Author’s response to reviews

Title: Renal effects of dexmedetomidine during coronary artery bypass surgery: a randomized placebo-controlled study

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Author's response to reviews: see over
Dear Executive editor Rachel Neilan,

February 28th

Thank you for the comments and constructive criticism provided by the two referees concerning our manuscript “Renal effects of dexmedetomidine during coronary artery bypass surgery: a randomized placebo-controlled study” (MS 2004991233433459). These comments have clearly improved the manuscript. Below you find our point-by-point response and revisions to suggested changes.

Referee I

- Major Compulsory Revisions

* What is the duration of the study? You should mention the period of this study.

The study was carried out in years 1994-1997 as we now state in the beginning of the results section.

* As we know, the dose of dexmedetomidine is body weight related; how could you know that you reached the steady-state plasma concentration of 0.6 ng/ml of dexmedetomidine without taking in consideration the body weight of patients?

We chose the steady-state concentration of 0.6 ng/ml and dosing of dexmedetomidine based on our previous experience with dexmedetomidine in CABG patients (Jalonen et al 1997) and simulation with then unpublished pharmacokinetic data now available from Talke et al (Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. Talke P, Richardson CA, Scheinin M, Fisher DM. Anesth Analg. 1997 Nov;85(5):1136-42.). We now provide that information in the methods section of the manuscript. Despite the lack of dexmedetomidine concentration measurements we are quite confident that the mean steady-state concentration of dexmedetomidine was very close to 0.60. We do admit that there might have been interindividual changes in the steady-state concentration according to body weight, as the referee points out. This is also now stated in the discussion.

* As we know, the use of mannitol in the ECC priming is actually aborted and especially when we use deep hypothermia (less than 33ºC). I think that this point is a bias in the study.

At the time of the study (1994-1997) nasopharyngeal temperature 30 ºC was common practice in our unit as in many others and was considered to be rather moderate hypothermia than deep hypothermia. Routine use of mannitol was common at that time. Things have changed and nowadays we apply 34 ºC in coronary surgery and use mannitol less frequently, though we still usually do as most of the other centers in Finland. We appreciate the criticism of the referee that the use of mannitol in the present study probably increased diuresis to some extent in both treatment arms. There are, however, a great variety of other parameters related to the open heart surgery that per se affect diuresis and we see the use of mannitol as a single factor among many others affecting diuresis in this setting. We tried carefully to standardize all these factors with our strictly-defined protocol. Mannitol was given similarly to both study groups and we are confident
that as such it does not invalidate the conclusions of the study with regard to dexmedetomidine.

Referee II

Major: Hemodynamics have to be reported to enable the reviewers and readers to judge, whether the presumed beneficial responses to study medication are influenced by side effects i.e. in the 1997 Anesthesiology paper (86: 331-345) Jalonen J et al. reported an increase of rate of hypotension during cardiopulmonary bypass as well as the need for more intravenous fluid with dexmedetomidine. Despite adherence to a study protocol mean blood pressure may well be different between groups in the present study.

The revised results section now provides detailed information of hemodynamics from the induction of anesthesia to the start of perfusion, during perfusion, after perfusion until ICU and in the ICU until 24 h from admission. We did not record these data beyond 24 h since we did expect that changes relevant to renal function would occur during that time period. MAP was higher in the dexmedetomidine group prior to ECC compared to the placebo group and vice versa after ECC until admission to ICU. Otherwise there were no differences in MAP during ECC and in SAP in the ICU. Consequently, there was no such difference in blood pressure that could account for mean 74 % increase in urine volume related to dexmedetomidine treatment.

In the same line the authors need to report the amount and type of i.v. fluid (e.g. hydroxethylstach and Ringer's acetate) given before, during and after CABG (up to 48h) in both groups. A higher fluid intake could completely explain the higher urine output reported with dexmedetomidine.

We now report the suggested fluid volumes intraoperatively and in the ICU until 24 h from insertion of urinary catheter. Unfortunately we were not able to record fluids up to 48 h. However, since there were no differences between the treatment arms either in given volume of Ringer's acetate or hydroxyethyl starch we consider this as a proof that our strict protocol worked quite well. There is nothing in our knowledge that would suggest anything else also between 24 and 48 h.

A major shortcoming in the design of the study is that baseline creatinine clearance (12-24 h) done before surgery is not reliable, since urine collection was relying on spontaneous voiding in 60 year old patients and because of the inherent risk of incomplete collection without urinary catheter placement. These considerations need also to be included in the discussion. The results of creatinine clearance should also be given quantitatively for the intention-to-treat population.

As our patients may have had problems in spontaneous voiding, residual volume in the bladder might contribute to urine output as and baseline creatinine clearance as suggested by the referee. If one considers the formula to determine creatinine clearance [i.e. creatinine clearance (ml/min) = U-Crea (µmol/l) x urine output (ml/min)/S-Crea (µmol/l)], urine output has a significant effect to the clearance. A smaller urine output results in smaller clearance values if U-Crea and S-Crea remain unchanged. However, we feel that as the mean preoperative creatinine clearance value is within the normal range (though at
the lower end) it is likely not that much affected by problems in spontaneous voiding and if it were both groups (the active treatment group with dexmedetomidine and the control group) would likely be affected similarly. Importantly the clearance values were similar in both groups indicating a similar systematic error (if any). Finally, this study is not on serial changes in creatinine clearance but on the effects of a pharmacological intervention on renal function in general compared to control group without this intervention to even out potential systematic errors. We have added the following sentence to the discussion section: “Eventual problems in spontaneous voiding might also have resulted in systematic underestimation of baseline creatinine clearance."

The results of creatine clearance are now reported also for the ITT population.

**Minor: The abbreviation ECC has to be explained. A few spelling errors need correction (Fig. 1 protocol-spesified; ref. #7 patogenesis ...).**

The abbreviation ECC i.e. extracorporeal circulation is now explained and the spelling errors have been corrected.

Thank you for the consideration of the manuscript.

Sincerely yours,

Kari Leino