

Kim *et al.*<sup>1</sup> concluded in patients undergoing total knee arthroplasty that the intraoperative DEX (0.5 µg/kg intravenously followed by 0.4 µg/kg/h intravenously) attenuates the postoperative level of interleukin-6 as well as lactate at 90 and 60 minutes after the tourniquet release, respectively. However, Kim *et al.* did not complete the sample size evaluation regarding the parameters, and from our calculation using SamplePower 3.0 (IBM Japan Inc., Tokyo, Japan), the authors will need an additional 12 to 17 cases to evaluate the intergroup difference of lactate and interleukin-6 at each time frame. Also, Kim *et al.* did not examine the cytokine levels at the earlier time frame, such as at 15 minutes after the tourniquet release.<sup>3</sup> Therefore, they might not notice the more critical pathology, including the augmented levels of cytokines derived from organ damage immediately after the release.<sup>3</sup> Moreover, we are not sure how much of the administered DEX was distributed within the tissues of the targeted lower limb, and why it was sufficient to reduce levels of cytokine or lactate, if any, more than 60 minutes after the tourniquet release. If one looks at the mean times of duration for surgery and tourniquet, the surgical procedures in each case were mostly done during the use of a tourniquet. The times from the commencement of DEX administration to the tourniquet application and those from the tourniquet release to the end of DEX are unclear, unfortunately. The points appear most critical to speculate the postoperative tissue levels of DEX in the lower limb.

Kim *et al.*<sup>2</sup> concluded in patients undergoing spine fusion surgery that the intraoperative DEX (0.4 µg/kg/h intravenously) reduces the postoperative stress responses including levels of plasma epinephrine and norepinephrine. The levels of plasma epinephrine and serum cortisol, values of mean arterial pressure and heart rate, intraoperative remifentanyl doses, and the degree of sympathetic activity were, in contrast, similar between control and DEX groups during the period.<sup>2</sup> We did not see any explanation and data in the paper of why only the plasma levels of norepinephrine in the DEX group decreased during surgery despite the above similarity between the groups.<sup>2</sup> Also, the numeric rating score expressing the pain intensity at 60 minutes after surgery in the DEX group was less than the control group while the remifentanyl doses were similar between the groups.<sup>2</sup> Therefore, why the intravenous DEX 0.4 µg/kg/h for less than 220 minutes without the loading was sufficient to reduce postoperative pain, as well as stress responses, even 60 minutes after the termination of infusion is still unclear in the study.

Collectively, we want to have additional data from both author groups to explain the above questions in future studies.

Yoshihisa MORITA<sup>1</sup>, Hiroyuki KINOSHITA<sup>2,3\*</sup>

<sup>1</sup>Division of Cardiac Anesthesia, Department of Anesthesia, Pain Management and Perioperative Medicine, Henry Ford Hospital, Detroit, MI, USA;

<sup>2</sup>Department of Anesthesiology, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan; <sup>3</sup>Department of Anesthesiology, IMS Fujimi General Hospital, Fujimi, Japan

\*Corresponding author: Hiroyuki Kinoshita, Department of Anesthesiology, Institute of Biomedical Sciences, Tokushima

University Graduate School, 3-18-15 Kuramoto, Tokushima 770-8503, Japan. E-mail: hkinoshi@krc.biglobe.ne.jp

## References

1. Kim SH, Kim DH, Shin S, Kim SJ, Kim TL, Choi YS. Effects of dexmedetomidine on inflammatory mediators after tourniquet-induced ischemia-reperfusion injury: a randomized, double-blinded, controlled study. *Minerva Anesthesiol* 2019;85:279–87.
2. Kim MH, Lee KY, Bae SJ, Jo M, Cho JS. Intraoperative dexmedetomidine attenuates stress responses in patients undergoing major spine surgery. *Minerva Anesthesiol* 2019;85:468–77.
3. Kinoshita H, Iranami H, Fujii K, Yamazaki A, Shimogai M, Nakahata K, *et al.* The use of bone cement induces an increase in serum astroglial S-100B protein in patients undergoing total knee arthroplasty. *Anesth Analg* 2003;97:1657–60.

*Conflicts of interest.*—Hiroyuki Kinoshita is a consultant for IMI Co. Ltd., Koshigaya, Saitama, Japan.

*Comment in:* Kim SH, Choi YS. Effects of dexmedetomidine on malondialdehyde and proinflammatory cytokines after tourniquet-induced ischemia-reperfusion injury in total knee arthroplasty. *Minerva Anesthesiol* 2020;86:223-4. DOI: 10.23736/S0375-9393.19.14058-8.

Kim MH, Cho JS. Protective effects of dexmedetomidine on stress and inflammatory responses. *Minerva Anesthesiol* 2020;86:222-3. DOI: 10.23736/s0375-9393.19.14097-7.

*Comment on:* Kim SH, Kim DH, Shin S, Kim SJ, Kim TL, Choi YS. Effects of dexmedetomidine on inflammatory mediators after tourniquet-induced ischemia-reperfusion injury: A randomized, double-blinded, controlled study. *Minerva Anesthesiol* 2019;85:279-87. DOI: 10.23736/S0375-9393.18.13015-X.

Kim MH, Lee KY, Bae SJ, Jo M, Cho JS. Intraoperative dexmedetomidine attenuates stress responses in patients undergoing major spine surgery. *Minerva Anesthesiol* 2019;85:468-77. DOI: 10.23736/S0375-9393.18.12992-0.

