Clinical Outcomes after Implementing a Computer-Based Protocol for Sustained Use of Sedation and Analgesia in the ICU

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Background: The SCCM recommends goal directed sedation with standardized medications. Few studies have evaluated how implementation of these recommendations affects clinical outcomes. **Methods:** An institution specific protocol based on SCCM guidelines for sustained sedation and analgesia was developed by a team of critical care physicians, nurses, and pharmacists. Recommendations were incorporated into a computerized decision support application that generated protocol-compliant orders. Adult medical ICU patients on mechanical ventilation were prospectively followed for ICU length of stay, duration of ventilation, development of delirium (using CAM-ICU), and mortality during phase I of implementation (summer of 2003). Treating physicians controlled the initiation and termination of the protocol. Patient outcomes were compared to historical control data obtained on 264 ventilated patients admitted to the same ICU during 2002. **Results:** Of 61 ventilated patients admitted during phase I of protocol implementation, 48 were placed on the sedation protocol. The implementation of the protocol was associated with a 1 day reduction in ICU length of stay [median (IQR) 4.1 (2.1,6.7) vs 5.1 (2.8,9.5), p=0.04], and a trend toward reduced time on the ventilator [median (IQR) 2.2 (0.7, 3.8) vs 2.7 (1.1,6.2), p=0.11]. There was no change in the prevalence of delirium (77% in both groups). Of delirious patients treated during protocol implementation, 32% received haloperidol or other drug targeting delirium. Mortality was similar between the intervention and pre-intervention patients [28% vs 31%, p>0.2]. **Conclusion:** Implementation of a protocol for sustained sedation and analgesia reduced ICU length of stay and likely ventilator duration.

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Evaluation of Outcomes in Mechanically Ventilated Patients Using the CAM (Confusion Assessment Method) - ICU Instrument

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Design: A prospective, single center, observational study to evaluate outcomes in mechanically ventilated patients using the CAM ICU instrument. **Setting:** The medical intensive care unit (19 beds) of an urban teaching hospital. **Patients:** Adult, intubated and mechanically ventilated. **Interventions:** Prospective outcomes in CAM (+) vs CAM (-) patients. **Measurements and Main Results:** Consecutive patients, mechanically ventilated for greater than 24 hours, were evaluated daily with the CAM ICU instrument. A total of 38 patients were enrolled. Of those, 13 (34%) were CAM (+) for delirium at least once while in the ICU, 10 (26%) CAM (-) and the rest, 15 (39%) UTA (unable to assess) using the CAM ICU tool due to ramsey sedation level. CAM (+) patients required significantly higher doses of benzodiazepines for sedation and higher restraint use compared to CAM (-) patients. Age, apache II score, ICU length of stay, or mortality did not differ significantly between the groups. **Conclusions:** CAM (+) patients differ from CAM (-) patients in the amount of benzodiazepines administered and the use of restraints. ICU length of stay and mortality, however, did not differ.

Main Results

	CAM (+) (n = 12)	CAM (-) (n=10)	UTA (n=15)
Age	55.8 ± 19.9	58.2 ± 21.3	60.7 ± 13.8
Apache II Score	19.3 ± 7.7	21.9 ± 4.9	30.5 ± 9.7*#
Restraints, days	3.5 ± 3.2	1.1 ± 1.4*	1.9 ± 2.2
Benzodiazapine Use, mg/kg/day	0.8 ± 0.6	0.1 ± 0.2*#	0.7 ± 0.9
ICU LOS, days	10.0 ± 6.0	9.4 ± 2.7	7.2 ± 3.7
Mortality, % dead	25%	33%	50%

*p<0.05 comparing CAM (+) to CAM (-); #p<0.05 comparing CAM (-) to UTA; #p<0.05 comparing CAM (+) to UTA.

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Impact of Scheduled Bolus Administration of Lorazepam and Daily Interruption of Sedation on Duration of Mechanical Ventilation

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Rationale: Our objective was to assess the impact of a sedation protocol including scheduled intermittent bolus administration of lorazepam and daily interruption of sedation on duration of mechanical ventilation (MV). Methods: A new sedation protocol was initiated in October 2001 in our medical ICU as part of a clinical trial comparing scheduled bolus dosing of lorazepam with continuous propofol infusion. The trial included patients with anticipated need for MV > 48 hours and need for ≥ 10mg lorazepam within 24 hours. Sedation was interrupted daily for assessment of continued need for propofol or scheduled lorazepam. We retrospectively identified a cohort of patients who met inclusion criteria and no exclusion criteria for the trial from the two years preceding initiation of the protocol. Lorazepam was typically provided on an as needed basis without mandatory awakening during this period. Pre-protocol patients were compared to trial patients randomized to lorazepam with primary outcome defined as median ventilator days. Results: There were no differences between the two groups in age, APACHE II and SOFA scores.

	Pre-protocol (n=82)	Protocol (n=45)	p value
Total Lorazepam dose (mean±SD)	84.1±112.8 mg	175.9±203.4 mg	0.001
Ventilator days (median)	6.4	11.2	0.028
Ventilator days (mean± SD)	10.6±11.8	14.3±15.0	0.12
Ventilator days (mean±SD) adjusted for lorazepam*	12.1±11.2	11.6±15.6	0.83
ICU days (median)	7.7	12.3	0.005

*Adjusted for total lorazepam dose using multivariate linear regression.

