Effects of prolonged anesthesia with dexmedetomidine, fentanyl, or remifentanil on the self-renewal of mouse embryonic stem cells

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ABSTRACT. Previous study has indicated that exposure to anesthesia in early development leads to neuro-apoptosis and is followed by long-term cognitive dysfunction. Given that larger numbers of pregnant women currently receive anesthesia during the first trimester, we wanted to mimic this process *in vitro* using mouse embryonic stem cells (mESCs) and to explore how different anesthetics affect the self-renewal of mESCs. In the present study, mESCs were exposed to dexmedetomidine, fentanyl, or remifentanil at clinical concentrations for 48 h. The mESCs were then analyzed for cell proliferation and apoptosis. Furthermore, we used flow cytometry to analyze the cell cycle and quantitative real-time polymerase chain reaction to detect the gene expression during the cell cycle as well as the relevant stemness markers. We found that prolonged anesthesia with dexmedetomidine or fentanyl significantly inhibited mESC proliferation, with fewer cell numbers as well as decreased expression of *cyclin B* and *cyclin*

E mRNA compared to that in the control group; meanwhile, *p21* and *RB2* gene expression was increased. Additionally, increases or decreases in the proportion of cells in the G1 and S phases, respectively, were observed in the dexmedetomidine- and fentanyl-treated groups. These anesthetics also repressed the gene expression of mESC stemness makers such as *Oct4* and *Sox2*. However, remifentanil seemed to have no significant influence on the self-renewal of mESCs. These results demonstrated that prolonged anesthesia with dexmedetomidine or fentanyl, but not remifentanil, inhibited mESC proliferation by blocking the G1 to S transition, and repressed the maintenance of mESC stemness.

Key words: Dexmedetomidine; Remifentanil; Mouse embryonic stem cells; Fentanyl; Self-renewal