Article first published online: September 3, 2019. - Manuscript accepted: August 2, 2019. - Manuscript revised: July 18, 2019. - Manuscript received: July 3, 2019.

(Cite this article as: Morita Y, Kinoshita H. Incomplete clinical evaluation regarding protective effects of dexmedetomidine on stress and inflammatory responses. *Minerva Anesthesiol* 2020;86:221-2. DOI: 10.23736/S0375-9393.19.13985-5)

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*Minerva Anesthesiologica* 2020 February;86(2):222-3

DOI: 10.23736/S0375-9393.19.14097-7

## Protective effects of dexmedetomidine on stress and inflammatory responses

We would like to thank Dr. Hiroyuki Kinoshita for the attention and valuable comments regarding our manuscript.<sup>1</sup> In our study, intraoperative dexmedetomidine

administration during major spine surgery attenuated catecholamine increase and maintained the balance of autonomic nervous system.<sup>2</sup> Continuous variables with repeated measures, including catecholamine levels, heart rate variability data, and hemodynamic variables, were analyzed using a linear mixed model analysis to consider the group x time interaction. Serum epinephrine and norepinephrine levels were greater over time in the control group compared with the dexmedetomidine group, and the changes for catecholamine levels were statistically significant between the groups ( $P=0.001$  and  $<0.001$ , respectively). Serum epinephrine level increased during surgery in the control group, whereas it decreased in the dexmedetomidine group, indicating that dexmedetomidine attenuated catecholamine increase induced by surgical stress. The stress reducing effects of dexmedetomidine were also demonstrated the changes of autonomic nervous system balance assessed by the heart rate variability. In the control group, the high frequency (HF) power decreased and the low frequency (LF) power and the LF/HF ratio increased significantly during and 1 h after surgery compared with baseline values, which indicated sympathetic hyperactivation. In contrast, in the dexmedetomidine group, HF power, LF power, and the LF/HF ratio were maintained at the baseline values, which indicated maintained autonomic nervous system balance. The LF power and the LF/HF ratio were significantly lower over time in the dexmedetomidine group than in the control group ( $P=0.024$  and  $0.001$ , respectively), indicating that dexmedetomidine attenuated sympathetic hyperactivation.<sup>3</sup>

With regard to the results about hemodynamic parameters, anesthesia was performed with desflurane and remifentanyl to maintain the bispectral index within a range of 40-60 and the mean arterial pressure within 20% of preinduction values in both groups. The changes of arterial pressure and heart rate were similar between the control and dexmedetomidine groups. Although dexmedetomidine has the potential to cause hypotension or bradycardia due to systemic vasodilation *via* sympatholytic actions,<sup>4</sup> the dexmedetomidine group did not show any untoward hemodynamic adverse event in this study. Pain intensity 1 h after surgery was significantly lower in the dexmedetomidine group, which might be attributed to remained analgesic effect of dexmedetomidine infused during surgery, whereas pain intensities thereafter were similar between the groups. As intraoperative remifentanyl doses were similar between the groups, the possibility of remifentanyl-induced postoperative hyperalgesia could be excluded. Considering that stress response and pain extend across several days after the surgery, continuous administration of dexmedetomidine after surgery would have had more clinical impact on postoperative pain relief and recovery.

Myoung H. KIM, Jin S. CHO \*

Department of Anesthesiology and Pain Medicine,  
Severance Hospital, Anesthesia and Pain Research  
Institute, Yonsei University College of Medicine,  
Seoul, South Korea

\*Corresponding author: Jin S. Cho, Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea.  
E-mail: CHJS0214@yuhs.ac

## References

1. Morita Y, Kinoshita H. Incomplete clinical evaluation regarding protective effects of dexmedetomidine on stress and inflammatory responses. *Minerva Anestesiol* 2019;86:221-2.
2. Kim MH, Lee KY, Bae SJ, Jo M, Cho JS. Intraoperative dexmedetomidine attenuates stress responses in patients undergoing major spine surgery. *Minerva Anestesiol* 2019;85:468-77.
3. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput* 2006;44:1031-51.
4. Coursin DB, Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care* 2001;7:221-6.

*Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

*Comment on:* Morita Y, Kinoshita H. Incomplete clinical evaluation regarding protective effects of dexmedetomidine on stress and inflammatory responses. *Minerva Anestesiol* 2020;86:221-2. DOI: 10.23736/S0375-9393.19.13985-5.

Article first published online: December 6, 2019. - Manuscript accepted: September 25, 2019. - Manuscript revised: September 12, 2019. - Manuscript received: August 21, 2019.

(Cite this article as: Kim MH, Cho JS. Protective effects of dexmedetomidine on stress and inflammatory responses. *Minerva Anestesiol* 2020;86:222-3. DOI: 10.23736/S0375-9393.19.14097-7)

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*Minerva Anestesiologica* 2020 February;86(2):223-4  
DOI: 10.23736/S0375-9393.19.14058-8

## Effects of dexmedetomidine on malondialdehyde and proinflammatory cytokines after tourniquet-induced ischemia-reperfusion injury in total knee arthroplasty

We thank Drs. Morita and Kinoshita<sup>1</sup> for their comments and interest in our article.<sup>2</sup> We agree with their opinion that the sample size used might not be large enough to evaluate the intergroup differences of lac-