with intensities of 70% of baseline PTT (fixed) or 70% of PTT measured throughout the session (adaptive). Pain intensity of the conditioning stimulus was assessed on a numeric rating scale (NRS). Data were analyzed with repeated-measures ANOVA.

Results: No difference was found comparing the four PDTs assessed before CSs for the fixed and the adaptive paradigms. The CS pressure intensity for the adaptive paradigm was increasing during the four repeated assessments ($P < 0.01$). The pain intensity was similar during the fixed (NRS: 5.8 ± 0.5) and the adjusted paradigm (NRS: 6.0 ± 0.4). The CPM-effect was higher using the fixed condition compared with the adaptive condition ($P < 0.05$).

Conclusions: The current study found that sequential CPM paradigms using a fixed conditioning stimulus produced an increased CPM-effect compared with adaptive and increasing conditioning intensities.

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Combined treatment (Norspan, Gabapentin and Oxynorm) was found superior in pain management after total knee arthroplasty

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Background: Gabapentin (GAB) has recently been introduced for postoperative pain treatment in orthopedic surgery. As persistent postoperative pain is still a major problem in total knee arthroplasty (TKA), studies on the effect and side effects of Gabapentin in addition to the commonly used morphine (MOR), Oxynorm (OXY) and Norspan (NOR) are highly warranted. In the present study, four relevant treatment algorithms, gabapentin and morphine (GAB/MOR), gabapentin and Oxynorm (GAB/OXY), Oxynorm (OXY) and Gabapentin, Oxynorm and Norspan (GAB/OXY/NOR) were examined.

Patients and methods: A total of 241 patients were followed systematically during one month following TKA in four consecutive series: 60 patients were treated with GAB/MOR, 62 patients with GAB/OXY, 59 patients with OXY, and 60 patients with GAB/OXY/MOR. On the day before surgery and on postoperative day 1, 14, and 30, pain during rest, pain during walking and side effects (constipation, dizziness, and nausea) were reported (VAS).

Results: After 30 days, pain greatly decreased in all groups, with a superior effect of GAB/OXY/NOR for pain during rest and only slightly more side effects at day 1.

Conclusions: In management of postoperative pain following TKA, data indicated that GAB/OXY/NOR was superior, compared to GAB/MOR, GAB/OXY, and OXY.

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Effects of conditioned pain modulation on the withdrawal pattern to nociceptive stimulation in humans – Preliminary results

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Aims: Conditioned pain modulation (CPM) is a paradigm employed to assess descending control of spinal nociception.