Conclusion: A sedation protocol mandating scheduled bolus administration of lorazepam increases duration of MV. This is likely due to higher cumulative doses of lorazepam despite daily interruption of sedation.

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Occupational Risk Factors for Airflow Limitation in Industrial Workers

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Introduction: Using spirometry data from workplace screening programs conducted at 23 assorted manufacturing plants typically absent current regulated exposures, we estimate the effect of previous occupational exposure (as reported on a questionnaire at entry into the program) on baseline spirometry (FEV_1, FVC, and FEV_1/FVC). **Methods:** 17,878 workers participated in the annual spirometric monitoring programs implemented from 1984 to 2002. At each spirometric testing, questionnaire data were collected on previous occupational exposure to asbestos, sandblasting, mining, cotton dust, and chemical gases and the duration of each exposure. Smoking habits (status and number of cigarettes smoked) were also ascertained. Using the linear regression model, we estimated the effect of each previous occupational exposure (present/absent) and the duration of each exposure on lung function (% predicted), while we adjusted for the effects of smoking status, pack years, plant, and the calendar year. **Results:** Across all plants, previous occupational exposures to mining (5 yrs or more), chemical gases (10 yrs or more) and cotton dust (10 yrs or more) were associated with significantly lower FEV_1% pred. In specific plants, exposures to sandblasting and asbestos were also associated with significantly lower FEV_1. **Conclusion:** The results suggest that the effect of previous occupational exposures should be taken into consideration to obtain unbiased estimates of the effect of current occupational exposure on lung function.

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Particle Surface Modification Inhibits *In Vitro* and *In Vivo* Quartz-Induced Generation of Reactive Oxygen and Nitrogen Species

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Particle surface reactivity has been suggested to play a crucial role in quartz-induced pulmonary diseases, including fibrosis and cancer. Since oxidative stress is considered as a central mediator of these diseases, the present study has aimed to elucidate the involvement of the reactive particle surface in the *in vivo* generation of quartz-induced reactive oxygen and nitrogen species (ROS/RNS). Rats were intratracheally instilled with 2 mg native quartz (DQ12) or quartz coated with either polyvinylpyridine-N-oxide (PVNO) or aluminium lactate (AL). After 7 days, levels of pulmonary oxidants (H_2O_2, nitrite), trolox equivalent antioxidant capacity (TEAC) and marker of cell toxicity, i.e. alkaline phosphatase (AP), lactate dehydrogenase (LDH), total protein were evaluated in bronchoalveolar lavage (BAL) fluid. BAL cells were used to assess *ex vivo* phorbol myristate acetate (PMA)-induced H_2O_2 production and differential cell counting. Our data show that both PVNO and AL coating inhibited quartz-induced generation of H_2O_2 and NO_2. There was a close correlation between the number of phagocytes and ROS/RNS levels in the BAL. *Ex vivo* PMA-induced H_2O_2 generation was only observed in samples from rats exposed to native DQ12 which correlates with the % PMN in the BAL. Although enhanced oxidant generation in native DQ12-treated rats was paralleled with increased antioxidant capacity (TEAC), an increase in AP and LDH levels was observed, indicative of pulmonary toxicity. The present data provide evidence for a role of the reactive particle surface in quartz-induced *in vivo* ROS/RNS generation. Furthermore, since pulmonary oxidant production was paralleled by inflammatory cell influx, the data contribute to the general opinion on the involvement of secondary, inflammatory cell-related processes in particle-induced lung diseases.

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Crystalline Silica Activates Oxidant Sensitive Signaling Pathways and Upregulates Cyclooxygenase-2

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The well-documented carcinogenicity of crystalline silica may be attributed to its ability to induce oxidative stress and inflammation in the lung. Cyclooxygenase-2 (COX-2) promotes inflammation by catalyzing the synthesis of eicosanoids and leukotrienes, and is commonly upregulated in lung cancers. We demonstrate that sublethal doses of crystalline silica (DQ12) increased COX-2 expression by A549 and 16-HBE cells as detected by Western blot (Densitometry expressed as fold increase over control at 6 hours, mean (SEM): A549, 5μg/cm² – 2.99 (0.45), 10μg/cm²- 7.57 (0.24), 20μg/cm² -7.18 (0.08). 16-HBE, 5μg/cm2 – 2.55 (0.35), 10μg/cm²- 3.09 (0.20), 20μg/cm² –2.93 (0.24)). Moreover, treatment of A549 and 16-HBE cells with DQ12 induced synthesis of prostaglandin E2. COX-2 expression is under the control of the transcription factor, NF-κB, which can be activated by both p38 and ERK MAPK pathways. Activation of these pathways was also observed in response to DQ12 treatment (20μg/cm²), for example p38 MAPK levels by western blot in both A549 and 16-HBE cells (densitometry expressed as a ratio of phosphorylated p38 to native p38, mean (SEM): A549, control- 0.02 (0.022) DQ12 - 3.48 (0.375). 16-HBE, control - 0.01 (0.013), DQ12 - 2.29 (0.753)). Thus, we hypothesise that crystalline silica activates the p38 and ERK MAPK pathways, thereby inducing COX-2 expression, which results in PGE2 synthesis, propagating an inflammatory reaction.

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